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ORIGINAL ARTICLE

Systemic cervical cytology training and quality control programs can improve the interpretation of Papanicolaou tests

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Introduction There is no national cervical screening program or national standards for cervical cytology quality control in China. Since 2013, systematic training and quality control programs were implemented in the Papanicolaou testing process at Jinan KingMed Diagnostics. Pathologists were required to complete 1 year of cytology study in the KingMed Diagnostics Cytology School, including 6 months of a diagnostic course and 6 months of practical training in the clinical laboratory. In this study, we compared the Papanicolaou abnormal reporting rates before and after the implementation systematic training and quality control programs.

Materials and methods Systematic cytology training and quality control (QC) programs were implemented in 2013. Results from 997,162 cases of liquid-based cytology (LBC) and 100,066 cases of conventional Papanicolaou smears (CPS) rendered between 2008 and 2015 at Jinan KingMed Diagnostics were collected and analyzed.

Results After implementation of training and programs, the abnormal reporting rates of atypical squamous cells of unknown significance (ASC-US), low-grade squamous intraepithelial lesions (LSIL), atypical squamous cells cannot exclude HSIL (ASC-H), atypical glandular cells (AGC), and high-grade squamous intraepithelial lesions (HSIL) in LBC were significantly increased. Similar trends were also observed in CPS

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reporting, except for ASC-H, squamous cell carcinoma, and AGC, probably due to the small percentages of these categories.

Conclusions The study demonstrates the importance of the formal cytology training and QC programs to ensure standardized and effective cervical cancer screening in undeveloped countries, which account for the largest percentage of the world's annual incidence of cervical cancer and with a largely unscreened population.

Introduction

Cervical cancer is the fourth most common female malignancy worldwide, with 85% of cases in developing countries.[1] The screening Papanicolaou test emerged as a critical tool in the early diagnosis of cervical cancer in the last 60 years. After implementation of the Papanicolaou test, cervical cancer, once the most common cancer-related cause of death in women in the 1950s, has fallen to its current level as 15th cancer-related cause of death in the United States and Canada.[2] Similarly, cervical cancer—related mortality rates have also decreased 50% to 80% in Europe.[3] According to the American Cancer Society, compared with 1950, despite significantly increased human papillomavirus (HPV) infection rates, the incidence of cervical cancer has been reduced 85%.[4]

In the United States and the most other western countries, the Papanicolaou test is performed by cytotechnologists and/or cytopathologists who have completed Papanicolaou cytology training. In 1988, the US Congress passed the Clinical Laboratory Improvement Amendments of 1988 (CLIA 88), which detailed regulations governing US cytopathologic quality control. The College of American Pathologists (CAP) incorporated the regulations on cytology standardization, training, and quality control in its Laboratory Accreditation Program. In the US, all personnel who perform Papanicolaou test interpretation are required to annually pass a Papanicolaou proficient test with a passing score.[5-10]

China accounts for 14% of the world's annual incidence of cervical cancer and the decrease in the incidence and mortality associated with cervical cancer observed in western countries has yet to be seen in China. Currently, there is no well-established systematic national cancer registry or organized cervical screening program in China.[11,12] Furthermore, no uniform national standards for cervical cytology quality control exist for laboratories serving this still largely unscreened population.

Jinan KingMed Diagnostics began to perform cervical cytological testing in July 2008. Until 2013, all Papanicolaou tests were interpreted by histopathology practitioners with at least 15 years of cytologic diagnostic experience; however, these pathologists had not completed standardized cervical cytology training or participated any Papanicolaou proficiency testing. There was also very limited diagnostic quality control. Since 2013, a strict Papanicolaou test training and quality control (QC) system was developed and implemented in the laboratory. This study aimed to compare the Papanicolaou test abnormal reporting rates before (2008-2012) and after (2013-2015) the implementation of the training and QC program to examine the effect of systemic training and QC programs on the diagnostic quality of Papanicolaou testing.

Materials and methods

Patients and specimens

Jian KingMed Diagnostics provides clinical pathologic services for more than 900 hospitals in 17 cities in Shandong Province. A total of 1,079,507 Papanicolaou test reports including 997,162 liquid-based cytology (LBC) cases and 100,066 conventional Papanicolaou smears (CPS) performed between January 2008 and December 2015 were included in this study. Materials and supplies used for the preparation of LBC specimens were from LITUO Biotechnology Co., Ltd. (Hunan, China), New Century Bioengineering Co., Ltd. (Shijiazhuang, China), and Hologic (Bedford, MA). The Papanicolaou test collection methods were largely decided by clinicians. The Papanicolaou cytology specimens were collected from about 900 local hospitals, women's health centers, clinics, and physical examination centers in Shandong Province. Both LBC and CPS cases were prepared according to manufacturers' instructions, stained by the Papanicolaou method, and reviewed by pathologists at Jinan KingMed diagnostics.[13-15] All Papanicolaou tests were reported using the Bethesda System (TBS) 2001 terminology.

Training and QC programs

Beginning in 2013, systematic training and QC programs were implemented for the Papanicolaou testing process at Jinan KingMed Diagnostics. Pathologists were trained by completing 1 year of a cytology study program at the KingMed Diagnostics Cytology School in Guangzhou, including 6 months of a diagnostic course and 6 months of practical training in the clinical laboratory.[13-15] The program requires that the cervical cytological diagnostic service be only provided by certified cytopathologists who have completed formal cervical cytology training and passed the designed proficiency testing.

Table 1 Distribution of Papanicolaou test cases (LBC or CPS) from 2008 to 2015 at Jinan KingMed.

Year	LBC	CPS	Total
2008	8253	192	8445
2009	25,128	209	25,337
2010	42,592	3362	45,954
2011	52,315	10,193	62,508
2012	71,133	10,039	81,172
2013	123,708	22,029	145,737
2014	228,490	28,623	257,113
2015	427,822	25,415	453,237
Total	979,441	100,062	1,079,503

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

Since 2013 the QC measurements included: 1) A maximal test reading volume of 120/person/day, 17 slides/hour; 2) Ten percent of the negative cases and all abnormal cases were subjected to review and confirmation by senior cytopathologists before the reports were issued; 3) Monthly review of the ASC/SIL ratio to maintain a range of 1.5 to 3.0; 4) High-risk HPV positive rate in cases with atypical squamous cells of unknown significance (ASC-US) between 30% and 50%; and cytology-histology correlation for high-grade squamous intraepithelial lesions (HSIL) and carcinoma cases.[13-15] Cytopathologists with abnormal reporting rates that significantly deviated from established reference ranges were required to undergo retraining and recertification.

Statistical analysis

Total abnormal reporting rates and reporting rates for each abnormal category were and analyzed yearly, as well as before (pre-QC, 2008-2012) and after the implementation of the training and QC programs (post-QC, 2013-2015). The Pearson χ^2 test was used for statistical analysis conducted on an SAS 9.1 system (SAS Institute, Cary, NC). A value of $P < 0.05$ was considered statically significant.

Results

A total of 1,079,503 Papanicolaou tests performed between January 2008 and December 2015 were included in this study, including of 979,441 LBC cases and 100,062 CPS cases. The test volume increased gradually during the study period (Table 1). The overall TBS reporting rates for LBC and CPS are summarized in Table 2.

Yearly reporting rates for different abnormal cytologic categories are summarized in Table 3 for CPS and in Table 4 for LBC. There were limited CPS cases in the years 2008 and 2009. For CPS the abnormal reporting rates for ASC-US, low-grade squamous intraepithelial lesions (LSIL), HSIL and total abnormal reporting rates were lower in years 2010, 2011, and 2012 (pre-QC) as compared with the rates in years 2013, 2014, and 2015 (post-QC). There were no significant differences in the reporting rates for atypical squamous cells cannot exclude HSIL (ASC-H), atypical glandular cells (AGC), and carcinoma (Table 3). There were limited LBC cases in year 2008. The reporting rates for ASC-US, LSIL, HSIL, AGC, and total abnormal reporting rates were significantly higher in years 2013, 2014, and 2015 (post-QC) as compared to years 2009, 2010, 2011 and 2012 (pre-QC) in LBC. There were no significant differences in the reporting rates for ASC-H and cancer (Table 4).

Next, the reporting rates for each abnormal category for CPS cases were compared between the pre-QC and post-QC periods. When the data were grouped into pre-QC and post-QC based on specimen processing years, CPS cases were found to be associated with higher reporting rates for ASC-US

Table 2 Abnormal reporting rates with different cytology preparations.

Abnormal report categories	LBC cases n (%)	CPS cases n (%)	Total cases n (%)	Age, years mean (range)
ASC-US	31,676 (3.2)	1585 (1.6)	33,261 (3.1)	42.0 (15-94)
ASC-H	2430 (0.2)	151 (0.2)	2581 (0.2)	45.4 (18-91)
LSIL	10,598 (1.1)	364 (0.4)	10,962 (1.0)	39.5 (16-78)
HSIL	5207 (0.5)	180 (0.2)	5387 (0.5)	43.9 (19-84)
SCC	131 (0.01)	2 (0.002)	133 (0.01)	52.1 (31-87)
AGC	518 (0.05)	14 (0.01)	532 (0.05)	44.4 (19-90)
AIS/ADC	11 (0.001)	0 (0.0)	11 (0.001)	55.8 (45-67)
NILM	913,801 (93.3)	96,457 (96.4)	1,010,258 (93.6)	43.46 (15-98)
Unsatisfactory	15,069 (1.5)	1309 (1.3)	16,378 (1.5)	39.5 (17-96)
ASC:SIL ratio	2.1	3.2	2.2	
Total cases	979,441	100,062	1,079,503	43.65 (15-98)

Abbreviations: ASC-US, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; SCC, squamous cell carcinoma; AGC, atypical glandular cells; AIS/ADC, adenocarcinoma in situ/adenocarcinoma; NILM, negative for intraepithelial lesion or malignancy; LBC, liquid-based cytology; CPS, conventional Papanicolaou smear.

Table 3 Yearly abnormal reporting rates in CPS specimens.

	2008	2009	2010	2011	2012	2013	2014	2015	Total
ASC-US, n (%)	4 (2.1)	5 (2.4)	30 (0.9)	73 (0.7)	110 (1.1)	336 (1.5)	431 (1.5)	596 (2.3)	1585 (1.6)
ASC-H, n (%)	0 (0.00)	1 (0.5)	5 (0.1)	20 (0.2)	15 (0.1)	33 (0.1)	26 (0.1)	51 (0.2)	151 (0.2)
LSIL, n (%)	1 (0.5)	1 (0.5)	10 (0.3)	23 (0.2)	22 (0.2)	83 (0.4)	96 (0.3)	128 (0.5)	364 (0.4)
HSIL, n (%)	1 (0.5)	0 (0.0)	2 (0.06)	16 (0.2)	9 (0.09)	40 (0.2)	56 (0.2)	56 (0.2)	180 (0.2)
SCC, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.01)	0 (0.0)	1 (0.004)	0 (0.0)	2 (0.002)
AGC, n (%)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.01)	1 (0.01)	4 (0.02)	1 (0.004)	6 (0.02)	14 (0.01)
AIS/ADC, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
NILM, n (%)	185 (96.35)	202 (96.7)	3315 (98.6)	10,035 (98.4)	9871 (983)	21,096 (95.8)	27,438 (95.9)	24,315 (95.7)	96,457 (96.4)
Un-satisfactory, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	25 (0.3)	10 (0.1)	437 (2.0)	574 (2.0)	263 (1.0)	1309 (1.3)
ASC:SIL ratio	2.0	6.0	2.9	2.4	4.0	3.0	3.0	3.5	3.2
Total	192	209	3362	10,193	10,039	22,029	28,623	25,415	100,062

Abbreviations: ASC-US, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; SCC, squamous cell carcinoma; AGC, atypical glandular cells; AIS/ADC, adenocarcinoma in situ/adenocarcinoma; NILM, negative for intraepithelial lesion or malignancy; CPS, conventional Papanicolaou smear.

Table 4 Yearly abnormal reporting rates in LBC specimens.

	2008	2009	2010	2011	2012	2013	2014	2015	Total
ASC-US, n (%)	126 (1.5)	495 (2.0)	547 (1.3)	1083 (2.1)	1644 (2.3)	4953 (4.0)	8241 (3.6)	14,587 (3.4)	31,676 (3.2)
ASC-H, n (%)	16 (0.2)	38 (0.2)	84 (0.2)	121 (0.2)	164 (0.2)	419 (0.3)	668 (0.3)	920 (0.2)	2430 (0.2)
LSIL, n (%)	123 (1.5)	172 (0.7)	182 (0.4)	335 (0.6)	579 (0.8)	1685 (1.4)	2438 (1.1)	5084 (1.2)	10,598 (1.1)
HSIL, n (%)	64 (0.8)	73 (0.3)	92 (0.2)	229 (0.4)	387 (0.5)	757 (0.6)	1399 (0.6)	2206 (0.5)	5207 (0.5)
SCC, n (%)	4 (0.05)	13 (0.05)	10 (0.02)	7 (0.01)	13 (0.02)	21 (0.02)	21 (0.01)	42 (0.01)	131 (0.01)
AGC, n (%)	1 (0.01)	4 (0.02)	17 (0.04)	25 (0.05)	31 (0.04)	81 (0.07)	151 (0.07)	208 (0.05)	518 (0.05)
AIS/ADC, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.002)	3 (0.001)	6 (0.001)	11 (0.001)
NILM, n (%)	7853 (95.2)	23,221 (92.4)	39,697 (93.2)	49,532 (94.7)	66,901 (94.1)	111795 (90.4)	212823 (93.1)	401979 (94.0)	913801 (93.3)
Un-satisfactory, n (%)	66 (0.8)	1112 (4.4)	1963 (4.6)	983 (1.9)	1414 (2.0)	3995 (3.2)	2746 (1.2)	2790 (0.7)	15,069 (1.5)
ASC:SIL ratio	0.74	2.07	2.22	2.11	1.85	2.18	2.31	2.11	2.14
Total	8253	25,128	42,592	52,315	71,133	123,708	228,490	427,822	979,441

Abbreviations: ASC-US, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; SCC, squamous cell carcinoma; AGC, atypical glandular cells; AIS/ADC, adenocarcinoma in situ/adenocarcinoma; NILM, negative for intraepithelial lesion or malignancy; LBC, liquid-based cytology.

Table 5 Comparison of TBS reporting rates in CPS between pre-QC and post-QC.

	Pre-QC (2008-2012)		Post-QC (2013-2015)		*P*-value (abnormal reporting rate)
	No. cases (%)	Age, years mean (range)	No. cases (%)	Age, years mean (range)	
ASC-US	222 (0.9)	42.5 (20-80)	1363 (1.8)	43.8 (17-76)	<0.001
ASC-H	41 (0.2)	44.2 (30-64)	110 (0.1)	47.9 (21-72)	0.361
LSIL	57 (0.2)	38.8 (26-57)	307 (0.4)	39.6 (20-76)	<0.001
HSIL	28 (0.1)	44.3 (45-62)	152 (0.2)	46.3 (27-74)	0.008
SCC	1 (0.004)	64 (64)	1 (0.001)	56 (56)	0.389
AGC	3 (0.01)	46.7 (40-50)	11 (0.01)	41.3 (30-56)	0.823
NILM	23,608 (98.4)	43.6 (18-86)	72,849 (95.8)	46.5 (18-82)	<0.001
Unsatisfactory	35 (0.1)	44.2 (25-61)	1274 (1.7)	48.1 (22-76)	<0.001
ASC:SIL ratio	3.06		3.20		
Total	23,995	43.5 (18-90)	76,067	46.8 (17-96)	

Abbreviations: ASC-US, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; SCC, squamous cell carcinoma; AGC, atypical glandular cells; AIS/ADC, adenocarcinoma in situ/adenocarcinoma; NILM, negative for intraepithelial lesion or malignancy; QC, quality control; CPS, conventional Papanicolaou smear.

(2.0x), LSIL (2.0x), HSIL (2.0x), and total abnormal reporting rate (1.9x), respectively, in the post-QC group as compared with the pre-QC group (Table 5). No statistically significant differences in the reporting rates of ASC-H, AGC, and cancer were observed between the two groups (Table 5). Unsatisfactory rate was 1.7% in post-QC cases, 9 times more than that in pre-QC cases (0.2%).

The reporting rates for each abnormal category in LBC cases were also compared between pre-QC and post-QC periods. LBC cases were found to be associated with a more than 1.5 times higher reporting rate of ASC-US, ASC-H, LSIL, HSIL, AGC, and total abnormal reporting rate, respectively, in the post-QC group as compared with the pre-QC group (Table 6). The reporting rate of cancer, however, was 50% lower in the post-QC group as compared with the pre-QC group, which may indicate that pathologists were more cautious to report malignancy after the formal cytopathology training.

Discussion

In this study, the abnormal TBS reporting rates for most categories in both the CPS and LBC samples from Jinan KingMed Diagnostics were found to be significantly increased after the implementation of system cytopathology training and QC programs, which demonstrates the importance of systematic pathologist training and QC in cervical cancer screening.

CAP regularly issues questionnaires to collect useful and relevant QC data, such as the abnormal reporting rate for cytological analysis including Papanicolaou testing,[7] the

Table 6 Comparison of TBS report rates in LBC specimens between Pre-QC and Post-QC.

	Pre-QC (2008-2012)		Post-QC (2013-2015)		*P*-value (abnormal reporting rate)
	No. cases (%)	Age, years mean (range)	No. cases (%)	Age, years mean (range)	
ASC-US (%)	3895 (2.0)	38.78 (16-85)	27,781 (3.6)	43.8 (17-94)	<0.001
ASC-H (%)	423 (0.2)	42.85 (21-91)	2007 (0.3)	46.3 (22-81)	<0.001
LSIL (%)	1391 (0.7)	37.44 (17-76)	9207 (1.2)	40.7 (16-78)	<0.001
HSIL (%)	845 (0.4)	41.65 (19-84)	4362 (0.6)	45.1 (21-74)	<0.001
SCC (%)	47 (0.02)	51.38 (32-85)	84 (0.01)	55.6 (31-87)	<0.001
AGC (%)	78 (0.04)	40.06 (24-57)	440 (0.06)	45.9 (19-90)	0.003
AIS/ADC (%)	0	0	11 (0.001)	55.2 (46-67)	0.095
NILM (%)	187,204 (93.9)	40.1 (16-96)	726,597 (93.2)	42.6 (16-94)	<0.001
Unsatisfactory (%)	5538 (2.8)	39.0 (17-90)	9531 (1.2)	41.1 (17-82)	<0.001
ASC:SIL ratio	1.89		2.18		
Total	199,421	39.9 (16-96)	780,020	42.8 (16-94)	

Abbreviations: ASC-US, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; SCC, squamous cell carcinoma; AGC, atypical glandular cells; AIS/ADC, adenocarcinoma in situ/adenocarcinoma; NILM, negative for intraepithelial lesion or malignancy; QC, quality control; LBC, liquid-based cytology.

HPV positive rate in the ASC-US high-risk population,[8] and concordance between cytologic and histologic analysis.[9] The abnormal reporting rate is the most common QC parameter and one of the required QC parameters to report based on CAP regulations established in 1988. The positive reporting rates for different ethnic populations vary significantly according to a 2010 CAP survey based on data collected from 386 hospitals and health organizations worldwide.[10] The survey showed that the LSIL reporting rate was 1.5% at the 10th percentile with a 4-fold increase of 6% at the 90th percentile. Similarly, HSIL positive rates were 0.2% at the 10th percentile and 1.3% at the 90th percentile, a 6.5-fold change. On the contrary, reporting rates remained relatively stable for the same ethnic population from the same geographic area. In China, the reference reporting rate data from large population studies are limited. Therefore, this study with a total of more than 100,000 cases of CPS and nearly 1 million cases of LBC from more than 900 hospitals and medical centers in 17 cities in Shandong Province is of special clinical relevance for establishing apossible reference range for this region of China.

The Guangzhou laboratory is the headquarters of KingMed Diagnostics. Systematic cytology school training and QC programs have long been established in the laboratory in Guangzhou, in concordance with CAP requirements.[13-16] After this initiative, Jinan KingMed Pathology Service began the implementation of systemic training and QC programs in 2010. From 2013, all cytopathologists serving in the cytology laboratory of Jinan KingMed must have completed the formal KingMed Cytology School training programs and participated the QC programs. The results of this study show that the reporting rates of ASC-US, LSIL, HSIL, and the total abnormal Papanicolaou test reporting rates for both CPS and LBC cases in post-QC increased significantly over those from pre-QC, with less variation.

In China, cervical cancer screening is mostly provided by histopathologists without formal cytological training, possibly resulting in lower screening efficiency and higher rates of misinterpretation. Additionally, data on unsatisfactory rates for conventional Papanicolaou testing was 0.1% in pre-QC, much lower than that in CAP benchmarks,[10] which reflects reluctance to report unsatisfactory results to clinicians servicing the laboratory's most cost-constrained patient population. The main reason for the lower unsatisfactory rate with conventional Papanicolaou testing is that many of those women had Papanicolaou tests by attending screening programs sponsored by the government. The clinicians in these governmental programs feel especially embarrassed and dissatisfied when the program receives information that the clinician has collected an unsatisfactory Papanicolaou sample. Furthermore, marketing competition also encourages laboratories to lower the requirements for a satisfactory Papanicolaou test in this setting. After cytopathology training and application of the QC program to the laboratory, the unsatisfactory rate was increased to 1.7%, compatible with the rate of CAP benchmarks.

Recently, Guangzhou KingMed Diagnostics reported the different categories of abnormal TBS reporting rates,[9-11] which were similar to the abnormal reporting rates of the post-QC group in current study. On the contrary, another study by Fudan University Obstetrics and Gynecology Hospital, including more than 150,000 CPS and 580,000 cases of LBC cervical cancer screening cases—interpreted by the histopathologists without the formal training—reported similar abnormal reporting rates as the pre-QC group.[17]

The study included large numbers of Papanicolaou test cases in the same geographic area and it was not unreasonable to assume that the disease profiles for patients in the pre-QC and post-QC groups in this analysis were similar. The main limitations of this study are the fact that we did not record detailed clinical characteristics of the women with Papanicolaou tests, nor did we record a histological follow-up result. Further conformational studies with more detailed patient clinical parameters and histological follow-up results are warranted.

In summary, this study emphasizes the importance of the formal cytology training and QC programs to ensure standardized and effective cervical cancer screening in undeveloped countries, which account for the largest percentage of the world's annual incidence of cervical cancer and which have a largely unscreened population.

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