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Correlation Analysis Between Cervicovaginal Cytologic and Histopathologic Diagnoses in Cervical Squamous Cell Neoplasm

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Background : The aim of this study was to confirm the usefulness of cervicovaginal smears in the screening of squamous cell neoplasms of the uterine cervix by comparative analysis between the cytologic diagnosis of cervicovaginal smears and the histologic diagnosis of tissue specimens. **Methods :** We selected 743 patients who had both cervicovaginal smears and histologic evaluations of the uterine cervix by colposcopic biopsy, conization, or hysterectomy at the Kangbuk Samsung Medical Center between January 2005 and December 2007. **Results :** The accuracy rate of cervicovaginal smears and histologic diagnoses was 93.0% (691/743) and showed a high correspondence (kappa value, 0.770, p-value, 0.000). The false-negative and false-positive rates were 0.5% (6/484) and 17.8% (46/259), respectively. The sampling and interpretation errors were identified in four and two cases of six false-negative cases and 29 and 17 cases of 46 false-positive cases, respectively. In screening high grade squamous cell neoplasms, there were no false-negative cases and only one false-positive case which resulted from sampling error. The false-negative rate of cervicovaginal smears and the false-positive rate in high-grade squamous cell neoplsams were very low. **Conclusions :** The cervicovaginal smear is a powerful tool for screening of cervical squamous cell neoplasms.

Key Words : Cervical smear; Histology; Correlation; Cervical squamous cell neoplsam; Screening

The cervicovaginal smear was introduced by Papanicolaou in 1943, and because of the inexpensiveness and simplicity of the method, the cervicovaginal smear has been used as a routine screening test for cervical cancer and has contributed to lowering the incidence and prevalence of cervical cancer in countries where organized screening programs have been introduced, such as Norway.[1] However, the cervicovaginal smear alone is reputed to have a low sensitivity and a high false negative rate. In fact, the Agency for Health Care Policy and Research (AHCPR) in the US reported that conventional cervicovaginal smears had a sensitivity of 51% and a specificity of 98%.[2] In Korea, several studies have reported high false negative rates associated with cervicovaginal smears in screening for cervical cancer, ranging 6.0-22.9%.[3-6] The causes of high false negative rates can be grouped as follows: 1) a sampling error committed during the sampling procedure from patients, i.e., sample preparation of the slide in the physician's office and slide manipulation in the laboratory, and 2) an interpretation error committed by the pathologist and cytotechnicians during diagnosis and screening. The causes of false negative cases differ among the existing studies. Most studies have reported that sampling errors are more frequent than interpretation or screening errors,[7-9] but in one study, it has been suggested that 50-90% of false negatives may be due to the limitation of vigilance and recognition in screening.[10]

In the current study, we performed a comparative analysis between the cytologic and histologic diagnoses (obtained by biopsy, conization, or hysterectomy) and assessed the diagnostic accuracy of cervicovaginal smears by calculating several accuracy parameters, including the sensitivity, specificity, and false negative and false positive rates. Furthermore, the causes of mismatched cases, including false negative or positive cases, were investigated by slide review. The current study provided a good opportunity for the re-evaluation of cervicovaginal smears as a screening tool for squamous cell neoplasms of the uterine cervix.

MATERIALS AND METHODS

Case selection

We identified patients who had cervicovaginal smears and histologic evaluation of the uterine cervix by colposcopic biopsy, conization, or hysterectomy at the Kangbuk Samsung Medical Center between January 2005 and December 2007. The patients who were diagnosed with glandular cell abnormalities were excluded. The cervicovaginal smears must have been performed before the histologic evaluation. The total number of enrolled patients was 743 and the selected patients were outpatients from the Department of Obstetrics and Gynecology or the Comprehensive Health Screening Center. Two hundred twenty-six of the 743 patients had conventional cervicovaginal smears and the remaining 517 patients had liquid-based cervicovaginal smears (Prepstain System [Surepath]; Tripath Imaging, Inc. Burlington, NC, USA). The histologic diagnosis was evaluated by punch biopsy in 164 patients, conization in 147 patients, and hysterectomy in the remaining 432 patients. The mean duration of time from the cervicovaginal smear to the histologic evaluation was 21.96 days (standard deviation, 40.07; range, 0-316 days).

Review of cervicovaginal smears and the histologic diagnoses

We searched both the cervicovaginal smears and histology slides which were reviewed by one expert cytopathologist and three cytotechnologists without the original cytologic and histologic diagnoses.

Diagnostic criteria for the cervicovaginal smear and the histologic diagnosis

The evaluation of cervicovaginal smears was performed according to the 2001 Bethesda system, which contains six categories,[11] as follows: 1) negative for intraepithelial lesions or malignancy, including benign cellular changes and infection, 2) atypical squamous cells (ASC), including atypical squamous cell of undetermined significance (ASCUS), and atypical squamous cells, but cannot exclude high-grade squamous intraepithelial lesions (ASC-H), 3) low-grade squamous intraepithelial lesion (LSIL) encompassing HPV and mild dysplasia (CIN 1), 4) high-grade squamous intraepithelial lesion (HSIL) encompassing moderate dysplasia (CIN 2), severe dysplasia (CIN 3), and carcinoma *in situ* (CIS), and 5) squamous cell carcinoma (SqCC). The histologic diagnoses were classified by a three-tiered system involving intraepithelial lesions of the cervix, as follows: 1) cervical intraepithelial neoplasia 1 (CIN 1; mild dysplasia) including HPV infection, 2) cervical intraepithelial neoplasia 2 (CIN 2; moderate dysplasia), and 3) cervical intraepithelial neoplasia 3 (CIN 3; severe dysplsia). Carcinoma *in situ* was included in CIN 3 and invasive squamous cell carcinoma (SqCC) was separate. Benign changes in histology included chronic or active cervicitis, squamous metaplasia, and, parakeratosis.

Comparative analysis between cytologic and histologic diagnoses and statistics

The accuracy rate, sensitivity, specificity, positive predictive value, negative predictive value, false positive rate, and false negative rate were calculated by definition. False positive cases indicate that the cytologic diagnosis is ASCUS or greater than ASCUS and the histologic diagnosis is benign changes. False negative cases indicate that the cytologic diagnosis is negative for intraepithelial lesions or malignancy, but the histologic diagnosis is CIN 1 or greater than CIN 1. The causes of false positive, false negative, or mismatched cases were categorized according to sampling and interpretation errors. When a cytologic diagnosis was not changed on a thorough review of a cervicovaginal smear slide, the cause of the discordance was a sampling error. In contrast, if review of a cervicovaginal smear revealed some cytologic features which changed the original cytologic diagnosis, the cause of the discordance was an interpretation error. Interpretation errors were categorized into over-diagnosis and under-diagnosis. The chi-square test was performed for comparative analysis and the results were considered statistically significant at p-values <0.05. All statistical analyses were conducted using SPSS11.0 (SPSS, Chicago, IL, USA).

RESULTS

The correlation between cervicovaginal and histologic diagnoses

The overall results of cervicovaginal and histologic diagnoses are summarized in Table 1. On cytologic diagnosis of cervicovaginal smears, the rates of negative for intraepithelial lesions or malignancy, ASCUS, ASC-H, LSIL, HSIL, and SqCC were 65.1% (484 of 743), 3.0% (22 of 743), 1.9% (14 of 743), 21.0% (156 of 743), 7.8% (58 of 743), and 1.2% (9 of 743), respectively. The

histologic diagnoses revealed that benign changes were found in 524 of 743 (70.5%), CIN 1 in 119 of 743 (16.0%), CIN 2 in 30 of 743 (4.0%), CIN 3 in 25 of 743 (3.4%), CIS in 25 of 743 (3.4 %), and SqCC in 20 of 743 (2.7%). On dichotomization of the cytologic and histologic diagnoses as negative or positive, the concordance rate was 93.0% (691/743), the sensitivity was 97.3% (213/219), the specificity was 91.2% (478/524), the false negative rate was 1.2% (6/484), the false positive rate was 17.7% (46/259), the positive predictive value was 82.2% (213/259), and the negative predictive rate was 98.8% (478/484). Excluding 36 ASC, including ASCUS and ASC-H, the concordance rate was 94.6% (699/707), the sensitivity was 97.0% (191/197), the specificity was 93.8% (478/510), the false negative rate was 1.2% (6/484), the false positive rate was 14.3% (32/233), the positive predictive value was 85.7% (191/223), and the negative predictive value was 98.8% (478/484). The concordance rate, specificity, and positive predictive value increased and the false positive rate decreased when ASC cases were excluded.

The accuracy of cytologic diagnoses

The overall concordance rate between the cytologic and histologic diagnoses was 93.0% and statistically high. The kappa value was 0.77 (p-value <0.000), which are excellent grade. When the histologic diagnosis was used as a gold standard, the accuracy rate of the cytologic diagnosis within the first grade was 89.7%, which implied that 634 cases of 707 revealed matched results between cytology and histology. The 634 matched cases were comprised of 478 negative cases, both in cytology and in histology, 105 LSIL cases with CIN 1 in histology, 44 HSIL cases with CIN 2, CIN 3, and CIS in histology, and 7 SqCC cases in both cytology and histology. All ASC cases, including ASCUS and ASC-H, were excluded from the population. When the accuracy was extended to the second grade between the cytologic and histologic diagnoses, the accuracy rate was 91.5% (647 of 707). The matched cases numbered 647 cases and included 478 negative cases, both in cytology and in histology, 105 LSIL cases with CIN 1 in histology, 55 HSIL cases with CIN 2, CIN 3, CIS, and SqCC in histology, and 9 SqCC cases in cytology showing CIS or SqCC in histology.

The analysis of false negative and false positive cases

The total number of false negative cases was six. All cases were confirmed as CIN 1 in histology, but were negative for intraepithelial lesions or malignancy in cytology. Four of six cases were due to sampling error and the remaining two cases resulted from interpretation error on review. All of the sampling error cases were liquid-based cytology and one of two interpretation error cases was a conventional cervicovaginal smear. The total number of false positive cases was 46 and is summarized in Table 2 according to the diagnosis. The rate of sampling error was 63.0% (29 of 46 cases) and the rate of interpretation error was 37% (17 of 46 cases). The rate of interpretation error in ASCUS and ASC-

Table 2. Analysis of 46 false positive cases

	ASCUS	ASC-H	LSIL	HSIL	SqCC	Total
Sampling error	5	1	22	1	0	29 (63.0%)
Interpretation error	6	2	9	0	0	17 (37.0%)
Total	11 (23.9%)	3 (6.5%)	31 (67.0%)	1 (2.2%)	0 (0%)	46 (100%)

ASCUS, atypical squamous cell of undetermined significance; ASC-H, atypical squamous cells, but cannot exclude high-grade squamous intraepithelial lesions; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; SqCC, invasive squamous cell carcinoma.

Table 1. Correlation between cervicovaginal smear and histologic diagnoses

Histologic diagnosis	Cervicovaginal smear diagnosis						Total
	Negative	ASCUS	ASC-H	LSIL	HSIL	SqCC	
Benign	478	11	3	31	1	0	524 (70.5%)
CIN 1	6	4	2	105	2	0	119 (16.0%)
CIN 2	0	2	2	11	15	0	30 (4.0%)
CIN 3	0	2	3	5	15	0	25 (3.4%)
CIS	0	2	3	4	14	2	25 (3.4%)
SqCC	0	1	1	0	11	7	20 (2.7%)
Total	484 (65.1%)	22 (3.0%)	14 (1.9%)	156 (21.0%)	58 (7.8%)	9 (1.2%)	743 (100.0%)

ASCUS, atypical squamous cell of undetermined significance; ASC-H, atypical squamous cells, but cannot exclude high-grade squamous intraepithelial lesions; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; SqCC, invasive squamous cell carcinoma; CIN 1, cervical intraepithelial neoplasia 1; CIN 2, cervical intraepithelial neoplasia 2; CIN 3, cervical intraepithelial neoplasia 3; CIS, Carcinoma *in situ*.

H was 54% and 66%, and seemed to be higher than LSIL (29%), but there was no statistical significance (p-value=0.259). No interpretation error was identified in HSIL and no false positive case was found in SqCC.

The accuracy of cytologic diagnoses according to grade

In comparative analysis of cytologic and histologic diagnoses according to the grade of cytologic diagnosis, such as the LSIL and HSIL groups, including HSIL and SqCC, the accuracy of diagnosis is summarized in Table 3. The sensitivity of the LSIL and HSIL groups was 92.9% (105 of 113) and 76.2% (64 of 84), respectively. The false positive rates were 19.9% (31 of 156) in the LSIL group and 1.5% (1 of 67) in the HSIL group. The positive predictive values were 67.3% (105 of 156) in the LSIL group and 95.5% (64 of 67) in the HSIL group. The sensitivity of the HSIL group was lower than the LSIL group, but the false positive rate was lower in the HSIL group than the LSIL group. These analyses had been performed, except for ASC.

The analysis of mismatched cases

The mismatched cases were defined as a discordant case between cytologic and histologic diagnoses, except false positive and false negative cases. They were categorized into under-diagnosis and over-diagnosis. The under-diagnosis cases implied that the cytologic diagnosis was lower than the histologic diagnosis in the positive cases. Thirty-one cases were under-diagnosed, which included 20 cases with LSIL cytology and more than CIN 2 on histologic diagnosis and 11 cases of HSIL cytology with SqCC on histologic diagnosis. The causes of under-diagnosed cases as LSIL in cytology were sampling errors in 10 cases and interpretation errors in 10 cases. The histologic diagnoses of sampling error cases were CIN 2 in two cases, CIN 3 in four cases, and CIS in four cases. Interpretation errors were noted in nine CIN 2 cases and only one case was a CIN 3 lesion. All 11 cases were diagnosed as HSIL on cytology, but histologically-confirmed as invasive SqCC. Four of 11 cases were sampling errors and the remaining seven cases were interpretation errors. Six of seven interpretation errors were liquid-based smears and only one case was a conventional smear. Four cases were over-diagnosed, which were diagnosed as HSIL or SqCC on cytology, but confirmed as CIN 2 or CIS on histologic evaluation. One case was a sampling error and the other three cases were interpretation errors. Two cases which were diagnosed as SqCC on cytology, but confirmed as CIS on histology were all interpretation errors on review and smeared by the conventional method. The Remaining two cases which were over-diagnosed as HSIL on cytology were CIN 2 lesions on histology.

The comparative analysis of diagnostic accuracy according to the smear methods

The frequency rate of cytologic diagnoses according to the smear method is summarized in Table 4. The rate of LSIL in liquid-based cytology was 23.8% (123 of 517) and was higher than the conventional method (p-value=0.05). The diagnostic accuracy between the two methods is compared in Table 5. The parameters

Table 3. Accuracy of cytologic diagnoses according to grade

	LSIL	HSIL or greater than HSIL
Sensitivity	92.9% (105/113)	76.2% (64/84)
False positive rate	19.9% (31/156)	1.5% (1/67)
Positive predictive value	67.3% (105/156)	95.5% (64/67)

LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.

Table 5. Comparative analysis of cytologic and histologic diagnoses according to smear method

	Conventional	Liquid-based
Concordance rate	93.4% (211/226)	93.8% (458/491)
Sensitivity	98.1% (53/64)	96.5% (138/143)
Specificity	97.5% (158/162)	92.0% (320/348)
False negative rate	0.6% (1/159)	1.5% (5/325)
False positive rate	7.0% (4/57)	16.9% (28/166)
Positive predictive value	93.0% (53/57)	83.1% (138/166)
Negative predictive value	99.4% (158/159)	98.5% (320/325)

Table 4. Frequency table of cytologic diagnosis according to smear method

	Negative	ASCUS	ASC-H	LSIL	HSIL	SqCC	Total
Conventional	159 (70.4%)	7 (3.1%)	3 (1.3%)	33 (14.6%)	19 (8.4%)	5 (2.2%)	226 (100%)
Liquid	325 (62.9%)	15 (2.9%)	11 (2.1%)	123 (23.8%)	39 (7.5%)	4 (0.8%)	517 (100%)

p-value=0.05.

ASCUS, atypical squamous cell of undetermined significance; ASC-H, atypical squamous cells, but cannot exclude high-grade squamous intraepithelial lesions; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; SqCC, invasive squamous cell carcinoma.

Table 6. Causes of discordance between cytologic and histologic diagnoses according to smear method

	Sampling error	Interpretation error		Total
		Over-diagnosis	Under-diagnosis	
Conventional	8 (30.8%)	7 (26.9%)	11 (42.3%)	26 (100%)
Liquid	43 (51.8%)	13 (15.7%)	27 (32.5%)	83 (100%)

p-value=0.159.

of accuracy in conventional smear methods were better than the liquid-based smear method, except the concordance rate. The causes of discordance are listed in Table 6 according to the smear method. In the conventional smear, the proportion of interpretation errors was higher than the sampling error (69.2% vs 30.8%, respectively). Conversely, the rate of sampling error was higher than the interpretation error in liquid-based cytology, but there was no statistical significance (p-value=0.159).

DISCUSSION

The cervicovaginal smear is considered to be a good method to evaluate the status of uterine cervical epithelium with low cost and easy methodology. Thus, this method has been widely used as a screening test for epithelial neoplasms of the uterine cervix in population-based cancer screening programs and a biannual cervicovaginal smear is recommended for women over the age 30 years by the national cancer screening program in Korea.[12]

The major problem with cervicovaginal smears is the rate of false negative cytology, which has been reported to range between 6 and 50% in several studies.[3,4,8,13-17] In the current study, the false negative rate was 1.2% (6 of 484 cases) and was much lower than previous studies.[3,4,8,13-17] All of the false negative cases were CIN 1 lesions and no false negative case was detected in CIN 2 or higher lesions. Because false negative cytology in CIN 3 lesions give false reassurance to patients and clinicians and postpones the diagnosis of early cervical cancer, which can be cured by conservative treatment, our results are encouraging for cancer screening. False negative cytology can result from inter-observer variation of interpretation, sampling method, smear method, and the expertiveness of pathologists and cytotechnologists.[18,19] In our study, four sampling errors of false negative cases were all liquid-based smears and the remaining two interpretation errors were noted in conventional smears. These traits were also identified in the entire cases.

The rate of false positive cases was 17.7% (46/259) and seems to be high, but most of the cases were LSIL or ASC and only one case was HSIL on cytology. Because the false positive test results of HSIL in cytology can lead a patient with unnecessary invasive treatment, such as biopsy or diagnostic conization, it is also important in quality control of cervicovaginal smears. The one false positive case of HSIL in our study was due to sampling error on review of a slide. The interpretation errors of false positive cases were almost always found in ASC and LSIL, especially ASC. The low reproducibility and high interobserver variance of ASC and LSIL was previously reported in a few studies,[20,21] and this trait was also confirmed in our study. The College of American Pathologists (CAP) use the ASCUS/SIL ratio as an index of quality management and recommends a range of <2-3.[22] Although the ASCUS/SIL ratio in the current study was not a true index of quality assurance because our study group was exclusively made up of cases which were histologically-confirmed, the ratio was 0.16 (36/223).

The rate of sampling error in liquid-based smears was higher than the conventional smear method, regardless of cytologic diagnoses. Conversely, interpretation error was higher in the conventional smear method than the liquid-based method. In general, liquid-based smears have been reported to lower interpretation and screening errors by reduction of unsatisfactory specimens, compared with the conventional smear method.[23,24] This trait was similarly identified in our study. Interpretation error of conventional smears usually results from unsatisfactory smear quality, which induces morphologic distortion. Conversely, interpretation error of liquid-based smears usually results from the clear background or unfamiliar morphologic perception. The liquid-based smear method supplies more clean background and vivid cellular details by removing the unnecessary mucus, blood, and inflammatory cells from the specimen via filter or density gradient centrifugation and by quick fixation without drying artifact. The clean background removes tumor diathesis and makes under-diagnoses of SqCC as CIS or HSIL. The vivid cellular details frequently lead to overdiagnose ASCUS or reactive cellular changes as LSIL, such as the human papillomavirus (HPV) cytopathic effect. A high rate of LSIL and the rate of misdiagnosis of Sqcc as CIS or HISL with the liquid-based smear method in our study can be explained by these characteristic of the liquid-based smear method. Another pattern of the interpretation error was the distinction of CIN 2 and CIN 3 lesions on cytology. In our study, 9 of 10 under-diagnosed cases of LSIL were confirmed as CIN 2 lesions on histology. The 2001 Bethesda system uses a two-tiered classification as low- and high-grade precursor lesions and sets the cytologic threshold between CIN 1 and CIN 2.[11] Because

the natural history of CIN 2 is closer to CIN 1 than CIN 3, some pathologists controvert the 2001 Bethesda system.[25] However, considering that the reproducibility of interpretation of CIN2 lesions in cytology is low, and the cervicovaginal smear test is a screening test, rather than a diagnostic test, the 2001 Bethesda system recommends the two-tiered classification.[11] Actually, the pathologists frequently confront the borderline cases between LSIL and HSIL and diagnose the more apparent grade to avoid over-diagnosis. The 2001 Bethesda system comments in explanatory note that this lesion can be reported as "SIL, grade cannot be determined" or "LSIL, but with rare cells suggestive of HSIL".[11]

The higher sampling error rate of liquid-based smear method may not only result from the unskilled sampling method or process, but also from the problem of the representativeness. Because the number of screened cells in the liquid-based smear method is generally lower than the conventional smear method, the representativeness of liquid-based smears can be debated. The 2001 Bethesda system reports that the liquid-based smear method is a more random sampling method than the conventional method and recommends a minimum cellularity of 5,000 cells for a liquid-based smear which may assure representativeness.[11] However, it has also been mentioned that additional studies relating sensitivity to cell number would be required for all preparation types.[11] Because the enrolled period (2005-2007) was the transitional period when the conventional cervicovaginal smear method was gradually replaced by the liquid-based smear method, the high sampling error rate of liquid-based smears in our hospital may have resulted from the inexperienced sampling method or process, rather than the representativeness of the test method.

CONCLUSION

The false-negative rate of cervicovaginal smears was very low in our institute and confined to LSIL without HSIL. Thus, the cervicovaginal smear is still a powerful and sensitive tool for screening of cervical squamous cell neoplasms.

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