GYNECOLOGY

# Histologic correlation between smartphone and coloposcopic findings in patients with abnormal cervical cytology: experiences in a tertiary referral hospital



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**BACKGROUND:** Smartphones recently have been applied in the medical setting. However, the literature evaluating the utility of smartphones in gynecologic oncology is limited.

**OBJECTIVE:** To evaluate the utility of a smartphone in the detection of uterine cervical lesions in patients with abnormal cervical cytology.

**STUDY DESIGN:** Seventy-five women with abnormal cervical cytology were enrolled. Two doctors independently inspected the uterine cervix by using smartphone or colposcopy. Images were captured using acetic acid, and biopsies were taken as standard-of-care procedures. The diagnostic performance of the smartphone for cervical intraepithelial neoplasm 1 or worse and cervical intraepithelial neoplasm 2 or worse were evaluated, and the kappa value was calculated to determine the chance corrected agreement of the histologic diagnoses based on the smartphone and colposcopic findings.

**RESULTS:** There was a substantial agreement between histologic diagnoses based on the smartphone and colposcopic findings, with a kappa value of 0.67 (95% confidence interval, 0.43—0.90). The sensitivity, specificity, positive predictive value, and negative predictive value of the smartphone in the diagnosis of cervical intraepithelial neoplasm 1 or worse were 0.89 (95% confidence interval, 0.79—0.96), 0.33 (95% confidence interval, 0.08—0.70), 0.91 (95% confidence interval, 0.81-0.97), and 0.30 (95% confidence interval, 0.07—0.65), respectively. The sensitivity, specificity, positive predictive value, and negative predictive value in the diagnosis of cervical intraepithelial neoplasm 2 or worse were 0.92 (95% confidence interval, 0.81—0.98), 0.24 (95% confidence interval, 0.09—0.45), 0.71 (95% confidence interval, 0.58—0.81), and 0.60 (95% confidence interval, 0.26—0.88), respectively.

**CONCLUSION:** We found that there was a substantial agreement between the histologic diagnoses based on the smartphone and colposcopic findings. The smartphone seems to be useful and may be an alternative to colposcopy.

**Key words:** cervical cancer screening, cervical intraepithelial neoplasm, colposcopy, smartphone

Colposcopy is the basis for the correct identification of the atypical transformation zone, the definition of the grade of the underlying lesion, and targeted biopsy in cases of high-grade cervical intraepithelial neoplasm (CIN). The performance of colposcopy varies according to the training and experience of the colposcopist as well as the clinical context in which it is used, ranging from primary care to referral practices.[1] Digital colposcopy has many potential advantages over optical colposcopy. Recently, a well-focused, high-resolution image on a high-definition monitor has been reported to be preferable to optical colposcopy, as it improves the detection of significant high-grade lesions and allows the sharing of the same colposcopic images between the supervising colposcopist and trainees.[2] Although digital videocolposcopy, which has recently become available, improves the accuracy of colposcopy when triaging patients diagnosed with abnormal cervical cytology, such equipment is only available in developed countries due to its high cost. Attention should be focused on the unmet needs for simple but cost-effective tools for the diagnosis of diseases of the female lower genital tract.

The use of smartphones, mobile networks, and associated health applications is now almost universal. Smartphones recently have been applied in the medical setting. For example, studies regarding the use of high-resolution camera smartphones in telepathology[3,4] or a smartphone-based system to improve drug adherence and lifestyle changes in patients with myocardial infarction[5] have been reported previously. However, the literature evaluating the utility of smartphones in gynecologic oncology is limited. We believe that continuing progress in digital imaging devices may allow the quality assurance of cervical cancer screening to be improved. The objective of the current study was to evaluate the utility of a smartphone in the detection of uterine cervical lesions in patients with abnormal cervical cytology.

## Materials and Methods

### Patient selection

The institutional review board of Osaka University Hospital approved the present study (approval number: 15095,

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**AJOG at a Glance**

**Why was this study conducted?**

The study was conducted to evaluate the utility of a smartphone in the detection of uterine cervical lesions in patients with abnormal cervical cytology.

**Key findings**

There was a substantial agreement between histological diagnoses based on the smartphone and colposcopic findings.

**What does this study add to what is known?**

The smartphone seems to be useful and may be an alternative to colposcopy.

date of approval: August 13, 2015). This study was conducted from August 2015 to March 2017. Female patients, who were referred to the Clinic for CIN Management of Osaka University Hospital due to abnormal cervical cytology, were enrolled. The patients' cytological status was assessed by liquid-based cytology (CellPrep; Roche Diagnostics Japan, K.K., Tokyo, Japan) using a central laboratory. Female patients of <20 years of age were excluded from the study. Written informed consent was obtained from all patients.

### Study protocol

For our study, we used the iPhone 5S (Apple Inc, Cupertino, CA) to inspect the uterine cervix. The iPhone 5S has an 8-megapixel camera, with an aperture size of F2.2, focal length of 30 mm, and a pixel size of 1.5 $\mu$m. For this purpose, we called the device, and its use as a cervical scope, a "Smartscopy," as described in the previous pilot study.[6] The smartphone was used solely for the purpose of this study.

The protocol was as follows. After the application of a 3% acetic acid solution to the cervix for 1 minute, 1 gynecologist (Dr A) inspected the uterine cervix using the smartscopy with flash mode activated to identify the biopsy site(s). Dr A then captured both still and moving pictures of the cervix. Dr A then recorded the areas of the "smartscopically" revealed abnormal epithelium, which required biopsy. Subsequently, another gynecologist (Dr B), who was not informed of the smartscopic findings, inspected the cervix of the same patient using a traditional colposcopy (OCS-500; Olympus, Tokyo, Japan). The magnification of the eyepiece was 10×, and manual operation by knob rotation allows for 6× zoom. Dr B then conducted a biopsy based on the colposcopic findings. If the location of the smartscopically abnormal epithelium was not the same as the biopsy site that was identified by Dr B, an additional biopsy was performed at the site identified by Dr A. The biopsy sites were thus determined based on both the smartscopic and colposcopic findings. Both Dr A and Dr B were experienced colposcopists, and they were in the same order. Although Dr A was the same clinician throughout the study, Dr B was not always the same.

The visibility of the squamocolumnar junction (SCJ) was reported as completely visible, partially visible, or not visible, according to the criteria of the Committee on Nomenclature of the International Federation of Cervical Pathology and Colposcopy.[7] When SCJ visibility was not visible, we routinely performed endocervical curettage.

All punch biopsies were made under colposcopic guidance, and the material was fixed in formalin, paraffin-embedded, and stained with hematoxylin and eosin. Finally, the correlation between the smartscopic findings and the histologic diagnosis was evaluated. The histologic diagnosis was made by at least 2 doctors (a pathologist and a gynecologic oncologist).

### Statistical analysis

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the smartphone for the diagnosis of CIN1 or worse (CIN1+) and CIN2 or worse (CIN2+) were evaluated. A kappa value was calculated to determine the chance corrected agreement between the histologic diagnoses based on the smartphone and colposcopic findings. Kappa values of <0.40, 0.41−0.60, 0.61−0.80, and 0.81−1.00 are considered poor-to-fair agreement, moderate agreement, substantial agreement, and excellent agreement, respectively.[8] The 95% confidence interval (CI) for the sample proportion, $p$, is given by $p$ −1.96×standard error to $p$+1.96×standard error, which is:

$$p \pm 1.96\sqrt{p(1-p)/n}$$

where $p$ is the sample proportion and $n$ is the sample size.

The sample size was calculated according to an estimated sensitivity of 0.75 (75%), a minimum sensitivity of 0.65 (65%), and a standard error was 0.05 (5%). The prevalence of CIN1+ of the uterine cervix was estimated to 100% (Osaka University Hospital was a tertiary referral hospital; thus, a high prevalence of diseases was expected). Thus, a minimum sample size of 75 patients was required to determine the diagnostic sensitivity of the smartphone.

Statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for the R software program (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

## Results

### Patients' characteristics

The patient characteristics are shown in Table 1. The median age of the 75 patients was 38 years (range, 20−57 years). Twenty-five of the 75 women (33%) had smoked, whereas 50 women (67%) had never smoked. The SCJ visibility was evaluated as follows: "completely visible" (n=57; 76%),

"partially visible" (n=10; 13%), and "not visible" (n=8; 11%). The results of the cervical cytology included atypical squamous cells of undetermined significance (n=8), atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesion (HSIL) (n=13), low-grade squamous intraepithelial lesion (LSIL) (n=17), HSIL (n=35), atypical glandular cells not otherwise specified (n=1), and adenocarcinoma in situ (n=1).

## Biopsy results and the utility of the smartphone in the detection of CIN1+ and CIN2+

The study was conducted in a diagnostic setting. The prevalence of CIN1+ was 88% (66 of 75). The histologic diagnoses included CIN1 (n=16), CIN2 (n=23), CIN3 (n=24), adenocarcinoma in situ (n=1), squamous cell carcinoma (n=2), and no lesion (n=9) (shown in Table 2 and Figure 1). Of the 66 patients with CIN1+, 59 patients were diagnosed by the smartphone. Of the 9 patients with no lesion, the smartscopic impression was "normal" in 3 patients. Thus, the sensitivity, specificity, PPV, and NPV of the smartphone for CIN1+ were 0.89 (95% CI, 0.79−0.96), 0.33 (95% CI, 0.08−0.70), 0.91 (95% CI, 0.81−0.97), and 0.30 (95% CI, 0.07−0.65), respectively (Tables 3 and 4). Of the 50 patients with CIN2+, 46 patients were diagnosed by the smartphone. Of the 25 patients with no lesion or CIN1, the smartscopic impression was "normal" in 6 patients. Thus, the sensitivity, specificity, PPV, and NPV of the smartphone for CIN2+ were 0.92 (95% CI, 0.81−0.98), 0.24 (95% CI, 0.09−0.45), 0.71 (95% CI, 0.58−0.81), and 0.60 (95% CI, 0.26−0.88), respectively (Tables 3 and 4).

Of the 75 patients, 59 cases were identified by both smartphone and colposcopy, 6 were unidentified by smartphone but identified by colposcopy, 1 was identified by smartphone but unidentified by colposcopy, and the remaining 9 cases were unidentified by both smartphone and colposcopy. There was a substantial agreement between the histologic diagnoses based on the smartphone and colposcopic findings, with a kappa value of 0.67 (95% CI, 0.43−0.90).

Nine cases in which no cervical disease was identified by either smartphone or colposcopy were followed with cytology and colposcopy. After 3−12 months of follow-up, 1 case of vaginal intraepithelial neoplasia 1 (initial cytology: LSIL), 1 case of CIN3 (initial cytology: HSIL), and 2 cases of CIN2 (initial cytology: HSIL and atypical squamous cells—cannot exclude HSIL, respectively) were diagnosed; these were considered to be cases that had been missed by both smartphone and

**TABLE 1**
**Patient characteristics**

| | |
|---|---|
| Median age, y (range) | 38 (20−57) |
| Parity | |
| Yes | 42 |
| No | 33 |
| Smoking status | |
| Never smoked | 50 |
| Currently or previously smoked | 25 |
| Results of cervical cytology | |
| ASC-US | 8 |
| ASC-H | 13 |
| LSIL | 17 |
| HSIL | 35 |
| AGC | 1 |
| AIS | 1 |
| SCJ visibility | |
| Visible | 57 |
| Partially visible | 11 |
| Not visible | 7 |

*AGC*, atypical glandular cells; *AIS*, adenocarcinoma in situ; *ASC-H*, atypical squamous cells—cannot exclude HSIL; *ASC-US*, atypical squamous cells of undetermined significance; *HSIL*, high-grade squamous intraepithelial lesion; *LSIL*, low-grade squamous intraepithelial lesion; *SCJ*, squamocolumnar junction.

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**TABLE 2**
**Histologic diagnosis**

| | Number of patients |
|---|---|
| No lesion | 9 |
| CIN1 | 16 |
| CIN2 | 23 |
| CIN3 | 24 |
| AIS | 1 |
| SCC | 2 |

*AIS*, adenocarcinoma in situ; *CIN*, cervical intraepithelial neoplasm; *SCC*, squamous cell carcinoma.

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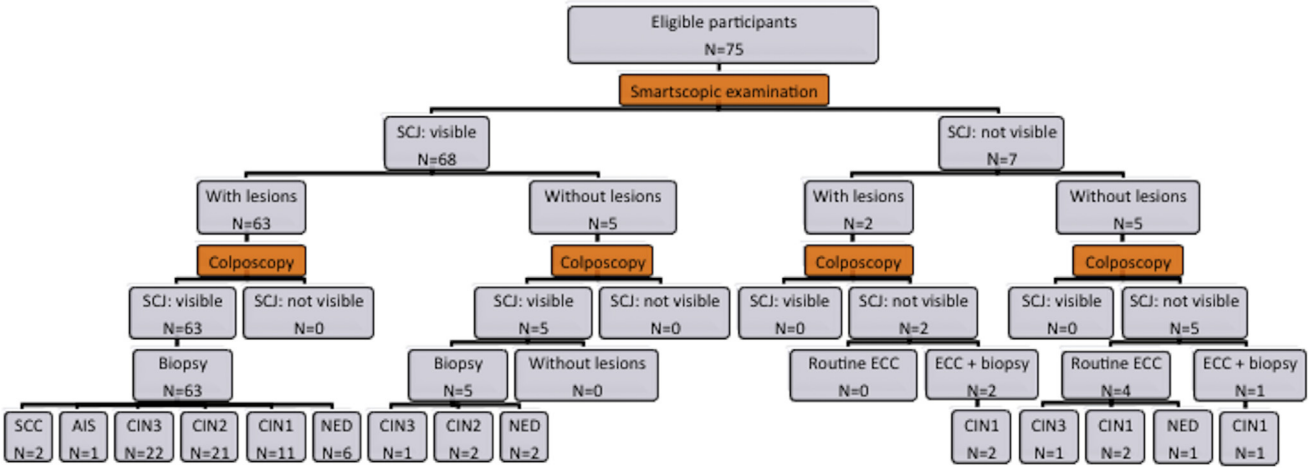
FIGURE 1
**Flow of participants through the study**




*AIS*, adenocarcinoma in situ; *CIN*, cervical intraepithelial neoplasm; *ECC*, endocervical curettage; *NED*, no evidence of disease; *SCC*, squamous cell carcinoma; *SCJ*, squamocolumnar junction.

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colposcopy. No evidence of disease was identified in the remaining 5 cases after the follow-up period.

## Comment

The aim of colposcopy is to identify and plan the treatment for premalignant diseases of the cervix, vagina, vulva, and perianal region.[9] However, colposcopy typically is not available in a primary care setting, and in many low- and middle-income countries, often the alternative is to visualize the cervix with the naked eye alone, which may result in missed diagnoses. Countries with low medical resources need additional assistance in their delivery of modern healthcare. This is particularly true when there are limited numbers of specialized physicians or nurses with respect to cancer screening. Attention should be focused on the unmet needs for simple and cost-effective diagnostic tools for diseases of the female lower genital tract.

Smartphones have become useful tools in our daily lives and have rapidly spread worldwide. Currently, 59% of the people in the world own a smartphone.[10] Smartphones and medical-related applications ("apps") are also rapidly emerging as a critical tool for cancer care from prevention to palliation, including cancer telegenetics, telepathology, the bundling of cancer-related teleapplications, remote chemotherapy supervision, symptom management, survivorship care, palliative care, and approaches to increase access to cancer clinical trials, some of which may use mobile technologies.[11]

The utility of the smartphone in oncology has been described in previous studies.[12,13] Some authors investigated the efficacy of the smartphone for telemedicine in low- and high-resource countries, supporting the use of telemedicine for the off-site diagnosis of CIN with diagnostic performance similar to that achieved on-site.[12] Another study evaluated the utility of smartphone apps in dermatologic oncology, comparing the diagnostic accuracy of 4 apps in detecting skin melanoma.[13] However, the study showed significant variability in specificity, with 3 applications misclassifying more than 30% of melanomas as benign. Currently, the US Food and Drug Administration is focused on the regulation of mobile medical apps, and various types of mobile medical apps have been approved by the US Food and Drug Administration.[14] The validation of these applications in

TABLE 3
**Smartscopic impression and histological diagnosis**

| | CIN1+ | No lesion | Total |
|---|---|---|---|
| Smartscopic impression "normal" | 7 | 3 | 10 |
| Smartscopic impression "abnormal" | 59 | 6 | 65 |
| Total | 66 | 9 | 75 |
| | **CIN2+** | **No lesion or CIN1** | **Total** |
| Smartscopic impression "normal" | 4 | 6 | 10 |
| Smartscopic impression "abnormal" | 46 | 19 | 65 |
| Total | 50 | 25 | 75 |

*CIN*, cervical intraepithelial neoplasm.

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**TABLE 4**
**Diagnostic performance of the smartphone for CIN1+ and CIN2+**

CIN1+

| Sensitivity (95% CI) | Specificity (95% CI) | Positive predictive value (95% CI) | Negative predictive value (95% CI) |
|---|---|---|---|
| 0.89 | 0.33 | 0.91 | 0.3 |
| (0.79–0.96) | (0.08–0.70) | (0.81–0.97) | (0.07–0.65) |

CIN2+

| Sensitivity (95% CI) | Specificity (95% CI) | Positive predictive value (95% CI) | Negative predictive value (95% CI) |
|---|---|---|---|
| 0.92 | 0.24 | 0.71 | 0.6 |
| (0.81–0.98) | (0.09–0.45) | (0.58–0.81) | (0.26–0.88) |

*CI*, confidence interval; *CIN*, cervical intraepithelial neoplasm.

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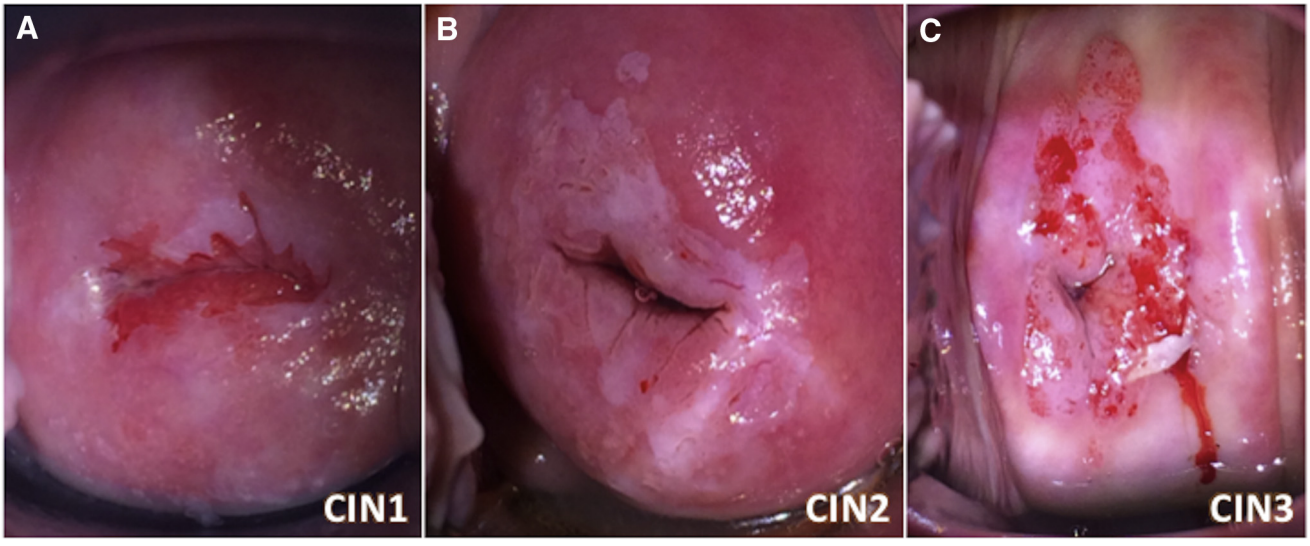
the clinical setting is a crucial step to ensuring patient safety.[15]

In the current study, both still and moving pictures of the cervix were captured (Figure 2 and Video 1). Video systems using a smartphone could be particularly useful for demonstrating the dynamic changes that occur in the cervical epithelium after the application of acetic acid.[6] The iPhone 5s has a limitation in that it is only capable of 5× magnification. In contrast, a colposcope is capable of greater magnification (eyepiece: 10×, manual operation by knob rotation: 6× zoom). Although 10× magnification is adequate for routine work, greater magnification is required to study details. The limitation of smartphone will be overcome by using high-spec smartphones that are currently available worldwide. High-resolution digital images will play an important role in gynecologic oncology. There was a substantial agreement between the histologic diagnoses based on the smartphone and colposcopic findings, which provides new insight into early detection of cervical cancer.

The study has several limitations. First, the smartphone showed high sensitivity and a high PPV in the detection of CIN, whereas specificity and NPV were low. The study was conducted in a

**FIGURE 2**
**The uterine cervix captured by a smartphone**




**A,** CIN1; note the acetowhite epithelium at 12 o'clock. **B,** CIN2; note the acetowhite epithelium and mosaic at 12 o'clock. **C,** CIN3; note the acetowhite epithelium and punctation at 12 o'clock.

*CIN*, cervical intraepithelial neoplasm.

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tertiary referral hospital, and the prevalence of high-grade CIN was always greater in comparison with the screening setting. PPV and NPV are influenced by the prevalence of disease. Results obtained from the current study cannot be generalized to other population. Although our results are limited to data obtained from diagnostic setting, the smartphone seemed to be useful, suggesting that it could be an alternative to colposcopy. Second, use of a smartphone by clinicians with less experience in colposcopy may not give similar results, and a study needs to be conducted using those clinicians. Third, the distribution of abnormal cytology in Japanese population may be inconsistent with that of US population. Therefore, the study should be repeated in a US population to ensure generalizability. Fourth, in the current study, women <20 years old were excluded. Inclusion criteria may lead to bias the study toward increased sensitivity of both colposcopy and the smartphone technique. Finally, although Dr A was the same clinician throughout the study, Dr B was not always the same. That may lead to potential bias in to our results.

In conclusion, we evaluated the utility of a smartphone in the diagnostic setting and found that there was a substantial agreement between the histologic diagnoses based on the smartphone and colposcopic findings. Smartphones will play a central role in the evaluation of women with diseases of the lower genital tract and in the worldwide fight against cervical cancer. ■

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