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Original Article

Validation of HPV triage in cytology-based cervical cancer screening for ASC-US cases using Japanese data

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ABSTRACT

Objective: In Japan, cervical cancer screening consists of a cytology examination performed once every 2 years. We verified whether the risk of cervical intraepithelial neoplasia (CIN) 3 disease or higher (CIN3+) was equivalent to that of cytology negative cases (negative for intraepithelial lesion or malignancy [NILM]) for patients with a cytological diagnosis of "atypical squamous cells of undetermined significance (ASC-US)" who tested negative for human papillomavirus (HPV).
Methods: Data from a total of 22,925 cases who had undergone cervical cancer screening at least twice or who had completed follow-up examinations after cervical screening at a single facility between April 2013 and April 2018 were analyzed. The cumulative incidence of CIN3+ was calculated for each category of initial cytology finding and HPV result (NILM, > ASC-US, ASC-US/HPV (unknown), ASC-US/HPV$^+$, and ASC-US/HPV$^-$). The statistical analysis was conducted using the Cox proportional hazards model.
Results: The hazard ratio for the cumulative incidence of CIN3+ in 2 years relative to that for NILM cases was 2.7 (95% confidence interval=1.0–7.8) for > ASC-US cases, 0.5 (0.1–1.7) for ASC-US/HPV (unknown), 0.8 (0.3–2.4) for ASC-US/HPV$^+$ cases, and 0.3 (0.1–1.0) for ASC-US/HPV$^-$ cases.
Conclusion: Because the cumulative incidence of CIN3+ at 2 years for the ASC-US/HPV$^-$ cases was sufficiently low, compared with that of the NILM cases, we considered it reasonable and safe to perform HPV triage for ASC-US cases and to allow HPV-negative cases to return for their next screening in 2 years, which is the same follow-up schedule as that for NILM cases.

Keywords: Cervical Cancer; Screening; ASC-US; HPV Triage; Cumulative Incidence

Synopsis

In this study the safety of HPV triage for ASC-US cases was evaluated using Japanese data. As a result, the cumulative incidence of CIN3 and invasive cancer in 2 years for ASC-US/HPV negative cases was found to be as low as that for cases with NILM. It is the first time that it has been demonstrated in cases derived from actual screening in Japan.

Conflict of Interest
Dr. Daisuke Aoki declares the receipt of honoraria from Roche Diagnostics K. K., ASKA Pharmaceutical. Co., Ltd. and Hologic Japan, Inc. and expert testimony fees from Sysmex Corporation and Sekisui Medical Co., Ltd. (Inst). He also declares the receipt of research grants from Sysmex Corporation and ASKA Pharmaceutical. Co., Ltd. The other authors have nothing to declare.

Author Contributions
Conceptualization: A.E.S., A.D.; Data curation: A.E.S., S.K., K.K.; Formal analysis: A.E.S., S.K.; Investigation: S.K., K.K., M.T.; Methodology: S.K., A.D.; Project administration: A.D.; Supervision: K.K., A.D.; Validation: M.T.; Writing - original draft: A.E.S.; Writing - review & editing: A.E.S., S.K., K.K., M.T., A.D.

INTRODUCTION

In Japan, cervical exfoliative cytology is used as the primary screening modality for cervical cancer in Community Health and Health Promotion Projects (community screening) [1], and the Bethesda system for reporting cervical cytological diagnoses has been used since fiscal 2014. The system is based on the premise that human papillomavirus (HPV) infection is associated with the development of cervical intraepithelial neoplasia (CIN) and cervical cancer. It also refers to the triage of subjects with atypical squamous cells of undetermined significance (ASC-US) by testing for HPV infection [2].

In Japan, while there is only one follow-up examination option for subjects with abnormal cytological findings other than ASC-US (immediate colposcopy + biopsy), three follow-up examination options are available for cases with a cytological diagnosis of ASC-US: 1) immediate colposcopy + biopsy; 2) immediate triage by HPV testing, followed by colposcopy + biopsy for HPV$^+$ subjects or a 12-month follow-up cytology examination for HPV$^-$ subjects; or 3) repeat cytology every 6 months and colposcopy + biopsy for cases with ASC-US results or worse (**Fig. 1**) [1]. Of the three follow-up examination options, colposcopy + biopsy is

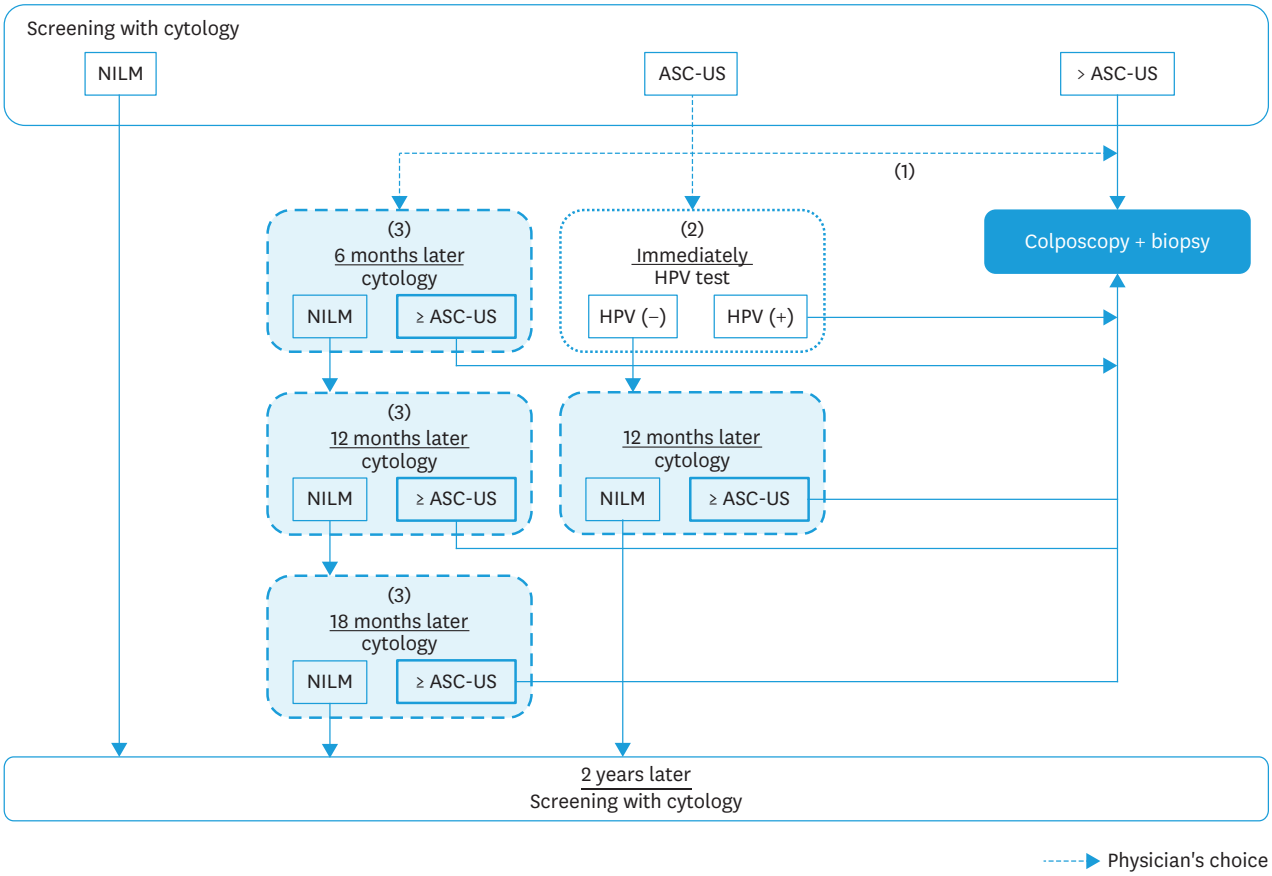

Fig. 1. Algorithm of community screening for cervical cancer: current status in Japan.
Three follow-up options are available for cases with ASC-US: 1) immediate colposcopy and biopsy, 2) immediate triage using HPV testing, and 3) repeat cytology every 6 months.
ASC-US, atypical squamous cells of undetermined significance; HPV, human papillomavirus; NILM, negative for intraepithelial lesion or malignancy.

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highly invasive, and a repeat cytology examination every 6 months has been difficult to implement successfully. Consequently, we have been unable to tabulate the outcomes of repeat cytology every 6 months. The triage of cases with a cytological diagnosis of ASC-US (ASC-US cases) according to HPV testing, which enables the number of cases requiring immediate colposcopy + biopsy to be narrowed down to those who are HPV$^+$, seems reasonable in terms of reducing the disadvantages of the invasive colposcopy and biopsy procedures. Thus, the management of ASC-US cases would be easier if they could be integrated into the HPV triage system, and HPV$^-$ cases could be advised to return for their next regular screening in 2 years.

To validate the use of the HPV triage system for ASC-US cases in Japan, we evaluated the risk of the occurrence of CIN3 and invasive cancer (CIN3+) in ASC-US/HPV$^-$ cases, compared with that in cases diagnosed as negative for intraepithelial lesion or malignancy (NILM). In addition, since the protocols for cytological diagnosis vary among countries [3], we examined whether there were any significant problems in ASC-US diagnosis in Japan, where the Bethesda system has been widely used for statistical purposes since 2014.

MATERIALS AND METHODS

Subjects who visited the Tokyo Health Service Association (THSA) between April 2013 and March 2018 and who met either of the following inclusion criteria were enrolled in the study: 1) subjects who had undergone cervical cancer screening at THSA on at least 2 occasions; or 2) subjects with abnormal cytology results detected during cervical cancer screening at THSA or other gynecological facilities who underwent further examination and follow-up at THSA. Subjects whose first cytology results were completed after April 1, 2016, were excluded to allow the 2-year cumulative incidence to be analyzed.

THSA is a major institute responsible for cytological and histological diagnoses of the cervix in Tokyo, and the facility is commissioned by more than half of the local governments in Tokyo to process cytological specimens for cervical cancer screening. The institute maintains a database of all cytological and histological results, in chronological order, for each case.

All the cytology specimens were collected by gynecologists and processed using conventional or liquid-based cytology methods. Both the cytological and histological diagnoses were made at THSA. In principle, HPV triage is performed immediately for subjects with ASC-US, while a colposcopy and biopsy are performed immediately for those with abnormal cytology results other than ASC-US. HPV triage for ASC-US cases consists of a colposcopy + biopsy for ASC-US/HPV$^+$ cases and a repeat cytology examination after 12 months for ASC-US/HPV$^-$ cases; subjects with any result other than NILM at the 12-month repeat cytology examination undergo colposcopy + biopsy. In some cases that were enrolled early during this study, a colposcopy + biopsy was performed immediately for ASC-US cases.

The follow-up system for patients with abnormal cervical cytology results at THSA is as follows. In principle, follow-up is performed by colposcopy + biopsy + cytology, and patients with histologically diagnosed CIN3 or invasive cancer are immediately referred to appropriate treatment facilities. In addition, patients with persistent CIN2 who are found to have HPV16, 18, 33, 35, 52, or 58 [4], which are considered to be associated with a high risk of progression to invasive cancer in Japanese women, are also referred to treatment facilities, and the follow-

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up is recorded as having been completed. If a CIN2 patient does not consent to treatment or is found to harbor other HPV types, follow-up is continued at THSA. If the CIN disappears and the cytology results show NILM, the follow-up is recorded as having been completed and the patient returns to a regular screening schedule.

In this study, all the participants were followed for more than 2 years. We calculated the cumulative incidences of cervical invasive cancer, CIN3+ and CIN2+ as well as the hazard ratios (HRs) of these cumulative incidences for subgroups classified according to the initial cytology finding and HPV result using the Cox proportional hazards model. The subgroups were as follows: 1) the initial cytology finding was NILM (NILM subgroup); 2) the initial cytology test was ASC-US, and the concurrent or triage HPV test result was negative (ASC-US/HPV$^-$ subgroup); 3) the initial cytology test was ASC-US, and the concurrent or triage HPV test result was positive (ASC-US/HPV$^+$ subgroup); 4) the initial cytology test was ASC-US, and no concurrent or triage HPV test was performed (ASC-US/HPV [unknown] subgroup); and 5) the initial cytology test was > ASC-US (> ASC-US subgroup). We calculated the cumulative incidence and HRs adjusted for age. The statistical analysis was performed using Statistical Analysis System (SAS) software, version 9.4 (SAS Institute, Cary, NC, USA).

This study was approved by the Institutional Review Board of the International University of Health and Welfare (No. 5-17-60).

RESULTS

A total of 22,925 women were included in the analysis. The average age of the subjects at the time of their first cytology examination was 44.4 years (95% confidence interval [CI]=44.2–44.6 years), with 57.2% of the subjects in the 30 to 49 years age category (**Table 1**). The average observation period until the final test results was 2.44 years (2.43–2.46 years). The initial cytology findings and HPV test results showed that NILM was the most common finding (84.4%), followed by > ASC-US (11.9%) and ASC-US (3.6%) (**Table 1**). The breakdown of the 836 ASC-US cases was as follows: ASC-US/HPV$^+$, 274 cases; ASC-US/HPV$^-$, 274 cases; and ASC-US/HPV (unknown), 288 cases (**Table 1**).

As shown in **Table 2**, in the three groups classified according to the initial cytology results (NILM, ASC-US, and > ASC-US), the cumulative incidences of all invasive cancer, CIN3+, and CIN2+ cases from immediately after cytology until 2 years later were consistently highest among cases with a cytological diagnosis of > ASC-US (> ASC-US cases), followed by ASC-US cases; the cumulative incidences were the lowest among the NILM cases.

When the ASC-US cases were divided into 3 subgroups according to the results of HPV testing, the ASC-US/HPV$^-$ and NILM cases showed consistent trends in the cumulative incidences of CIN3+ and CIN2+ over time, and the ASC-US/HPV$^+$ and ASC-US/HPV (unknown) cases showed the same trends in terms of the cumulative incidences of CIN3+ and CIN2+ (**Figs. 2** and **3**). In addition, the ASC-US/HPV$^+$ and ASC-US/HPV (unknown) cases were associated with consistently higher cumulative incidences of CIN3+ and CIN2+ when compared with the ASC-US/HPV$^-$ and NILM cases, but lower cumulative incidences of CIN3+ and CIN2+ when compared with the > ASC-US cases (**Figs. 2** and **3**). As shown in **Table 2**, the 2-year cumulative incidence of CIN3+ was 14.3% (8.8%–22.9%) for the ASC-US/HPV$^+$ cases and 13.0% (7.2%–23.1%) for the ASC-US/HPV (unknown) cases. The incidence of CIN2+ was

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Table 1. Characteristics of the subjects

Variables	Number of participants (%)
Age	
Under 30	2,695 (11.8)
30–49 years old	13,111 (57.2)
50–69 years old	6,457 (28.2)
Over 70	662 (2.9)
Observation years	
Less than 1 year	3,334 (14.5)
Less than 2 years	5,215 (22.7)
Less than 3 years	6,169 (26.9)
Less than 4 years	4,829 (21.1)
Less than 5 years	3,378 (14.7)
Initial screening results	
Cytodiagnosis	
> ASC-US	2,735 (11.9)
ASC-US	836 (3.6)
NILM	19,354 (84.4)
Combination of cytology and HPV results	
> ASC-US	2,735 (11.9)
ASC-US/HPV$^+$	274 (1.2)
ASC-US/HPV$^-$	274 (1.2)
ASC-US/HPV (unknown)	288 (1.3)
NILM	19,354 (84.4)

ASC-US, atypical squamous cells of undetermined significance; HPV, human papillomavirus; NILM, negative for intraepithelial lesion or malignancy.

Table 2. Two-year cumulative incidence according to initial test results (cervical cancer, CIN3 or higher, CIN2 or higher), adjusted for age

Variables	Invasive cervical cancer	CIN3+	CIN2+
Total	2.6% (1.9%–3.4%)	21.6% (19.8%–23.5%)	42.1% (39.8%–44.4%)
> ASC-US	3.0% (2.3%–4.1%)	28.3% (25.8%–30.9%)	54.1% (51.1%–57.0%)
ASC-US	2.4% (1.0%–5.7%)	11.8% (8.2%–16.9%)	29.5% (23.9%–36.0%)
ASC-US/HPV$^+$	3.2% (1.1%–8.8%)	14.3% (8.8%–22.9%)	35.4% (27.0%–45.5%)
ASC-US/HPV$^-$	0.7% (0.1%–5.0%)	4.2% (1.2%–14.2%)	10.9% (4.9%–23.3%)
ASC-US/HPV (unknown)	2.0% (0.3%–13.4%)	13.0% (7.2%–23.1%)	31.8% (22.7%–43.4%)
NILM	0.4% (0.1%–2.7%)	2.9% (1.5%–5.8%)	5.5% (3.3%–8.9%)

Cumulative incidence rates with 95% confidence intervals were adjusted for age group.
ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; NILM, negative for intraepithelial lesion or malignancy.

35.4% (27.0%–45.5%) for the ASC-US/HPV$^+$ cases and 31.8% (22.7%–43.4%) for the ASC-US/HPV (unknown) cases. On the other hand, the incidence of CIN3+ was 4.2% (1.2%–14.2%) for the ASC-US/HPV$^-$ cases and 2.9% (1.5%–5.8%) for the NILM cases. The incidence of CIN2+ was 10.9% (4.9%–23.3%) for the ASC-US/HPV$^-$ cases and 5.5% (3.3%–8.9%) for the NILM cases.

The HRs of the cumulative incidence for each initial screening result are shown in **Table 3**. Based on the cytology results alone, the HRs of CIN3+ and CIN2 were significantly higher for the > ASC-US cases than for the NILM cases (CIN3+, 2.7 [1.0–7.3] and CIN2+, 4.7 [2.1–10.4]), although no significant difference in the risk of invasive cancer was seen. On the other hand, no significant differences in the HRs for the risk of invasive cancer, CIN3+, or CIN2+ were seen between the ASC-US and NILM cases. When the ASC-US cases were divided into 3 groups according to the results of HPV testing, the HRs for invasive cancer, CIN3+ and CIN2+ were not significantly different from those of the NILM cases in any of the 3 groups (**Table 3**).

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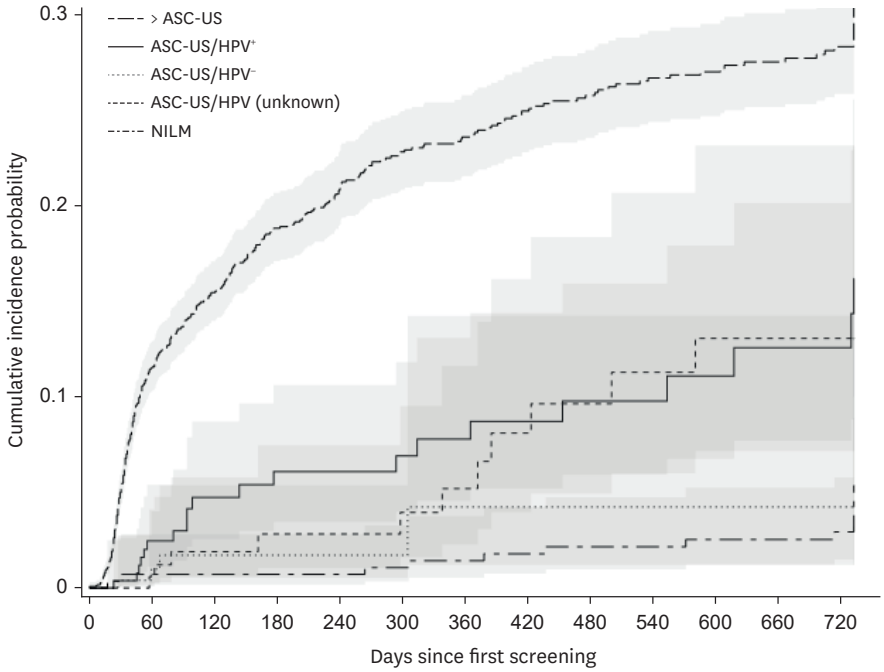

Fig. 2. Cumulative incidences of CIN3 and invasive cancer (CIN3+) probability.
The 2-year cumulative incidence curves for CIN3+ according to each initial screening result are shown.
ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; NILM, negative for intraepithelial lesion or malignancy.

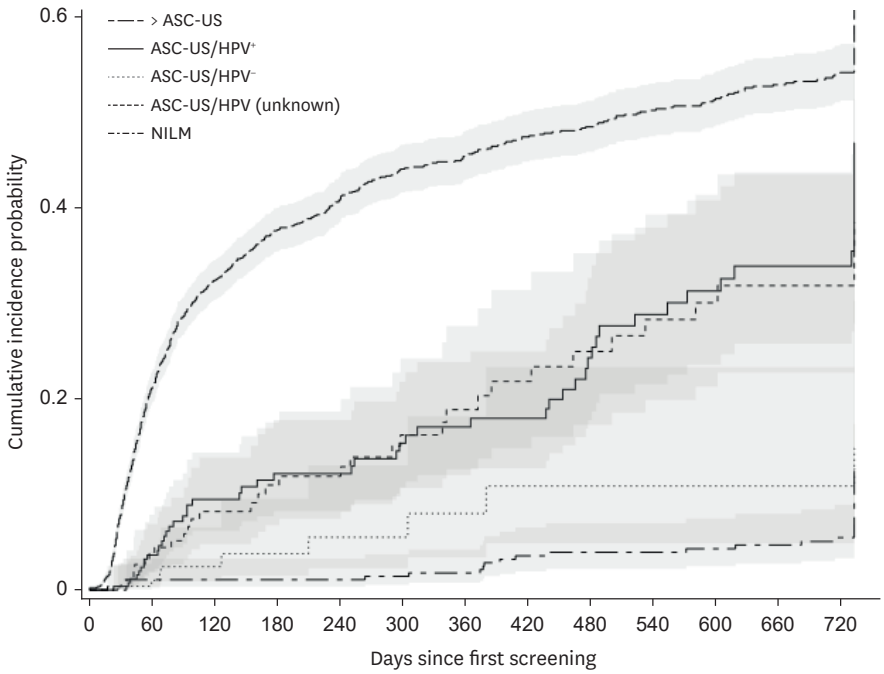

Fig. 3. Cumulative incidences of CIN2, CIN3 and invasive cancer (CIN2+) probability.
The 2-year cumulative incidence curves for CIN2+ according to each initial screening result are shown.
ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; NILM, negative for intraepithelial lesion or malignancy.

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Table 3. HR for disease detection within 2 years, adjusted for age

Variables	Invasive cervical cancer	CIN3+	CIN2+
Initial screening results			
> ASC-US	1,627,328.0	**2.7** (1.0–7.3)	**4.6** (2.1–10.3)
ASC-US/HPV$^+$	792,499.4	0.8 (0.3–2.4)	1.3 (0.5–3.0)
ASC-US/HPV$^-$	290,622.4	0.3 (0.1–1.0)	0.4 (0.1–1.1)
ASC-US/HPV (unknown)	1.0	0.5 (0.1–1.7)	1.5 (0.6–3.6)
NILM	Ref.	Ref.	Ref.
Initial cytodiagnosis			
> ASC-US	590,881.3	**2.7** (1.0–7.3)	**4.7** (2.1–10.4)
ASC-US	147,854.1	0.5 (0.2–1.5)	1.1 (0.5–2.5)
NILM	Ref.	Ref.	Ref.

HRs with 95% confidence intervals were adjusted for age group.
ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HR, hazard ratio; NILM, negative for intraepithelial lesion or malignancy.

DISCUSSION

Cervical cancer screening in Japan consists of a primary cytology examination performed once every two years; in 2014, the Bethesda system for cytology reporting was adopted, and the histological classification of dysplasia was also shifted to the CIN classification. Since 2014, community screening data on the incidences of invasive cancer, CIN3, CIN2, and CIN1 in cases with ASC-US or worse cytology results can be obtained from the community health promotion project report, which is a nationwide statistical database [5]. However, this database does not include incidences of invasive cancer and CINs by each cytological diagnosis. The results of this analysis using data derived from screening in Japan showed that the 2 year incidences of invasive cancer, CIN3+, and CIN2+ in subjects initially evaluated as ASC-US according to the Bethesda system were located between those for >ASC-US cases and NILM cases. This indicates that the diagnosis of ASC-US in cervical cancer screening in Japan works reasonably well. At the same time, the results of this study indicate that many ASC-US lesions do not progress to invasive cancer, CIN3+ or CIN2+; hence, medical intervention for these lesions would be excessive.

In this study, we combined the results of ASC-US and HPV testing and found that the risk of the development of CIN3+ and CIN2+ lesions in ASC-US/HPV$^-$ cases was as low as that in NILM cases at the end of 2 years of observation (**Figures 2**, **3**; **Tables 2**, **3**). These findings are noteworthy because in the context of the current cervical cancer screening system of "primary cytology examination performed once every two years" that is being used in Japan, they suggest the validity and safety of immediate HPV triage for all ASC-US cases, with HPV$^-$ cases then being advised to return for their next screening in 2 years.

Despite the expected higher incidences of CIN3+ in the ASC-US/HPV$^+$ group than in the ASC-US/HPV (unknown) group, the incidence of CIN3+ was similar between the ASC-US/HPV$^+$ and ASC-US/HPV (unknown) subgroups in our results. This similarity was seen for the incidence of CIN2+. For these phenomena, the possibility that the ASC-US/HPV (unknown) group might have contained a considerable number of ASC-US/HPV$^+$ cases cannot be ruled out. As shown in **Figs. 2** and **3**, CIN2+ and CIN3+ continued to occur over a 2-year period in the ASC-US/HPV$^+$ and ASC-US/HPV (unknown) groups. Therefore, it would not be safe to discontinue follow-up examinations after only one repeat cytology examination and without HPV triage for ASC-US cases. In the present study, the 2-year cumulative incidence of ASC-US/HPV$^+$ was not significantly different from that of NILM, but this may be due to a lack of statistical power or the characteristics of the Cox proportional hazards model.

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According to the FY2019 Community Health and Health Promotion Project Report, the positive rate of cervical cancer screening by cytology in Japan was 2.2%, and ASC-US accounted for about 50% of the cases [5]. Kono et al. reported that about 50% of ASC-US cases were HPV^+ and about 50% were HPV^- [6], so by using an algorithm that incorporated HPV triage for all ASC-US cases, about 25% of cases with cytological abnormalities could be immediately determined as candidates for subsequent screening after 2 years. Also, from the perspective of simplifying the management of the screening program, it would be very useful to unify this algorithm. Previous reports also provide evidence of the usefulness of performing HPV triage for ASC-US cases. According to the ASC-US LSIL Triage Study [7,8], the 2-year sensitivity of the detection of CIN3+ in ASC-US cases was equivalent among direct colposcopy, HPV triage, and repeat cytology [7,8]. The ALTS group members especially focused on ASC-US cases and found that the repeat cytology strategy required at least two follow-up cytology examinations to ensure the same sensitivity as one HPV triage, resulting in a fivefold higher number of cases eligible for colposcopy than HPV triage [9]. The Japanese algorithm also allows repeat cytology examinations every 6 months for 2 years (**Fig. 1**), but there is no system for reporting each result, and adherence to this schedule remains unclear. Arbyn et al. [10] conducted a systematic review comparing HPV triage and repeat cytology as triage methods for ASC-US cases. They reported that the pooled sensitivity of HPV triage using Hybrid Capture II was significantly higher than that of repeat cytology at cut-off ASC-US+ to detect CIN2+ in triage of ASC-US cases (relative sensitivity=1.27; 95% CI=1.16–1.39; p<0.0001), and the pooled specificity of the triage methods did not differ significantly from each other (relative specificity=0.99; 95% CI=0.97–1.03; p=0.98) [10]. Thus, HPV triage, rather than repeat cytology, can be recommended to triage women with ASC-US.

Currently in Japan, the 2019 edition of the Japanese Guideline for Cervical Cancer Screening recommends that primary cytology screening or primary HPV screening be performed. Primary HPV screening is for women over the age of 30 years, and primary cytology screening continues to be performed for women in their 20s [11]. To continue the good management of primary cytology screening, the results of this study lend validity to the notion that the triage of ASC-US cases using HPV testing is both practical and feasible.

This study is an analysis of screening-derived cases that were actually performed. Also, it shows the cumulative incidence of CIN3+ and CIN2+ in ASC-US/HPV^- cases compared to NILM cases, which has not been shown in Japanese data.

There is no certainty that the results of this study apply to other regions of Japan.

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REFERENCES

1. Ministry of Health, Labour and Welfare. Guidelines for focused health education for cancer prevention and implementation of cancer screening (partially revised on October 1, 2021) [Internet]. Tokyo: Ministry of Health, Labour and Welfare; 2021 [cited 2022 Oct 17]. Available from: https://www.mhlw.go.jp/content/10900000/000838645.pdf.
2. Sherman ME, Abdul-Karim FW, Berek JS, Powers CN, Sidawy MK, Tabbara SO. Chapter 4. Atypical squamous cells. In: Nayar R, Solomon D, editors. The Bethesda System for reporting cervical cytology. Definitions, criteria, and explanatory notes. 2nd ed. Tokyo: Springer; 2004. p. 67-87.
3. Hamashima C, Shibuya D, Yamazaki H, Inoue K, Fukao A, Saito H, et al. The Japanese guidelines for gastric cancer screening. Jpn J Clin Oncol 2008;38:259-67.
PUBMED | CROSSREF
4. Matsumoto K, Oki A, Furuta R, Maeda H, Yasugi T, Takatsuka N, et al. Predicting the progression of cervical precursor lesions by human papillomavirus genotyping: a prospective cohort study. Int J Cancer 2011;128:2898-910.
PUBMED | CROSSREF
5. Ministry of Health, Labour and Welfare. Report on regional public health services and health promotion services [Internet]. Tokyo: Ministry of Health, Labour and Welfare; 2022 [cited 2022 Oct 17]. Available from: https://www.e-stat.go.jp/stat-search/files?page=1&toukei=00450025.
6. Kono K, Morisada T, Saika K, Aoki ES, Miyagi E, Ito K, et al. The first-round results of a population-based cohort study of HPV testing in Japanese cervical cancer screening: baseline characteristics, screening results, and referral rate. J Gynecol Oncol 2021;32:e29.
PUBMED | CROSSREF
7. ASCUS-LSIL Traige Study (ALTS) Group. Results of a randomized trial on the management of cytology interpretations of atypical squamous cells of undetermined significance. Am J Obstet Gynecol 2003;188:1383-92.
PUBMED | CROSSREF
8. Schiffman M, Solomon D. Findings to date from the ASCUS-LSIL Triage Study (ALTS). Arch Pathol Lab Med 2003;127:946-9.
PUBMED | CROSSREF
9. Safaeian M, Solomon D, Wacholder S, Schiffman M, Castle P. Risk of precancer and follow-up management strategies for women with human papillomavirus-negative atypical squamous cells of undetermined significance. Obstet Gynecol 2007;109:1325-31.
PUBMED | CROSSREF
10. Arbyn M, Roelens J, Simoens C, Buntinx F, Paraskevaidis E, Martin-Hirsch PP, et al. Human papillomavirus testing versus repeat cytology for triage of minor cytological cervical lesions. Cochrane Database Syst Rev 2013;28:CD008054.
PUBMED | CROSSREF
11. National Cancer Center Japan. Japanese Guideline for Cervical Cancer Screening [Internet]. Tokyo: National Cancer Center Japan; 2020 [cited 2022 October 17]. Available from: https://cc-screening-algorithm.jp/pdf/shikyukeiguide2019.pdf.

https://doi.org/10.3802/jgo.2023.34.e14