Human papillomavirus vaccine effectiveness by age at first vaccination among Japanese women

Mamiko Onuki | Kasumi Yamamoto | Hideaki Yahata | Hiroyuki Kanao | Harushige Yokota | Hisamori Kato | Kumi Shimamoto | Kazuhiro Takehara
Shoji Kamiura | Naotake Tsuda | Yuji Takei | Shogo Shigeta | Noriomi Matsumura | Hiroyuki Yoshida | Takeshi Motohara | Hidemichi Watari | Keiichiro Nakamura | Akihiko Ueda | Nobutaka Tasaka | Mitsuya Ishikawa | Yasuyuki Hirashima | Wataru Kudaka | Ayumi Taguchi | Takashi Iwata | Fumiaki Takahashi | Iwao Kukimoto | Hiroyuki Yoshikawa | Nobuo Yaegashi | Koji Matsumoto

1Department of Obstetrics and Gynecology, Showa University School of Medicine, Tokyo, Japan
2Department of Gynecologic Oncology, Hyogo Cancer Center, Hyogo, Japan
3Department of Gynecology and Obstetrics, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
4Department of Gynecology, Cancer Institute Hospital, Tokyo, Japan
5Department of Gynecology, Saitama Cancer Center, Saitama, Japan
6Department of Gynecology, Kanagawa Cancer Center, Kanagawa, Japan
7Gynecology Service, NHO Kyushu Cancer Center, Fukuoka, Japan
8Department of Gynecologic Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan
9Department of Gynecology, Osaka International Cancer Institute, Osaka, Japan
10Department of Obstetrics and Gynecology, Kurume University School of Medicine, Kurume, Japan
11Department of Obstetrics and Gynecology, Jichi Medical University, Tochigi, Japan
12Department of Obstetrics and Gynecology, Tohoku University Graduate School of Medicine, Sendai, Japan
13Department of Obstetrics and Gynecology, Faculty of Medicine, Kindai University, Osaka, Japan
14Department of Gynecologic Oncology, Saitama Medical University International Medical Center, Saitama, Japan
15Department of Obstetrics and Gynecology, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan
16Department of Obstetrics and Gynecology, Hokkaido University Graduate School of Medicine and Faculty of Medicine, Sapporo, Japan
17Department of Obstetrics and Gynecology, Dentistry and Pharmaceutical Sciences, Okayama University Graduate School of Medicine, Okayama, Japan
18Department of Gynecology and Obstetrics, Kyoto University Graduate School of Medicine, Kyoto, Japan
19Department of Obstetrics and Gynecology, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan
20Department of Gynecology, National Cancer Center Hospital, Tokyo, Japan
21Division of Gynecology, Shizuoka Cancer Center Hospital, Shizuoka, Japan
22Department of Obstetrics and Gynecology, Graduate School of Medicine, University of the Ryukyus, Okinawa, Japan
23Department of Obstetrics and Gynecology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
24Department of Obstetrics and Gynecology, Keio University School of Medicine, Tokyo, Japan
25Division of Medical Engineering, Department of Information Science, Iwate Medical University, Yahaba, Japan
26Pathogen Genomics Center, National Institute of Infectious Diseases, Tokyo, Japan

Abbreviations: AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; ICC, invasive cervical cancer; LA, linear array.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2022 The Authors. Cancer Science published by John Wiley & Sons Australia, Ltd on behalf of Japanese Cancer Association.
1 | INTRODUCTION

The Japanese government initiated an HPV vaccination program for girls aged 12-16 years in 2010. In Japan, a bivalent vaccine against HPV16 and HPV18 was licensed in October 2009, and a quadrivalent vaccine against HPV6, HPV11, HPV16, and HPV18 was licensed in July 2011. Recently, a next-generation 9-valent vaccine, which extends coverage to HPV31, 33, 45, 52, and 58, was licensed in July 2020. Currently, the Japanese National Immunization Program against HPV includes bivalent and quadrivalent HPV vaccines but not yet the 9-valent HPV vaccine. In the Japanese guidelines, catch-up vaccination is recommended up to age 26 years for women but not yet the 9-valent HPV vaccine. In Japan, adolescents aged 15-16 years are also included as a target population for routine vaccination. However, few studies have addressed the differences in the effectiveness of HPV vaccines based on age at first vaccination in Japan.

To our knowledge, the MINT study is the largest nationwide study monitoring HPV vaccination impact and HPV genotypespecific disease incidence in Japan. We selected changes in HPV16/18 prevalence among young women with cervical diseases as the primary end-point because: (a) a decrease in HPV16/18 prevalence is expected to occur quickly as the earliest measure of vaccine impact; and (b) monitoring HPV genotypes detected in cervical lesions can distinguish vaccine impact from screening effects and changes in lifestyle factors and sexual behaviors. During the earlier years of this project, we reported the preliminary results on vaccine effectiveness according to age at vaccination, but the analysis had limitations due to the small sample size of vaccinated women. Using a larger sample size over a longer surveillance period, we updated the previous findings and provided new data regarding age at first sexual intercourse. Our additional data support greater vaccine effectiveness among Japanese girls vaccinated at a younger age. This age information is very important because the Japanese government has recently decided to resume proactive recommendation of HPV vaccination in April 2022, along with a catch-up vaccination program for women who missed routine HPV vaccination at age 12-16 years. Our findings...
have important implications for the optimal target age population for routine and catch-up HPV vaccination in Japan.

2 | MATERIALS AND METHODS

2.1 | Study design

We undertook a collaborative hospital-based study (MINT studies I and II) to monitor the long-term population-level impact of HPV vaccination in Japan. Details regarding the design and methods have been provided elsewhere. Briefly, study participants consist of all women aged 16-39 years (age at registration) newly diagnosed with CIN, AIS, or ICC. Women with previous history of treatment for cervical diseases are excluded. All participants enter the study only after voluntarily providing signed informed consent and are registered together with their vaccine history. In the MINT study I, a total of 7709 women with CIN1 (n = 589), CIN2-3/AIS (n = 5828), or ICC (n = 1292) were registered at 21 participating institutions between August 2012 and December 2017. The MINT study II uses almost the same study design and is currently in progress. In the MINT study II, 1750 women with CIN1 (n = 281), CIN2-3/AIS (n = 1243), or ICC (n = 226) were recruited at 23 participating institutes between October 2019 and June 2021. Most vaccine clinical trials and population-based surveys have evaluated vaccination effectiveness against CIN2 or higher (CIN2+) because CIN2 is the standard threshold for immediate treatment. In the present study, we also focused on data analyses from women with CIN2-3/AIS.

Both studies relied on self-reported information regarding vaccination status because official vaccination records were not available to determine vaccination status. In the present study, women with at least one HPV vaccine dose were defined as "vaccinated". Information on sexual history, sexually transmitted disease history, and smoking status was obtained from a self-administered questionnaire in the MINT study II but not collected in the MINT study I. Data from the questionnaires were self-reported and not validated.

Institutional ethical and research review boards of the participating institutions have approved the study protocol. The MINT studies I and II were registered in the UMIN Clinical Trials Registry as UMIN000008891 and UMIN00038883, respectively.

2.2 | Human papillomavirus genotyping procedures

Human papillomavirus genotypes in cervical samples were determined using the LA assay (Roche Molecular Systems) in the MINT study I and the PGMY-CHUV assay in the MINT study II. Both assays are L1 consensus primer-based PCR methods that use a primer set designated as PGMY09/11. Details of these HPV genotyping assays have been provided elsewhere. Briefly, exfoliated ectocervical and endocervical cells were stored in ThinPrep PreservCyt solution (Hologic) until DNA extraction. Total cellular DNA was extracted using a QIAamp MinElute Media kit (Qiagen) in the MINT study I and a MagNA Pure LC Total Nucleic Acid Isolation kit (Roche) in the MINT study II. The PGMY-CHUV PCR products were subjected to reverse line blot hybridization for both methods. The LA assay detects 37 individual HPV genotypes, and the PGMY-CHUV assay detects 31 genotypes. The two assays detect 28 genotypes in common (HPV6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 66, 68, 69, 70, 73, 82, 83, and 84).

All HPV DNA assays were carried out by individuals masked to the results and clinical profile of each patient.

2.3 | Statistical methods

Positive rates for vaccine types HPV16 or HPV18 were analyzed according to disease severity, HPV vaccination history (HPV vaccine status and age at vaccination), and age at first sexual intercourse. For binary comparisons of HPV16/18 positivity, Fisher’s exact probability and Cochran–Armitage trend tests were used. The P values obtained in all tests were considered significant at less than 0.05. The R version 3.5.1 statistical package (R Foundation for Statistical Computing) was used for statistical analysis.

3 | RESULTS

The present analysis included 4466 women with CIN2-3/AIS who had HPV genotyping results and vaccine history information; their characteristics are summarized in Table 1. Of 4466 women with CIN2-3/AIS, 3319 and 1147 women were registered in the MINT studies I and II, respectively. The vaccine uptake rate was 3.8% (169/4466).

We evaluated HPV vaccine effectiveness by age at first vaccination. The youngest age at time of first vaccination was 12 years. Unfortunately, information regarding age at first dose was unavailable for five vaccinated women. The attribution of vaccine-targeted types HPV16 or HPV18 to CIN2-3/AIS was 47.0% for unvaccinated women (n = 4297) but 0.0%, 13.0%, 35.7%, and 39.6% for women who received their first dose at ages 12-15 years (n = 36), 16-18 years (n = 23), 19-22 years (n = 14), and >22 years (n = 91), respectively (P < .0001) (Figure 1). Human papillomavirus 16/18 prevalence in CIN2-3/AIS was considerably reduced among women aged 18 years or younger at first vaccination compared to those aged more than 18 years at first vaccination (5.1% vs. 39.0%, P < .0001). The HPV16/18 prevalence in CIN2-3/AIS was approximately 10% lower among women aged more than 18 years at first vaccination compared with those aged 12-15 years (39.0% vs. 47.0%), but the difference did not reach statistical significance (P = .11). Among vaccinated women, HPV16/18 prevalence in CIN2-3/AIS was similar between women vaccinated with three doses (n = 92) and those vaccinated with one or two doses (n = 71) (27.4% vs. 26.8%). Thus, separate analyses for women fully and partially vaccinated did not affect these findings (data not shown).
In the MINT study II, information on age at first sexual intercourse was obtained from a self-administered questionnaire in 69.8% (801/1147) of those with CIN2-3/AIS. The median age at first sexual intercourse was 17 years (range, 9-30 years) among those with CIN2-3/AIS (Figure 2). The cumulative proportion of sexually active women was 9.2% by age 14, 47.2% by age 16, and 77.1% by age 18.

Information regarding both age at first vaccination and sexual debut was obtained from 39 women with CIN2-3/AIS. When the data were analyzed according to the timing of vaccination in relation to sexual debut, HPV16/18 prevalence in CIN2-3/AIS was 0.0%, 12.5%, and 40.0% among women vaccinated before (n = 16), within 3 years after (n = 8), and more than 3 years after (n = 15) first sexual intercourse, respectively (P = .004) (Figure 3).

### DISCUSSION

Human papillomavirus vaccination effectiveness is highly dependent on age at the first immunization. In this study, we reported the greater effectiveness of HPV vaccination among Japanese girls aged 18 years or younger at first vaccination outside clinical trial settings. Similar findings have been observed in other countries. Recently, several registry-based studies reported HPV vaccine effectiveness against invasive cervical cancer in a real-world setting. In a UK study, the relative risk reduction for invasive cervical cancer was 87%, 62%, and 34% for women vaccinated at 12-13 years, 14-16 years, and 16-18 years, respectively, compared with those who were unvaccinated.

### TABLE 1 Characteristics of human papillomavirus (HPV)-type-specific analysis cohorts

| CIN2-3 or AIS (N = 4466) |
|-------------------------|
| **History of HPV vaccination** |
| Vaccinated | 169 |
| Bivalent | 51 |
| Quadrivalent | 47 |
| Unclear | 71 |
| Unvaccinated | 4297 |
| **Registration year** |
| 2012 | 178 |
| 2013 | 607 |
| 2014 | 610 |
| 2015 | 627 |
| 2016 | 662 |
| 2017 | 635 |
| 2019 | 82 |
| 2020 | 683 |
| 2021 | 382 |
| **Age at registration (y)** |
| 20-24 | 261 |
| 25-29 | 958 |
| 30-34 | 1637 |
| 35-39 | 1610 |
| **Birth cohort** |
| 1973-75 | 275 |
| 1976-78 | 654 |
| 1979-81 | 819 |
| 1982-84 | 998 |
| 1985-87 | 751 |
| 1988-90 | 525 |
| 1991-93 | 300 |
| 1994-96 | 108 |
| 1997-99 | 23 |
| ≥2000 | 13 |
| **HPV genotype** |
| Oncogenic<sup>a</sup> | 4080 |
| HPV16 | 1792 |
| HPV18 | 330 |
| Nononcogenic | 171 |
| Negative | 213 |

Abbreviations: AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia.

<sup>a</sup>Oncogenic HPV types include HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.
The risk of invasive cervical cancer was remarkably reduced among women vaccinated at age 16 years or younger in a Denmark study and at age 17 years or younger in a Swedish study. In another Swedish study, HPV vaccination effectiveness against CIN2+ was statistically significant for women aged 19 years or younger at first vaccination but not those aged 20 years or older at first vaccination. Similarly, a US population-based case-control study of over 25,000 women showed significant protection against CIN2+ in women who received their first HPV vaccine dose at 14-20 years old but not for women aged 21 years or older at first vaccination. In Scotland, the protective effect of three-dose catch-up vaccination against CIN2+ was significant among women first vaccinated at age 14-17 years but not those first vaccinated at age 18 years or older. Our findings were consistent with these real-world data reporting the greater effectiveness of HPV vaccination at a younger age; however, the magnitude of this effect and the age range of women who benefit from HPV vaccination could vary from country to country.

Because HPV acquisition generally occurs soon after first sexual activity, data regarding age at first intercourse, especially among women who develop CIN2+, are crucial to optimize the HPV vaccination strategy. However, in Japan, few studies have assessed the sexual behaviors of women who developed cervical diseases to date. In the present study, 9.2% of women with CIN2-3/AIS were sexually active by age 14 but the proportion quickly increased to 47.2% by age 16 and 77.1% by age 18 (Figure 2). The percentage of sexually active women by age 15 was 14.1% in young cohorts born in fiscal years 1993-1996 but 24.6% in our study population. Among Japanese women aged 20-41 years who participated in a cervical cancer screening program during 2014-2016, the proportion of sexually active women was 27.4% by 16 years old, which is lower than the 47.2% among our study subjects. These observations were consistent with previous studies reporting earlier age at first intercourse among women with cervical cancer and precancer.

Our data revealed complete protection against HPV16/18-positive CIN2-3/AIS among girls vaccinated before 15 years old or sexual debut and higher HPV vaccine effectiveness among those vaccinated at 18 years old or younger. Furthermore, the proportion of sexually active females was less than 10% at age 14, but rapidly...
increased to 50% by 16 years old and to 80% by 18 years old. These results indicate that HPV vaccination should be initiated before 14 years of age for the National Immunization Program in Japan and support the Japanese guideline recommendations of HPV vaccination mainly for girls aged 14 years or less. Furthermore, Japanese physicians, pediatricians, and gynecologists should be aware of these data when discussing the optimal time point of HPV vaccination with female adolescent patients and their parents.

Our data also suggested the limited effectiveness of catch-up vaccination in women older than 18 years. However, the present study might have evaluated only HPV vaccine effectiveness against cervical precancer caused by HPV infections acquired at young ages. The effectiveness of catch-up vaccination against CIN2+ for women older than 18 years is one of the most important issues in HPV vaccination, especially in Japan, because the vaccination rate in women born in or after 2000 is extremely low (less than 1%) due to the Japanese government’s suspension of the vaccination recommendation in 2013. In the present study, the attribution of HPV16/18 to CIN2-3/AIS was reduced by 10%, even among women vaccinated at age older than 18 years compared with unvaccinated women, although the difference did not reach statistical significance. To determine the upper age limit for effective HPV vaccination among Japanese women, long-term surveillance studies in real-world settings are warranted.

The present study has several limitations. First, our study included only women who developed cervical diseases under the age of 40 years, but not women with normal cytology. As mentioned above, sexual activity of our study subjects appears to be higher than that previously reported among Japanese women. Thus, our findings might not be generalizable to general Japanese populations because of selection bias. Our data showed substantial effectiveness of HPV vaccination among girls and adolescents vaccinated at age 18 years or younger, even in a special population with high sexual activity. Second, vaccination status was based on self-reports and not validated against official vaccination registries. In a recent study verifying self-reported HPV vaccination status through the vaccine register, approximately 20% of young Japanese women incorrectly reported their HPV vaccination status. Therefore, possible misclassification of vaccination status might have affected our findings. However, the Japanese municipal registries are not perfect because: (a) vaccination records are not transferred when female adolescents move to another city after routine HPV vaccination; and (b) catch-up vaccination of female individuals older than 16 years is not recorded in the Japanese municipal registries. Third, the HPV genotyping methods were different between 2012-2017 (LA) and 2019-2021 (PGMY-CHUV). Changes in laboratory methods might have affected our findings. However, in our previous study comparing HPV genotyping results by both methods, we observed complete agreement between LA and PGMY-CHUV for the detection of HPV6, 11, 16, 18, 33, and 45, and near-complete agreement for HPV31 and 58 (98% and 99%, respectively). Fourth, the response rate to the self-administered questionnaire regarding sexual activity was approximately 70%. Accordingly, 420 women lacking data collected from self-reports were excluded from the analysis of age at first intercourse. Although demographic characteristics and HPV type distributions were similar between the included and excluded women (data not shown), this rate of loss could have influenced the results. Fifth, we were unable to exclude the effects of confounding factors, such as changes in sexual behaviors, oral contraceptive use, and smoking rates. However, these changes are less likely to affect the rates of HPV16/18 detected from cervical lesions compared with the incidence rates of cervical lesions. Finally, despite the larger sample size over the longer surveillance period of the present study compared with our previous report, the small sample size might still have influenced the research outcomes.

In conclusion, the present study updated HPV vaccine effectiveness information related to age at first vaccination and provided additional data on age at first sexual intercourse among Japanese women with CIN2-3/AIS. Our data indicated complete protection against HPV16/18-positive CIN2-3/AIS among girls vaccinated before 15 years old or sexual debut (most were likely HPV naive at vaccination) and the greater HPV vaccine effectiveness among girls and adolescents vaccinated at age 18 years or younger. The proportion of sexually active females was approximately 10% at age 14 years but rapidly increased to 50% by age 16 years. Taken together, our data support routine HPV vaccination for girls aged 12-14 years and catch-up vaccination for adolescents aged up to 18 years in Japan. However, to address the benefits of HPV vaccination at older ages and determine the optimal target age group for HPV vaccination, further research is warranted.

4.1 Participating institutions (the MINT Study Group)

The participating institutions are as follows: Hokkaido University Graduate School of Medicine and Faculty of Medicine; Tohoku University Graduate School of Medicine; Jichi Medical University; University of Tsukuba; Saitama Cancer Center; Saitama Medical University International Medical Center; National Cancer Center Hospital; Cancer Institute Hospital; Keio University School of Medicine; Showa University School of Medicine; The University of Tokyo; Kanagawa Cancer Center; Kyoto University Graduate School of Medicine; Kindai University Faculty of Medicine; Osaka International Cancer Institute; Hyogo Cancer Center; Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences; National Hospital Organization Shikoku Cancer Center; Kyusyu University; NH Kyusyu Cancer Center; Kurume University School of Medicine; Kumamoto University; and University of the Ryukyus.

ACKNOWLEDGMENTS

This work was supported by grants obtained from the Foundation for Advancement of International Science (FAIS), the Japan Agency of Medical Research and Development (AMED) (grant number: JP21fk0108098), and Japan Society for the Promotion of Science.
KAKENHI (grant number: JP20K09677). We thank Shido Inc. for research support and Edanz for editing a draft of this manuscript.

DISCLOSURE
The authors have no conflict of interest relevant to this article.

ORCID
Kazuhiro Takehara https://orcid.org/0000-0001-8808-3338
Keiichiro Nakamura https://orcid.org/0000-0002-4609-5258
Akihiko Ueda https://orcid.org/0000-0001-8139-9292
Koji Matsumoto https://orcid.org/0000-0001-6184-618X

REFERENCES
1. Kawaguchi R, Matsumoto K, Ishikawa T, et al. Guideline for Gynecological Practice in Japan: Japan Society of Obstetrics and Gynecology and Japan Association of Obstetricians and Gynecologists 2020 edition. J Obstet Gynaecol Res. 2021;47(1):5-25. 10.1111/jog.14487
2. Hildesheim A, Herrero R, Wacholder S, et al. Effect of human papillomavirus 16/18 L1 viruslike particle vaccine among young women with preexisting infection: a randomized trial. JAMA. 2007;298:743-753.
3. Winer RL, Hughes JP, Feng Q, et al. Condom use and the risk of genital human papillomavirus infection in young women. N Engl J Med. 2006;354:2645-2654.
4. Centers for Disease Control and Prevention (CDC), Immunization Schedules. https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html Accessed September 30, 2021
5. Australian Government Department of Health, National Immunisation Program (NIP) Schedule. https://www.health.gov.au/health-topics/immunisation/immunisation-throughout-life/national-immunisation-program-schedule Accessed September 30, 2021
6. European Centre for Disease Prevention and Control: Guidance on HPV vaccination in EU countries: focus on boys, people living with HIV and 9-valent HPV vaccine introduction. https://www.ecdc.europa.eu/sites/default/files/documents/Guidance-on-HPV-vaccination-in-EU-countries-2020-03-30.pdf Accessed September 30, 2021
7. Matsumoto K, Yaegashi N, Iwata T, et al. MINT Study Group. Monitoring the impact of a national HPV vaccination program in Japan (MINT Study): rationale, design and methods. Jpn J Clin Oncol. 2014;44:1000-1003.
8. Matsumoto K, Yaegashi N, Iwata T, et al. Early impact of the Japanese immunization program implemented before the HPV vaccination crisis. Int J Cancer. 2017;141:1704-1706.
9. Matsumoto K, Yaegashi N, Iwata T, et al. Reduction in HPV16/18 prevalence among young women with high-grade cervical lesions following the Japanese HPV vaccination program. Cancer Sci. 2019:110:3811-3820.
10. Kurokawa T. Is the catch-up program of HPV vaccination for Japanese adult women effective or not? Cancer Sci. 2020;111:1435-1436.
11. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med. 2007;356:1915-1927.
12. Pasanen J, Naud P, Salmerón J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA); final analysis of a double-blind, randomised study in young women. The Lancet. 2009;374(9686):301-314. 10.1016/S0140-6736(09)61248-4
13. Falcaro M, Castaño A, Ndlela B, et al. The effects of the national HPV vaccination programme in England, UK, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: a register-based observational study. The Lancet. 2021;398(10316):2084-2092. 10.1016/S0140-6736(21)02178-4
14. Kjaer SK, Dehlendorff C, Belmonte F, Baandrup L. Real-world effectiveness of human papillomavirus vaccination against cervical cancer. J Natl Cancer Inst. 2021;113:1329-1335.
15. Lei J, Ploner A, Elfström KM, et al. HPV vaccination and the risk of invasive cervical cancer. N Engl J Med. 2020;383:1340-1348.
16. Herweijer E, Sundström K, Ploner A, Uhnio I, Sparén P, Arnhem-Dahlström L. Quadrivalent HPV vaccine effectiveness against high-grade cervical lesions by age at vaccination: A population-based study. Int J Cancer. 2016;138:2867-2874. Erratum. Int J Cancer. 2016;2017(141):E1-E4.
17. Silverberg MJ, Leyden WA, Lam JO, et al. Effectiveness of catch-up human papillomavirus vaccination on incident cervical neoplasia in a US health-care setting: a population-based case-control study. Lancet Child Adolesc Health. 2018;2:707-714.
18. Kavanagh K, Pollock KG, Cuschieri K, et al. Changes in the prevalence of human papillomavirus following a national bivalent human papillomavirus vaccination programme in Scotland: a 7-year cross-sectional study. Lancet Infect Dis. 2017;17:1293-1302.
19. Gravitt PE, Peyton CL, Alesi TQ, et al. Improved amplification of genital human papillomaviruses. J Clin Microbiol. 2000;38:357-361.
20. Kukimoto I, Matsumoto K, Takahashi F, et al. Human papillomavirus (HPV) genotyping assay suitable for monitoring the impact of the 9-Valent HPV vaccine. Tohoku J Exp Med. 2020;251:287-294.
21. Kudo R, Yamaguchi M, Sekine M, et al. Bivalent human papillomavirus vaccine effectiveness in a Japanese population: high vaccine-type-specific effectiveness and evidence of cross-protection. J Infect Dis. 2019;219:382-390.
22. Yamaguchi M, Sekine M, Hanley SJ, et al. Risk factors for HPV infection and high-grade cervical disease in sexually active Japanese women. Sci Rep. 2021;11:2898.
23. Schiffman MH, Brinton LA. The epidemiology of cervical carcinogenesis. Cancer. 1995;76:1888-1901.
24. Louie KS, de Sanjose S, Diaz M, et al. Early age at first sexual intercourse and early pregnancy are risk factors for cervical cancer in developing countries. Br J Cancer. 2009;100:1191-1197.
25. Campos NG, Chaturvedi AK, Kreimer AR. Real-world HPV vaccine effectiveness studies: guideposts for interpretation of current and future studies. J Natl Cancer Inst. 2021;113(10):1270-1271. 10.1093/jnci/djab081
26. Hanley SJ, Yoshioka E, Ito Y, Kishi R. HPV vaccination crisis in Japan. Lancet. 2015;385:2571.
27. Yagi A, Ueda Y, Egawa-Takata T, et al. Realistic fear of cervical cancer risk in Japan depending on birth year. Hum Vaccin Immunother. 2017;13:1700-1704.
28. Yamaguchi M, Sekine M, Kudo R, et al. Differential misclassification between self-reported status and official HPV vaccination records in Japan: Implications for evaluating vaccine safety and effectiveness. Papillomavirus Res. 2018;6:6-10.

How to cite this article: Ouku M, Yamamoto K, Yahata H, et al; for the MINT Study Group. Human papillomavirus vaccine effectiveness by age at first vaccination among Japanese women. Cancer Sci. 2022;113:1428-1434. doi:10.1111/cas.15270