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

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

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## Abstract

In Japan, the National Immunization Program against human papillomavirus (HPV) targets girls aged 12-16 years, and catch-up vaccination is recommended for young women up to age 26 years. Because HPV infection rates increase soon after sexual debut, we evaluated HPV vaccine effectiveness by age at first vaccination. Along with vaccination history, HPV genotyping results from 5795 women younger than 40 years diagnosed with cervical intraepithelial neoplasia grade 2-3 (CIN2-3), adenocarcinoma in situ (AIS), or invasive cervical cancer were analyzed. 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 vaccinated at ages 12-15 years (n = 36), 16-18 years (n = 23), 19–22 years (n = 14), and older than 22 years (n = 91), respectively, indicating the greater effectiveness of HPV vaccination among those initiating vaccination at age 18 years or younger ($P < .001$). This finding was supported by age at first sexual intercourse; among women with CIN2-3/AIS, only 9.2% were sexually active by age 14 years, but the percentage quickly increased to 47.2% by age 16 and 77.1% by age 18. Additionally, the HPV16/18 prevalence in CIN2-3/AIS was 0.0%, 12.5%, and 40.0% for women vaccinated before (n = 16), within 3 years (n = 8), and more than 3 years after (n = 15) first intercourse, respectively ($P = .004$). In conclusion, our data appear to support routine HPV vaccination for girls aged 12-14 years and catch-up vaccination for adolescents aged 18 years and younger in Japan.

**KEYWORDS**
adenocarcinoma *in situ*, cervical cancer, cervical intraepithelial neoplasia, human papillomavirus, vaccination

## 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 not previously vaccinated.[1]

Human papillomavirus vaccination prevents new HPV infections but does not treat pre-existing HPV infections or HPV-related diseases.[2] Because HPV infection rates increase soon after first sexual intercourse,[3] HPV vaccination is recommended by the WHO for routine immunization in 9- to 14-year-old girls in most countries. For instance, the current target ages for girls in the National Immunization Programs are 11-12 years in the US, 12-13 years in Australia, 11-13 years in the UK, 11-14 years in France, and 9-14 years in Germany.[4-6] In Japan, adolescents aged 15-16 years are also included as a target population for routine vaccination.[1] 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 nation-wide study monitoring HPV vaccination impact and HPV genotype-specific disease incidence in Japan.[7-9] 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,[9] but the analysis had limitations due to the small sample size of vaccinated women.[10] 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.[7-9] 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.[11-18] 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.[19] Details of these HPV genotyping assays have been provided elsewhere.[20] 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 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 with 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 unvaccinated women (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).

**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[a] | 4080 |
| HPV16 | 1792 |
| HPV18 | 330 |
| Nononcogenic | 171 |
| Negative | 213 |

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

[a]Oncogenic HPV types include HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.

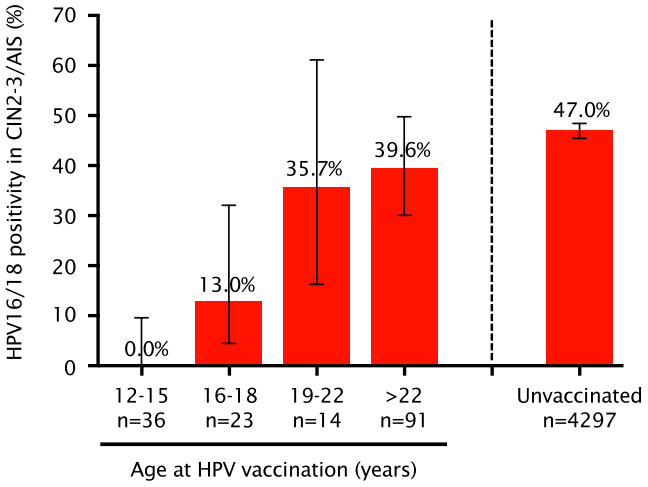


**FIGURE 1** Attribution of human papillomavirus type 16 (HPV16) and HPV18 to cervical intraepithelial neoplasia grade 2 or 3 or adenocarcinoma in situ (CIN2-3/AIS) by age at first vaccination. Prevalence of HPV16/18 in CIN2-3/AIS was 0.0% for women who received their first dose at ages 12-15 years (n = 36), 13.0% for those aged 16-18 years at first vaccination (n = 23), 35.7% for those aged 18-22 years at first vaccination (n = 14), 39.6% for those older than 23 years at first vaccination (n = 91), and 47.0% for those who were unvaccinated (n = 4297). Error bars indicate 95% confidence intervals. Among vaccinated women, the attribution of HPV16 and HPV18 to CIN2-3/AIS was significantly lower among those aged 18 years or younger at first vaccination than among those older than 18 years at first vaccination (5.1% vs. 39.0%, $P$ <.001)

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).

## 4 | DISCUSSION

Human papillomavirus vaccination effectiveness is highly dependent on age at the first immunization.[13-18] 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.[13-15] 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

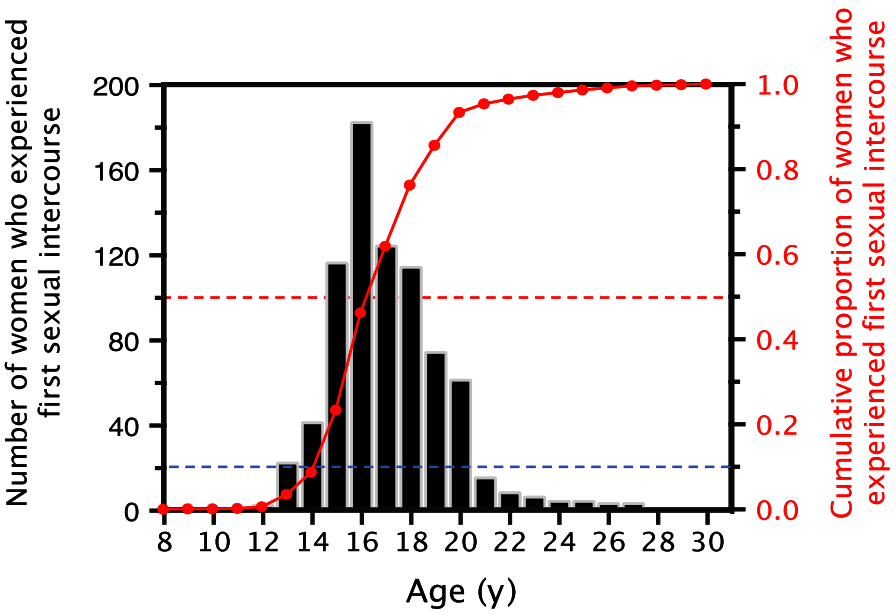


FIGURE 2 Age at first sexual intercourse among Japanese women with cervical intraepithelial neoplasia grade 2 or 3 or adenocarcinoma in situ (CIN2-3/AIS). Black bars and left axis show the number of women who experienced first sexual intercourse at age indicated on the X axis; red line and right axis indicate the cumulative proportion of women who experienced first sexual intercourse at the indicated age. Blue and red dotted lines show 10% and 50% of the cumulative proportion of women who experienced first sexual intercourse, respectively. Median age at first sexual intercourse was 17 years (range, 9-30 years)

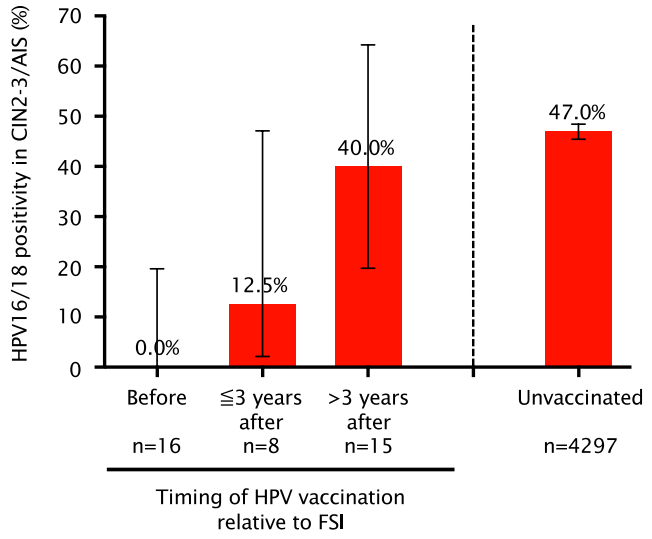


FIGURE 3 Attribution of human papillomavirus type 16 (HPV16) and HPV18 to cervical intraepithelial neoplasia grade 2 or 3 or adenocarcinoma in situ (CIN2-3/AIS) by the timing of HPV vaccination relative to first sexual intercourse. Prevalence of HPV16/18 in CIN2-3/AIS was 0.0% among women vaccinated before first sexual intercourse (FSI) (n=16), 12.5% among those vaccinated within 3 years after FSI (n = 8), and 40.0% (n = 15) among those vaccinated more than 3 years after FSI (n = 15) ($P$ = .004). Error bars indicate 95% confidence intervals

with those unvaccinated.[13] The risk of invasive cervical cancer was remarkably reduced among women vaccinated at age 16 years or younger in a Denmark study[14] and at age 17 years or younger in a Swedish study.[15] 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.[16] 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.[17] 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. [18] Our findings were consistent with these real-world data reporting the greater effectiveness of HPV vaccination at a younger age;[13-18] 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,[3] 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 experienced women in our study population increased more rapidly after age 14 compared with those previously reported in general Japanese populations. The percentage of sexually active women by age 15 was 14.1% in young cohorts born in fiscal years 1993-1996[21] 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,[22] 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.[23,24]

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.[1] 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.[25] 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.[26,27] 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.[21,22] 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.[28] 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).[19] 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,[8,9] 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 naïve 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; NHO Kyusyu Cancer Center; Kurume University School of Medicine; Kumamoto University; and University of the Ryukyus.

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## DISCLOSURE

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

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