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Human papillomavirus vaccine impact on invasive cervical cancer in Japan: Preliminary results from cancer statistics and the MINT study

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Abstract

The first prophylactic vaccine against human papillomavirus (HPV) 16 and HPV18 was licensed in Japan in 2009. HPV vaccine effectiveness against high-grade cervical lesions has been demonstrated among young Japanese women, but evidence of its effects on invasive cervical cancer (ICC) is lacking. Using data from two different cancer registries, we compared recent trends of new ICC cases by age group using Poisson regression analysis. We also analyzed time trends in HPV16/18 prevalence among 1414 Japanese women aged <40 years newly diagnosed with ICC in the past decade. Based on the population-based cancer registry, the incidence of ICC among young women aged 20–29 years showed a significant decline from 3.6 to 2.8 per 100 000 women-years during 2016–2019, but no similar decline was observed for older age groups ($p < 0.01$). Similarly, using data from the gynecological cancer registry of the Japan Society of Obstetrics and Gynecology, the annual number of ICCs among women aged 20–29 years also decreased from 256 cases to 135 cases during 2011–2020 ($p < 0.0001$). Furthermore, a declining trend in HPV16/18 prevalence in ICC was observed only among women aged 20–29 years during 2017–2022 (90.5%–64.7%, $p = 0.05$; Cochran–Armitage trend test). This is the first report to suggest

Abbreviations: APC, annual percent change; DCO, death certificate only; HPV, human papillomavirus; ICC, invasive cervical cancer; JSOG, Japan Society of Obstetrics and Gynecology; LA, Linear Array assay; M/I, mortality to incidence ratio; MINT study, Monitoring project for the Impact of National HPV vaccinaTion program in Japan study.

†Members of the Monitoring project for the Impact of National HPV vaccination program in Japan study present in Appendix A.

population-level effects of HPV vaccination on ICC in Japan. Although the declining trend in HPV16/18 prevalence among young women with ICC supports a causal linkage between vaccination and results from cancer registries, further studies are warranted to confirm that our findings are attributable to vaccination.

KEYWORDS
cancer registry, cervical cancer, human papillomavirus, incidence, vaccination

1 | INTRODUCTION

In Japan, the first prophylactic vaccine against human papillomavirus (HPV) 16 and HPV18 was licensed in 2009, and a quadrivalent vaccine against HPV6, HPV11, HPV16, and HPV18 was licensed in July 2011. The Japanese Government initiated an HPV vaccination program for girls aged 12–16 years in 2010. HPV vaccine effectiveness in preventing high-grade cervical lesions has been shown among young Japanese women in a real-world setting,[1–3] but population-level evidence of its effect on invasive cervical cancer (ICC) is lacking in Japan because of the lack of a national cancer registry linked to the screening and immunization database.

Recently, registry-based studies in European countries showed HPV vaccine effectiveness against ICC in a real-world setting.[4–6] In a UK study, the relative risk reduction for ICC was 87% for women vaccinated at age 12–13 years compared with those who were unvaccinated.[4] The ICC risk was remarkably reduced among women vaccinated at age ≤ 16 years in a Danish study[5] and at age ≤ 17 years in a Swedish study.[6] These findings showed that the HPV vaccine substantially reduces a woman's risk of developing ICC, especially in women who were immunized at a younger age.

In the present study, we analyzed recent trends in newly diagnosed ICC cases among young Japanese women using data from two different cancer registries with high completeness and data validity.[7,8] These nationwide registries cover a long period of ≥18 years both before and after the introduction of the HPV vaccination program but have no information on which HPV types caused the included ICC cases. To provide more vaccine-specific evidence, we also evaluated prevalence trends of vaccine types HPV16 and HPV18 among young Japanese women newly diagnosed with ICC in the past decade.

2 | MATERIALS AND METHODS

2.1 | Population-based cancer registry

The Cancer Information Service of the National Cancer Center Japan has collected cancer registry data from local governments in Japan since 1975.[7] The number of regional cancer registries used for the estimation of national cancer incidence increased gradually during 1975–2015, as follows: five (Miyagi, Yamagata, Osaka, Nagasaki City, and Hiroshima City) in 1975, 10 in 1990, 11 in 1995, 11 in 2000, 12 in 2005, 28 in 2010, and 43 in 2015.[9] Subsequently, the nationwide hospital-based cancer registry was established in 2016 to improve the quality of the cancer registry.

The incidence data obtained from its website are publicly available for analysis, without the service's approval.[7] We downloaded the population-based data obtained between 1975 and 2019 from the website and analyzed year-on-year trends of cervical cancer incidences. Incidence rates were reported as the number of cases per 100,000 women-years.

2.2 | Gynecologic cancer registry

We also analyzed nationwide hospital-based data from the gynecological cancer registry of the Japan Society of Obstetrics and Gynecology (JSOG). Annual patient reports from 2003 to 2020 were available on the JSOG Gynecologic Tumor Committee website.[8] These published data are also publicly available for analysis without the approval of the JSOG Ethics Committee. In this cancer registry, patients with gynecological malignancies were registered from 247 institutions in 2003 and from 473 institutions in 2020. In 2020, 90.1% (426/473) of the JSOG member institutions were also included in the population-based cancer registry.[8,10]

The Institutional Ethical and Research Review Board exempted data analyses from two cancer registries because of the use of publicly available and deidentified data.

2.3 | The MINT study

We conducted a collaborative hospital-based study (MINT studies I [2012–2018] and II [2019–present]) to monitor the long-term population-level impact of HPV vaccination in Japan. Details regarding the design and methods have been provided elsewhere.[11] Briefly, study participants are all women aged 16–39 years newly diagnosed with cervical cancer and precancer at participating institutions. Women with a 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. A total of 10,643 women with cervical diseases were registered at 24 participating institutions between 2012 and

2022 (Appendix A), of which fixed data from 1414 Japanese women with ICC were used for statistical analysis. The study period was divided into 2-year periods: 2011–2012, 2013–2014, 2015–2016, 2017–2018, 2019–2020, and 2021–2022. We compared time trends of HPV16/18 attribution to ICC between two age groups (20–29 years and 30–39 years).

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

2.4 | Human papillomavirus genotyping procedures

HPV Human papillomavirus genotypes in cervical samples were determined using the Linear Array (LA) assay (Roche Molecular Systems, Pleasanton, CA, USA) in the MINT study I (2012–2018) and the PGMY-CHUV assay in the MINT study II (2019–present). 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.[12] In our previous study comparing HPV genotyping results using both methods, we confirmed complete agreement between LA and PGMY-CHUV for the detection of HPV6, HPV11, HPV16, HPV18, HPV33, and HPV45 and near-complete agreement for HPV31 and HPV58 (98% and 99%, respectively).[12] All HPV DNA assays were performed by individuals masked to the results and clinical profile of each patient.

2.5 | Statistical methods

Using log-linked Poisson models, we analyzed recent trends in the incidence and annual numbers of ICC from cancer registries with stratification according to 10-year interval age groups (20–29, 30–39, 40–49, 50–59, 60–69, 70–79 and ≥80 years). ICC cases were aggregated by age group and calendar year in each cancer registry. The models used the number of ICC cases as a response variable and age group, calendar year and their interaction terms as covariates. The corresponding at-risk population estimates and the number of registry institutions in each year were included after logarithmic transformation as an offset for time-trend analyses of the population-based data and the JSOG data, respectively. In these analyses, the incidences or numbers of ICC diagnoses were assumed to follow a Poisson distribution to estimate annual percent changes (APCs) and identify any year in which a significant change in trends occurred.

In the MINT data analyses, linear regression analysis was used to compare year-on-year trends of HPV16/18 prevalence stratified by age (20–29 years vs. 30–39 years). Cochran–Armitage trend tests were used for time-trend analyses of HPV16/18 positivity among ICC cases aged 20–29 years and 30–39 years.

All statistical tests were two-sided, and *p*-values were considered significant at <0.05. The R version 3.5.1 statistical package (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis.

3 | RESULTS

3.1 | Population-based cancer registry

Figure 1 shows time trends in ICC incidence between 1975 and 2019 stratified by age group, based on data of 418 918 ICC cases from the national estimates of cancer incidence (1975–2015) and the national cancer registry (2016–2019).[7] The incidence of ICC among Japanese women aged 20–29 years significantly increased during 1975–2011 (APC 5.9, 95% confidence interval [95%CI] 5.6 to 6.1, $p<0.001$), in line with previous reports,[13–15] but converted to a decreasing trend from 8.0 to 2.8 (reduction rate 65.0%) during 2011–2020 (APC −13.5, 95%CI −11.9 to −14.5, $p<0.001$). No similar decline was observed for older age groups. The differences in time trends between the 20–29 years age group and other age groups were statistically significant ($p<0.0001$; Poisson regression analysis). In this population-based cancer registry, the methods for data collection were changed from 2016 for better registration. Even when the analysis was confined to the 2016–2019 registry data, the incidence trend in the age group of 20–29 years was significantly different from those in other age groups ($p<0.01$; Poisson regression analysis).

3.2 | Japan Society of Obstetrics and Gynecology gynecologic cancer registry

Using data ($n=116,124$) from the JSOG gynecological cancer registry, we also confirmed the decreasing trend in ICC diagnoses among

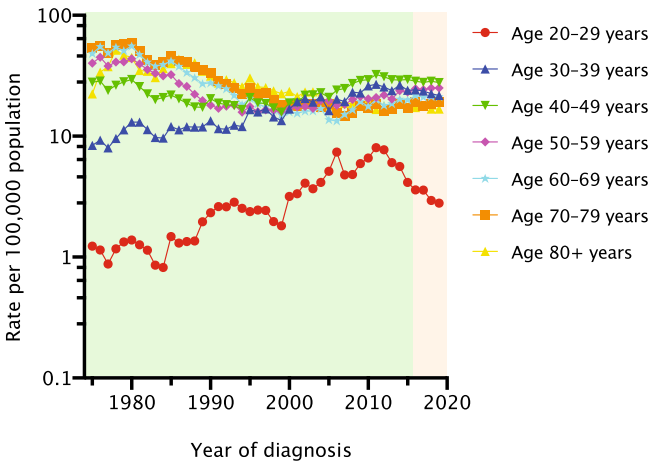

FIGURE 1 Trends in invasive cervical cancer incidence in Japan by age group: Population-based cancer registry, 1975–2019. Time trends in invasive cervical cancer incidence stratified by age group were based on data of the national estimates of cancer incidence (1975–2015, green background) and the national cancer registry (2016–2019, pink background).[7]

Japanese women younger than 30 years (Figure 2). The annual number of ICC diagnoses among women aged 20–29 years dramatically decreased from 256 cases to 135 cases during 2011–2020, while the annual numbers of new ICC cases in older age groups were relatively stable or slightly decreased. These differences also reached statistical significance ($p < 0.0001$; Poisson regression analysis) in both crude and adjusted analyses for the annual numbers of the JSOG registry institutions.

3.3 | The MINT study

We evaluated time trends in positive rates for vaccine types HPV16/18 among Japanese women with ICC according to age group (20–29 years and 30–39 years; Figure 3). The vaccine uptake rate was 1.6% (22/1414) for the overall study population: 1.5% (21/1403) for 1973–1993 birth cohorts and 9.1% (1/11) for 1994–1999 birth cohorts (HPV vaccine target population). Using a linear regression model, attribution of HPV16 and HPV18 to ICC decreased in young women aged 20–29 years by −1.2% (95%CI, −3.9% to 1.5%) per year for the last 10 years, but gradually increased in women aged 30–39 years by 0.6% (95%CI, −1.3% to 2.4%) year by year. The difference in these linear trends did not reach statistical significance ($p = 0.26$). However, when the analysis was confined to 2017–2022 data, HPV16/18 prevalence decreased from 90.5% to 64.7% among young women aged 20–29 years, and this progressive decrease was marginally significant ($p = 0.05$; Cochran-Armitage trend test).

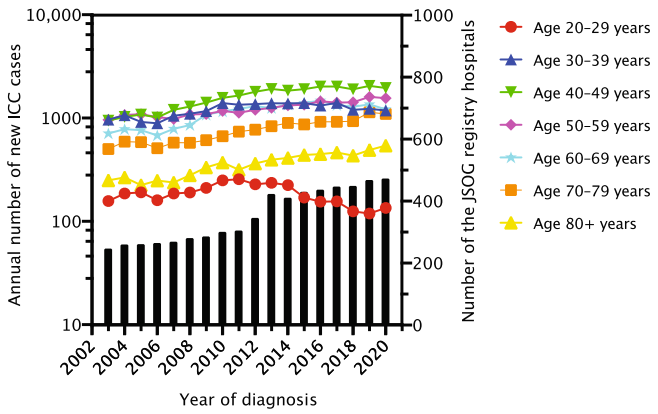

FIGURE 2 Trends in annual numbers of invasive cervical cancer in Japan by age group: Japan Society of Obstetrics and Gynecology (JSOG) gynecological cancer registry, 2003–2020. Lines and left axis (logarithmic scale) show the annual number of cases newly diagnosed with invasive cervical cancer (ICC) in each calendar year, as indicated on the x-axis, by age group; black bars and right axis indicate the number of hospitals participating in the JSOG cancer registry in the indicated year. Although the number of the JSOG registry hospitals continued to increase from 247 institutions in 2003 to 473 institutions in 2020, the annual number of new ICC cases among women aged 20–29 years peaked in 2011 and decreased thereafter.

4 | DISCUSSION

Using data from nationwide cancer registries, we showed declining trends in newly diagnosed ICC cases among young Japanese women aged 20–29 years after the introduction of the HPV vaccination program; no similar trend was observed for older age groups. These results were statistically significant and consistent between two different cancer registries. Therefore, these observations strongly suggest HPV vaccine effectiveness against ICC in Japan. However, the main limitation of our findings was an insufficient linkage between vaccination and the decrease in ICC incidence among young Japanese women. These results may be confounded by screening effects and changes in lifestyle factors and sexual behaviors. Positive effects of vaccination on screening behavior and a recent increase in cervical cancer screening rates among young Japanese women have been reported.[16–18] Furthermore, low sexual activity among young populations have been observed in Japan.[19,20] In a recent online survey, 29.7% of Japanese women aged 20–29 years had never experienced sexual intercourse.[19] In another report, the proportion of female university students who had experienced sexual intercourse had decreased remarkably from 62.2% in 2005 to 36.7% in 2017.[20] In addition to these confounding factors, the possible effects of early vaccination before the introduction of the vaccination program as well as catch-up vaccination at older ages may explain this earlier than expected decrease in ICC incidence.

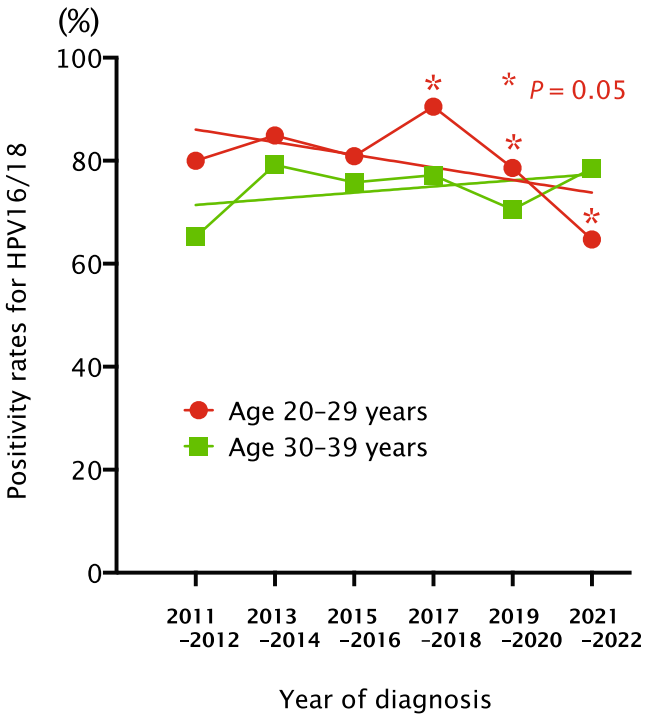

FIGURE 3 Trends in attribution of HPV16 and HPV18 to invasive cervical cancer by age group: The MINT study, 2011–2022. Year-on-year trends of HPV16/18 prevalence (broken lines) and estimated prevalence trends (straight lines) among women diagnosed with invasive cervical cancer are shown for two age groups (20–29 years [red] and 30–39 years [green]). Asterisks indicate a marginally significant decline ($p = 0.05$).

To provide more vaccine-specific evidence, we evaluated time trends in HPV16/18 prevalence among young Japanese women recently diagnosed with ICC. In line with results from cancer registries, attribution of vaccine types HPV16 and HPV18 to ICC was reduced only among young women aged 20–29 years, supporting population-level effects of HPV vaccination on ICC incidence. This decline in ICC became measurable approximately 7 years later than the declines in low- and high-grade cervical lesions.[1] Given the long incubation time from HPV infection to cancer development, this delay may be convincing. Additionally, the delay in detection may be due to our study design. Because women who have benefited from vaccination are not registered in the MINT study, women registered with ICC were more likely to be unvaccinated. Thus, the decrease in HPV16/18-positive rates in ICC may have taken longer to be seen than expected. In this study, the vaccination rate among ICC cases born in 1994–1999 was far lower than that among general 1994–1999 birth cohorts (9% vs. 50%–70%),[21,22] also suggesting that highly vaccinated cohorts may be much less likely to develop ICC (rough estimate of relative risk based on comparison of vaccination rates, 0.04–0.10).

The 2023 US cancer statistics report showed a 65% reduction in ICC incidence rates among women in their early 20s from 2012 to 2019.[23] Because a routine HPV vaccination program was initiated in the United States for girls aged 11–12 years in 2006, the first cohorts of vaccinated girls and adolescents are now in their 20s. Although this cancer registry is not linked to vaccination information, the significant decrease in cervical cancer rates among women aged 20–24 years is most likely due to HPV vaccination effectiveness. Another recent study also reported a significant decline in incidence rates of HPV16/18-positive cervical precancer among US women aged 20–24 years during 2008–2016.[24] These observations are very similar to our findings and a previous report.[1]

In both cancer registries, the incidence rate and the annual number of new ICC cases in women aged 30–39 years also appear to have decreased gradually for the past 10 years, although we found no change in HPV16/18 prevalence in this age group. This smaller reduction may be the first sign of a decline extending to women aged 30–39 years. Besides HPV vaccination, the JSGO clinical guidelines recommend the introduction of HPV testing to cervical cancer screening for women aged 30 years or older,[25] which is also expected to reduce ICC incidences because of the higher sensitivity in detecting cervical precancer.[26] When time trends in ICC incidence are evaluated after changes in cervical screening policy, monitoring HPV genotypes detected in cervical diseases will be more important to distinguish vaccine impact from screening effects.

Both nationwide cancer registries are very useful to assess the impact of HPV vaccination on ICC because Japan has no national healthcare registry system linked to the screening or immunization database. However, cancer statistics depend on data quality of cancer registries. In the population-based cancer registry, the data sources and collection methods were not identical during 1975–2019.[7,9] DCO% (death certificate only: proportion of cases reported by death certificate only) of <10% and optimal M/I (mortality to incidence ratio) of 0.40–0.45 are indicators of high-quality cancer registries in Japan.[27] DCO% indicated the high quality of this population-based cancer registry during 2011–2019 (<10%), especially during 2016–2019 (<4%). Meanwhile, M/I was 0.40–0.45 during 2010–2015 and 0.37–0.38 during 2016–2019.[9,28] Although our results were consistent with a recent study using the 1985–2015 data from only three prefecture cancer registries of higher quality (Yamagata, Fukui, and Nagasaki),[15] earlier registry data from the national estimates of cancer incidence (1975–2015) should be interpreted with caution. Similarly, time trend analyses of ICC incidence using combined data of the national estimates of cancer incidence (1975–2015) and the national cancer registry (2016–2019) are not particularly reliable. Further, the JSOG cancer registry included 247 member institutions in 2003 but 473 institutions in 2020, indicating an approximately 1.9-fold increase in number.[8] This suggests lower quality of earlier JSOG registry data. In the early 2000s, hospitals participating in the JSOG cancer registry were likely to be highly specialized. Accordingly, the annual number of new ICC cases per institution in the 2000s may be overestimated. However, we confirmed that the declining trends of new ICC cases among Japanese women aged 20–29 years were statistically significant using recent registry data of the population-based cancer registry for 2016–2019 and the JSOG cancer registry for 2011–2020. In addition, HPV16/18 prevalence in ICC was reduced only among young women aged 20–29 years during 2017–2022. These observations may suggest a more evident impact of HPV vaccination on ICC in the late 2010s.

It is now 14 years since the first licensure of HPV vaccines in Japan. Although it is still too early to assess the full impact of HPV vaccination, this is the first report to suggest population-level effects of HPV vaccination on ICC in Japan. Although the vaccine type-specific findings support a causal linkage between vaccination and results from cancer registries, our findings included no direct comparison between vaccinated and unvaccinated populations. Therefore, our results may be confounded by screening effects and changes in sexual behaviors among young Japanese women. Further studies are warranted to confirm that our results are attributable to vaccination.

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CONFLICT OF INTEREST STATEMENT

Takashi Iwata received research funds from MSD K.K. Junzo Hamanishi and Kazuhiro Takehara received lecture fees from MSD K.K. The other authors declare no conflict of interest.

ETHICS STATEMENT

Approval of the research protocol by an institutional reviewer board: The institutional ethical review board of the Showa University School of Medicine exempted data analyses from two cancer registries because of the use of publicly available and deidentified data. For the MINT study, the institutional ethical and research review boards of the participating institutions approved the study protocol.
Informed consent: In the MINT study, written informed consent was obtained from all patients.
Registry and the registration no. of the study/trial: The MINT studies I and II were registered in the UMIN Clinical Trials Registry as UMIN000008891 and UMIN00038883, respectively.
Animal studies: N/A.

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APPENDIX A

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