INTRODUCTION

Cervical cancer is a global public health problem, where the number of new cases is ranked 9th among all cancers with an estimated incidence of 604,127, and mortality of 341,831 in 2020 around the world.\(^1\) Cervical cancer incidence has decreased in many high-resource countries with organized cervical screening programs.\(^2\)-\(^4\) Additionally, recent analyses confirmed that well integrated HPV vaccine programs have also resulted in a reduction in cervical cancer.\(^5\)-\(^7\)
In Japan, the Japanese government first offered financial support for cervical cancer screening in 1982. Currently, the target age for population-based screening is 20 years and older, and is recommended every 2 years. The screening rate has gradually improved, from 22.6% in 2001 to 43.8% in 2019, but remains low compared to other OECD countries. Public funding for HPV vaccination became available in 2010, and was included in the national immunization program for girls aged 12-16 years, from April 2013. In June 2013, proactive recommendation of the HPV vaccine program was suspended by the Ministry of Health, Labour and Welfare due to the concern of potential adverse effects reported in the media. On November 12, 2021, the Counsel of Health Sciences agreed on terminating the suspension of proactive recommendation of HPV vaccines.

A previous analysis reported in July 2021 shows that age-adjusted incidence and mortality rate for all ages combined is increasing in Japan, in contrast to the decreasing trend observed in many developed countries. Cervical cancer is mostly known to occur in young and middle adults, and is frequently diagnosed between the ages of 35 and 55 years. However, an assessment of the impact of the current system for cervical cancer in Japan for both incidence and mortality within this high-risk age group has not yet been examined. Therefore, this study aimed to examine trends in cervical cancer incidence and mortality in young and middle adults, by analyzing trends in 10-year interval age-groups in order to characterize the impact of current cervical cancer control strategies in Japan.

2 | MATERIALS AND METHODS

Cancer incidence data were obtained from population-based cancer registries in three prefectures (Fukuoka, Nagasaki, and Yamagata) from years 1985 to 2015. These were acquired in the framework of the Monitoring of Cancer Incidence in Japan project, where data from the three prefectures were selected due to their availability of long-term high-quality data. This dataset has been validated by usage for trend analyses and widely used in previous studies. For cancer mortality, the number of annual cancer deaths and population data for the years 1985–2019 were obtained by released vital statistics. The International Classification of Diseases version 10 code was used: C53 for malignant neoplasm of the cervix uteri; code D06 for CIN, grade III, with or without mention of severe dysplasia (excluding melanoma in situ and severe dysplasia of cervix) was included in the additional analysis. We classified age groups by 10-year intervals between ages 20 and 59 years to analyze trends in young and middle adults. We limited our analysis to this age range to specifically understand the trends among generations in the first peak with high prevalence of HPV infection. All data analyzed in this study are publicly available (http://ganjoho.jp) with open access. No personal identifiers were recorded or used, and ethical approval was not required based on Ethics Guidelines.

3 | RESULTS

Figure 1 shows the observed crude rates in cervical cancer incidence from 1985 to 2015 by 10-year interval age-groups from ages 20 to 59 years in the three selected prefectures in Japan. The crude incidence was the highest among those aged 50-59 years at 25.42 per 100,000 population at the beginning of the observation period in 1985. However, it dropped to its lowest at 10.40 in 1990 and has shown higher rates thereafter. Age group 40–49 years had the second highest incidence in 1985 at 20.32, and increased to hit the highest rate in 2010 at 32.30. Age group 30–39 years had a rate of 9.64 in 1985, intermittently increased and peaked at 33.69 in 2001, which is
the highest among all analyzed age groups, with no steady decrease seen thereafter. As a result, the rates for 30- and 40-year-old age groups have exceeded those for 50-year-olds in recent years. The rate for those aged 20-29 years was the lowest in 1985 at 0.90 and has increased since, with the highest marked in 2012 at 9.09.

Figure 2 shows the modeled annual trends for cervical cancer incidence from 1985 to 2015 by 10-year interval age-groups from ages 20 to 59 years in the three selected prefectures in Japan. Trends by ASR among women aged 20-59 years combined are also presented with plotted observed ASRs. Table 1 shows the results of Joinpoint regression analysis of the trends, with corresponding APC and 95% CIs. Overall trend of incidence using the ASR for ages 20-59 years showed a significant increase throughout the whole period. Both crude and ASR sustainably increased from 1985 to 2015 with a significant APC of +1.6% (95% CI, 1.1, 2.1) and +1.7% (1.2, 2.3), respectively. Similarly, high levels of increase were seen in the 20-, 30-, and 40-year-old age groups, especially among 20s and 30s, with significant APCs of +4.0% (2.2, 5.9), +3.0% (2.1, 4.0) and +1.8% (1.2, 2.5) respectively. Among 50-59-year-olds, although the incidence significantly decreased from the first year of observation until 1990 (APC, −12.3% [-19.5, −4.5]), it leveled off thereafter.

Observed and modelled crude rates with CIN, grade III, with or without mention of severe dysplasia (excluding melanoma in situ and severe dysplasia of cervix) included (Figures S1, S2 and Table S1) also showed a significant rapid increase in incidence in all analyzed age groups combined until 2012. Similar to the trends without CIN, ages 30-39 and 40-49 years showed significant gain in APC throughout the years, and unlike the main analysis, this significant increasing trend was also seen in the 50-59-year-olds from 2006 to 2015.

Figure 3 shows annual trends in observed crude mortality rates for cervical cancer by 10-year interval age-groups from age 20 to 59 years, obtained from the national data of Japan from 1985 to 2019. Observed mortality rate among age groups from highest to lowest was 50-, 40-, 30-, and 20-year-olds at the beginning of the observation period in 1985, with rates of 5.37, 2.75, 0.85, 0.11 per 100,000 population, respectively, and the order remains the same until 2019. The lowest observed mortality was marked in 1994 for women aged 40-49 and 50-59 years, 1989 for those aged 30-39 years, and 1988 for women aged 20-29 years, and it increased thereafter in all age groups. In 2019, mortality was 6.51, 4.53, 2.29, and 0.19, respectively.

Figure 4 shows the modeled annual mortality trends from 1985 to 2019 by 10-year interval age-groups from 20 to 59 years old, along with the modelled and observed ASRs for ages 20-59 years combined. Results of Joinpoint regression analysis on the trends in mortality by age group are shown in Table 2 with corresponding APC and 95% CI. For ages 20-59 years combined, both the crude rate and ASR have significantly increased since the early 1990s. The ASR increased from 1991 with significant APCs of +3.5% (2.4, 4.6) (1991-2002), and +0.8% (0.3, 1.2) (2002-2019). For each individual age group, women aged 20-29 years and 40-49 years showed significant gain in APC throughout the years, and unlike the main analysis, this significant increasing trend was also seen in the 50-59-year-olds from 2006 to 2015.

### Table 1: Results of Joinpoint regression analysis on the trends in cervical cancer incidence by age group: Data from three Japanese prefectures (1985-2015)

| Age (y) | Number of joinpoints | Line segment | 95% confidence interval |
|---------|-----------------------|--------------|------------------------|
|         | Start                | End          | Annual % change       | Lower | Upper |
| 20-59   | 0                    | 1985 2015    | 1.6<sup>b</sup>       | 1.1   | 2.1   |
| Crude   | 0                    | 1985 2015    | 1.7<sup>b</sup>       | 1.2   | 2.3   |
| ASR     | 0                    | 1985 2015    | 4.0<sup>b</sup>       | 2.2   | 5.9   |
| 20-29   | 0                    | 1985 2015    | 3.0<sup>b</sup>       | 2.1   | 4.0   |
| 30-39   | 0                    | 1985 2015    | 1.8<sup>b</sup>       | 1.2   | 2.5   |
| 40-49   | 0                    | 1985 2015    | -12.3<sup>b</sup>     | -19.5 | -4.5  |
| 50-59   | 1                    | 1990 2015    | 0.7                    | -0.2  | 1.6   |

Abbreviation: ASR, age standardized rate.

<sup>a</sup>Yamagata, Fukui, and Nagasaki prefectures.

<sup>b</sup>Annual % change statistically significantly different from zero (P < .05).
an increasing inclination until 2006 and 2011, respectively, but no significant trend was seen after those years. The 30-39 years age group showed a significant continuous increasing trend throughout the observed periods. The greatest increase of this period was also observed in this age group; the APC was $+5.4\% (3.7, 7.1)$ from 1985 to 2000, followed by $+1.1\% (0.1, 2.0)$ from 2000 to 2019. A significant decreasing trend was observed in women aged 50-59 years in the early period, from 1985 to 1992 (APC $-2.8 \, [-4.3, -1.2]$) but a significant increase was also seen in this age group after 1992. The APCs were $+2.4\% (1.1, 3.6)$ from 1992 to 2001, and $+0.8 (0.5, 1.1)$ from 2001 to 2019.

### DISCUSSION

This study analyzed the trend in incidence and mortality of cervical cancer in young and middle-aged women in Japan by 10-year interval age-groups. The incidence of cervical cancer significantly increased throughout the observation period for ages 20-29, 30-39, and 40-49 years, and overall young and middle adults from ages 20 to 59 years. Similarly, mortality also showed significant rising trends in women aged 30-39, 50-59, and overall 20-59 years. Our results revealed that more women in their young and middle adult stages of life are being diagnosed and are dying of cervical cancer. The incidence and mortality due to cervical cancer among women of all ages are both increasing in Japan, and is also predicted to grow in the absence of effective prevention and intervention strategies.13,14,28-31 This paper highlighted the need for further cervical cancer prevention strategies for this age group in Japan.

Contrary to this study, the incidence of cervical cancer has been decreasing in other high-resource countries.2-4 This includes other East Asian countries whose success is considered to be the result of a combination of cervical cancer control measures, particularly organized cervical screening.4,32-34 Cervical screening with a highly sensitive and precise test has been proven to reduce the incidence and mortality of cervical cancer by increasing early detection.35-37 Countries with high screening rates have been effective in lowering the incidence and mortality due to cervical cancer.4,32 In Japan, cytology screening was introduced in the late 1950s, and became systematized in 1982.38 Although the nationwide screening coverage rate has increased over the past 10 years, from 37.7% in 2010 to 43.7% in 2019 among women aged 20-69 years, this is still low compared to other countries such as the United States (72.6%), UK (74.4%), and Korea (51.9%).10,39 Therefore, in Japan, although improvement is reported in cervical screening participation, it has not been reflected in the decrease of the incidence of cervical cancer cases to date.

Evidence from many countries, including Japan, has indicated the effectiveness of the HPV vaccine; a second-generation nonavalent HPV vaccine provides direct protection against approximately 90% of cervical cancers globally.2,6,15,31,40 In Japan, vaccination coverage has remained below 1%.41 This is a result of the suspension of proactive recommendation for the national immunization program for girls aged 12-16 years due to reports in 2013 of potential adverse events following immunization.42 It was estimated that a delay in the resumption of vaccination would likely result in as many as an additional 27,300 cases and 5,700 deaths in the near future, the impact of which has also been projected at municipal and national levels in Japan.29,31,43 Global estimates show decreases in incidence and mortality in proportion to increasing screening and vaccination rates.37,44,45 In 2021, after 8 years of intermission, the government of Japan has decided to end the state of withholding active recommendation for routine HPV vaccination, after confirming the safety,

![FIGURE 3](image1.png) **FIGURE 3** Annual trends in observed crude mortality rate in cervical cancer (1985-2019) by age group. Data from Japanese national vital statistics

![FIGURE 4](image2.png) **FIGURE 4** Annual trends in modelled mortality rate in cervical cancer (1985-2019) by age group. Data from Japanese national vital statistics.
and strengthening the support system for the vaccine. In continuation, to follow the success of long-term reduction of cervical cancer burden in many other countries, Japan needs to increase cervical screening participation and promote coverage of the HPV vaccination program.31,42

4.1 | Strengths and limitations

The representativeness of the data is a major strength of this study. Incidence data were derived from three prefectures with long-term high-quality data, and mortality data were from a complete mandatory reporting system, based on the national vital statistics. Although incidence data were not obtained from all prefectures, past reports have confirmed its validity in terms of secular trends.19 In addition, the data used for past reports published on cervical cancer trends in Japan are mainly based on a single city or prefecture, which also makes our population-based study more precise.28-30,46

Previous reports on the trends in Japanese cervical cancer mortality should be interpreted with caution because the vital statistics registry could have included the shift from cancer of the uterus, NOS.14 However, the proportion of NOS had been stable since the late 1990s.14 Our study limited the year range from 1985 to make the result more comparable with the incidence analysis. Therefore, it can be assumed that this will not significantly affect the results of our analysis. The age range for this study was also limited to 20 to 59 years, to explore the situation of cervical cancer in young and middle adults in Japan. Additional analyses for women aged 60 years and older are shown in the Tables S2 and S3 and Figures S3–S6; where incidence rates showed decreasing or insignificant trends among these age groups. For mortality, significant increase was seen in the 60–69 years age group. Furthermore, our analysis was only descriptive. It was also not grouped into clinically relevant subtypes, but previous reports have shown that incidence and relative survival of women did not differ between HPV-related subtypes.6,36

In summary, by examining trends of cervical cancer incidence and mortality in young and middle adults in 10-year interval age-groups, we observed increasing trends in incidence and mortality of cervical cancer in young and middle adults in Japan. This study revealed that current cervical cancer control strategies in Japan have not been effective in reducing the incidence and mortality due to cervical cancer in young and middle adults. Increasing participation in cervical cancer screening and implementation of a national vaccination program are urgently needed to reduce the incidence and mortality due to cervical cancer in Japan.

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DISCLOSURE

There are no financial or other relations that could lead to a conflict of interest regarding this study.

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### TABLE 2 Results of Joinpoint regression analysis on the trends in cervical cancer mortality by age group: Data from viral statistics (1985-2019)

| Age (y) | Number of joinpoints | Line segment | 95% confidence interval |
|---------|-----------------------|--------------|------------------------|
|         | Start     | End     | Annual % change | Lower  | Upper  |
| 20-59   | Crude     |         |                |        |        |
|         | 1985      | 1993    | 0.1            | −1.4   | 1.6    |
|         | 1993      | 2000    | 4.4a           | 2.2    | 6.7    |
|         | 2000      | 2019    | 1.3a           | 0.9    | 1.6    |
|         | ASR       |         |                |        |        |
|         | 1985      | 1991    | −1.1           | −3.5   | 1.5    |
|         | 1991      | 2002    | 3.5a           | 2.4    | 4.6    |
|         | 2002      | 2019    | 0.8a           | 0.3    | 1.2    |
| 20-29   | 1         |         |                |        |        |
|         | 1985      | 2006    | 4.2a           | 2.4    | 6.1    |
|         | 2006      | 2019    | −3.0           | −6.6   | 0.7    |
| 30-39   | 1         |         |                |        |        |
|         | 1985      | 2000    | 5.4a           | 3.7    | 7.1    |
|         | 2000      | 2019    | 1.1a           | 0.1    | 2.0    |
| 40-49   | 1         |         |                |        |        |
|         | 1985      | 2011    | 2.7a           | 2.3    | 3.2    |
|         | 2011      | 2019    | −1.0           | −3.2   | 1.3    |
| 50-59   | 2         |         |                |        |        |
|         | 1985      | 1992    | −2.8a          | −4.3   | −1.2   |
|         | 1992      | 2001    | 2.4a           | 1.1    | 3.6    |
|         | 2001      | 2019    | 0.8a           | 0.5    | 1.1    |

Abbreviation: ASR, age standardized rate.

*Annual % change statistically significantly different from zero (P < .05).
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