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ORIGINAL ARTICLE

Effectiveness of catch-up and routine program of the 9-valent vaccine on cervical cancer risk reduction in Japan

Asami Yagi[1] | Satoshi Nakagawa[1] | Yutaka Ueda[1] | Emiko Oka[1,2] | Sayaka Ikeda[1] | Mamoru Kakuda[1] | Eiji Kobayashi[3] | Yuri Ito[2] | Kayoko Katayama[4] | Kei Hirai[5] | Tomio Nakayama[6] | Tadashi Kimura[1]

[1]Department of Obstetrics and Gynecology, Osaka University Graduate School of Medicine, Osaka, Japan

[2]Department of Medical Statistics, Research and Development Center, Osaka Medical and Pharmaceutical University, Takatsuki, Oita, Japan

[3]Department of Obstetrics and Gynecology, Oita University Graduate School of Medicine, Ufu, Oita, Japan

[4]Faculty of Informatics, Gunma University, Maebashi, Gunma, Japan

[5]Clinical Psychology, Graduate School of Human Sciences, Osaka University, Osaka, Japan

[6]Center for Public Health Sciences, National Cancer Center, Tokyo, Japan

Correspondence
Yutaka Ueda, Department of Obstetrics and Gynecology, Osaka University Graduate School of Medicine, 2-2, Yamadaoka, Suita, Osaka 565-0871, Japan.
Email: y.ueda@gyne.med.osaka-u.ac.jp

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Abstract

In 2013, the national human papillomavirus (HPV) immunization program began. However, in June 2013, Japan's Ministry of Health, Labor and Welfare (MHLW) announced a "temporary" suspension of its recommendation for the human papillomavirus vaccine. Finally, in November 2021, the MHLW ended its suspension of the recommendation of the HPV vaccine. To address the 9-year gap in HPV vaccinations the suspension had caused, the MHLW conducted a program of catch-up vaccinations from April 2022 to March 2025. Finally, in April 2023, the 9-valent HPV vaccine was approved for both the routine and catch-up vaccination programs in Japan. In this study, we investigated the potential effects of the introduction of the 9-valent vaccine on the increased risk of cervical cancer in females born after fiscal year (FY) 2000. We estimated the lifetime relative risk of cervical cancer incidence and death using the improved routine and catch-up vaccination rates after the recent resumption of the governmental recommendation for women and girls to have the HPV vaccination. These relative risks were calculated using a lifetime risk of 1.000 for cervical cancer incidence and death for females born in FY 1993. We predicted that even if a 90% vaccination rate were to be achieved by FY 2024 with the 9-valent vaccine among women born between FY 2000 and FY 2005, the risk would remain higher than for the vaccination generation. Therefore, for women born between FY 2000 and FY 2005, it will be necessary to significantly improve the cervical cancer screening rate to compensate for this increased risk.

KEYWORDS
cervical cancer, health communication, HPV vaccine, Japan, suspension of recommendation

Abbreviations: FY, fiscal year; HPV, human papillomavirus; MHLW, Ministry of Health, Labor and Welfare; WHO, the World Health Organization.

Asami Yagi and Satoshi Nakagawa contributed equally to this work.

1 | BACKGROUND

In 2020, the global incidence and death rate of cervical cancer were estimated to be 600,000 and 340,000, respectively.[1] Most cervical cancers are caused by a persistent infection with one or more of the sexually transmitted high-risk strains of the human papillomavirus (HPV). The high-risk types of HPV are 6, 11, 16, 18, 31, 33, 45, 52, and 58, all of which the latest 9-valent HPV vaccines protect against. Cervical cancer is primarily prevented by vaccination against HPV during the preteen and early teenage years—before sexual activity begins. Secondary mitigation of cervical cancer occurs through early and frequent screening programs, which have been well established in advanced countries.

In 2020, the World Health Organization (WHO) launched an ambitious cervical cancer elimination strategy that sets goals for all countries to achieve 90% HPV vaccination coverage, 70% cervical screening coverage, and 90% access to cervical cancer treatment by the year 2030.[2] Unfortunately, Japan has been left lagging far behind in this global endeavor. In Japan, the age-adjusted incidence rate of cervical cancer has been increasing over the past 20 years.[3,4] In addition, Japan's future cervical cancer incidence and death rates are predicted to rise even further due largely to the dramatically decreased HPV vaccinations that occurred between 2013 and 2022. This vaccination gap was due to HPV vaccine hesitancy caused by a misguided policy decision based on spurious evidence of adverse side effects.[5,6]

Herein we describe important details of Japan's policies regarding the HPV vaccine, some of which have been strongly criticized by the WHO.[7] To set the stage for this discussion, a history of the HPV vaccine is in order. In Japan, the bivalent HPV vaccine that protects against types 16 and 18 was first approved in October 2009, followed by approval in July 2011 of the quadrivalent vaccine that protects against types 6, 11, 16, and 18. In November 2010, public subsidies from local and national governments were established for the vaccination of girls in the 7th to 10th grades. In April 2013, the national immunization program began including sixth grade girls (Table 1).

However, just as routine HPV vaccinations were hitting their stride in Japan, there was a flurry of media reports on possible serious adverse side effects from the vaccine. Out of an abundance of

TABLE 1 Major events in Japan regarding the HPV vaccine and eligibility for its immunization program.

		(1)			(2) (3)							(4)	(5)	(6)	(7)					
		2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028
Pre-introduction generation	1993	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
Vaccination generation	1994	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34
	1995	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33
	1996	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
	1997	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
	1998	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
	1999	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Vaccine-suspension generation	2000	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
	2001	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
	2002	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
	2003	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
	2004	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
	2005	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Re-introduction generation	2006	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
	2007	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
	2008	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
	2009	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
	2010	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
	2011		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
	2012			0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16

Note: (1) November 2010: Public subsidies from local and national governments begin for female students in 7th to 10th grade. (2) April 2013: The national immunization program begins for female students in 6th to 10th grade. (3) June 2013: The MHLW announces a suspension of its governmental recommendation of the HPV vaccination. (4) October 2020: The MHLW requests that local governments begin mailing individualized information to those who are eligible for routine vaccinations. (5) November 2021: The MHLW announces the abolition of its recommendation suspension. (6) April 2022: The government resumes its recommendation for HPV vaccination and begins a program of catch-up vaccinations. (7) April 2023: The 9-valent vaccine is approved and introduced for routine and catch-up vaccinations. Bold line: Eligibility for subsidies and national immunization programs. Cells in gray: Eligibility for catch-up vaccination.

Abbreviations: HPV, human papillomavirus; MHLW, Ministry of Health, Labor and Welfare.

caution, in June 2013, Japan's Ministry of Health, Labor and Welfare (MHLW) announced a "temporary" suspension of its recommendation for the HPV vaccine. The announcement of this policy decision was sensationalized by the media; understandably, the general public reacted to this uncertainty about the safety of the vaccine by almost entirely refusing to vaccinate their daughters.

The MHLW held discussions on the various reported post-inoculation symptoms. Then they conducted a comprehensive safety study and established a medical treatment system to address any relevant issues.[8] Strong pressure began to build among the medical community to reinstitute the vaccination recommendation. Finally, in October 2020, 7 years after they suspended the HPV vaccination recommendation, the MHLW requested that local governments recommence providing individualized information about HPV vaccination to girls who were eligible (based on their age) for subsidized routine vaccinations. However, they requested that this information not contain wording specifically recommending HPV vaccination. Most municipalities (61%) responded affirmatively by posting letters with information to the girls and their immediate families.[9] In November 2021, the MHLW formally ended its suspension of the HPV vaccination recommendation. In April 2022, they issued a notice to local governments nationwide to restart their own active vaccination recommendations.

To address the 9-year gap in HPV vaccinations the suspension had caused, the MHLW conducted a program of catch-up vaccinations from April 2022 to March 2025. This program would target females who had foregone their earlier vaccination opportunity due to the vaccine hesitancy surrounding the suspension of the governmental recommendation to have the HPV vaccination. According to their plan, girls born in FY 2006, now or soon to be in 11th grade, would be eligible for catch-up vaccinations in FY 2023 and 2024. Finally, in April 2023, the 9-valent HPV vaccine was approved for both the routine and catch-up vaccination programs in Japan.

We previously published a discussion on the statistical methodology difficulties in estimating the cumulative vaccination numbers, which can be found in the 26th Welfare Science Council Vaccination and Vaccine Subcommittee Side-Reaction Study Group Proceedings.[10,11] Our vaccination estimates were similar to those found subsequently during a survey of local governments. We have calculated the risks of cervical cancer incidence and death by using our estimates of vaccination rates and reported on the extent to which it might be possible to fill the void left by the suspension of the governmental recommendation of the HPV vaccination through a catch-up vaccination program.[12]

In the present study, we have recalculated the HPV vaccination rates for females born between FY 2005 and 2009 using data obtained up to March 2022. These rates included the number of vaccinations promoted by local governments providing individualized HPV health information from FY 2020 to FY 2021. We also estimated the lifetime relative risk of cervical cancer incidence and death using the latest vaccination rates and the assumed improved routine and catch-up vaccination rates after the recent resumption of the governmental recommendation of the HPV vaccine. We have attempted to delineate the consequences of the suspension of the governmental recommendation of the HPV vaccine. In particular, we have investigated the potential effects of the introduction of the latest approved 9-valent vaccine on the increased risk of cervical cancer in females born after FY 2000.

2 | METHODS

2.1 | Cumulative initial human papillomavirus vaccination rate by birth financial year

We calculated the cumulative initial HPV vaccination rate by birth FY using published statistical data from Japan's MHLW Science Council's Vaccination and Vaccine Subcommittee Side-Reaction Study Group, the implementation report of the emergency promotion project for HPV vaccination from FY 2010 to FY 2012, data from the regional public health services and health promotion service report from FY 2013 to FY 2021, and the population census from FY 2020. In most of these reports, the number of vaccinations was reported by age, which we converted into vaccinations by birth FY.[8,10,13] However, in one previous report, the seventh grade was used as the standard vaccination grade, as this was the grade where vaccination was most actively recommended. Due to the influence of the program providing individualized information, from FY 2020 onward, the 10th grade was actually the main target for vaccination, so the calculation formula for estimating the number of vaccinations from FY 2020 onward was changed accordingly.

2.2 | Lifetime relative risk of cervical cancer incidence and death by birth financial year

In our previous study, we calculated the relative risks for cervical cancer incidence and death assuming that only the bivalent and quadrivalent vaccines would be used for all future routine and catch-up vaccination programs.[5,12,14] In this new report, the lifetime relative risk of cervical cancer incidence and death for women born in 1993 (what we have dubbed the "pre-vaccine-introduction generation") was set as the "standard" of 1.000. The estimated relative risks for all following years were calculated for the following four situations: Scenario (1) included risks that would occur when there was no resumption of governmental recommendation nor a catch-up vaccination program, and the individual notifications from local governments provided by mail did not actively promote HPV vaccination; scenario (2) included risks that would occur when the rates for routine and catch-up vaccinations would be spread evenly between FY 2022 and FY 2024, and in FY 2024 would reach 50%, 70%, and 90% among females born in FY 1997 to FY 2008, using only

bivalent and quadrivalent vaccines; scenario (3) included risks that would occur exactly as in scenario (2), but from FY 2023 forward the 9-valent vaccine was the only vaccine used; and scenario (4) included risks when the rates of routine vaccination spread evenly from sixth to 10th grade and reached assumed rates of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, and 90% in 10th grades, when the bivalent and quadrivalent vaccines were used until FY 2022, but from FY 2023 forward the 9-valent vaccine was used. The assumptions that we set to estimate the lifetime relative risk of cervical cancer incidence and death by birth FY are shown in Table S1. The formulas that we used to estimate the lifetime relative risk of cervical cancer incidence and death by birth FY are shown in Table S2. The formulas were based on the concept shown in Figure S1. We tested the robustness of the results using a sensitivity analysis (Table S3).

Data from the Japanese Family Planning Association was used for the sexual experience rate, as follows: age 12: 0%, age 13: 1%, age 14: 2%, age 15: 5%, age 16: 15%, age 17: 25%, age 18: 42%, age 19: 55%, age 20: 66%, age 21: 72%, age 22: 75%, and lifetime: 85%.[15]

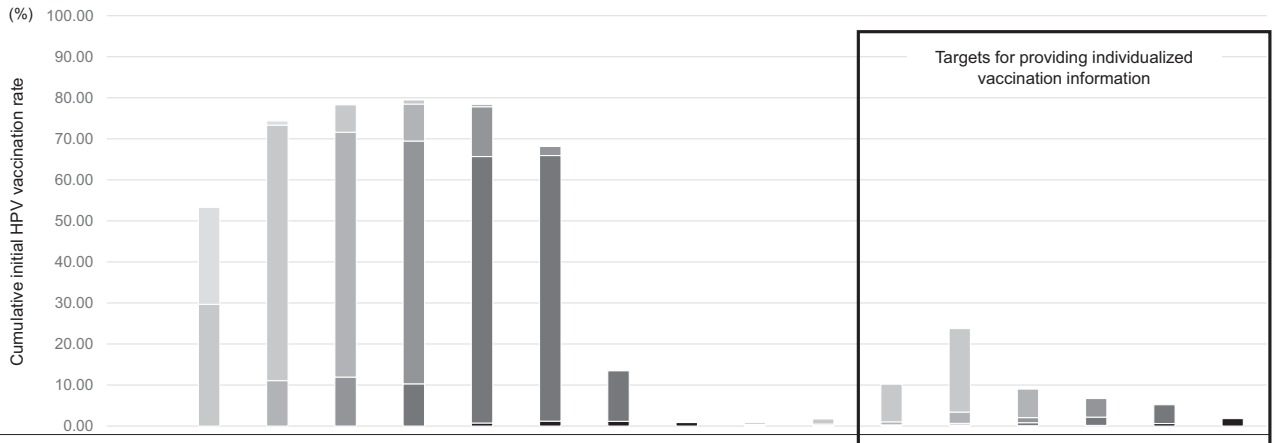
3 | RESULTS

3.1 | Cumulative human papillomavirus vaccination rate by birth fiscal year

The cumulative initial HPV vaccination rates by birth FY are shown in Figure 1. Women born in FY 1994 were, in FY 2010, the first girls in Japan to become eligible for public subsidies when they reached 16 (10th grade). When they finished 11th grade in FY 2011, their overall vaccination rate was 53.31%. Women born in FY 1995 were vaccinated from FY 2010 to FY 2012 (9th to 11th grade) and achieved a subsidized vaccination rate of 74.35%. Women born in FY 1996 were vaccinated from the 8th to 10th grade, and the vaccination rate was 78.26%. Women born in FY 1997 had the all-time highest vaccination rate, reaching 79.46%.

For women born in FY 1999, vaccinations started earlier in life, so by FY 2012, when the girls were in 7th grade, the vaccination rate was already 65.92%. However, in April FY 2013, when these girls were near the end of 8th grade, the MHLW announced the suspension of its governmental recommendation for them to receive further HPV vaccinations, even though they continued to offer subsidies for HPV vaccinations. As a direct result, the vaccination rate for 8th graders born in FY 1999 was only 2.28%, compared to 12.14% of their FY 1998 predecessors. Vaccination rates for females born in FY 2000 and thereafter remained negligible for the next 9 years, plummeting to 0.83% for those born in FY 2002, the lowest rate since the beginning of HPV vaccinations in Japan in FY 2009.

In 2020, the targets for providing individualized vaccination information from local governments were females born in FY 2004 or later. Among females born in FY 2004, the vaccination rate for 10th graders in 2020 was 9.18%, approximately 7.4 times the rate of 10th graders born in FY 2003. Among females born in FY 2005, the vaccination rate for 10th graders further increased to 20.31%. Even when born in FY 2006, the vaccination rate in each grade



Birth FY	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
6th grade	-	-	-	-	-	0.75	1.18	1.17	0.89	0.04	0.03	0.02	0.03	0.08	0.17	0.61	1.83
7th grade	-	-	-	-	10.29	64.95	64.74	12.34	0.25	0.15	0.09	0.12	0.26	0.73	2.02	4.59	-
8th grade	-	-	-	11.95	59.19	12.14	2.28	0.23	0.05	0.03	0.07	0.15	0.36	1.24	4.52	-	-
9th grade	-	-	11.07	59.65	9.00	0.66	0.11	0.19	0.09	0.14	0.31	0.74	2.79	6.95	-	-	-
10th grade	-	29.66	62.27	6.66	0.98	0.05	0.04	0.10	0.24	0.47	1.24	9.18	20.31	-	-	-	-
11th grade	-	23.65	1.01	-	-	-	-	-	-	-	-		-	-	-	-	-
Total	-	53.31	74.35	78.26	79.46	78.55	68.35	14.03	1.52	0.83	1.74	10.21	23.75	9.00	6.71	5.20	1.83

FIGURE 1 Cumulative initial HPV vaccination rate by birth FY calculated using the latest data from regional public health and health promotion services and the FY 2020 population census. FY, fiscal year; HPV, human papillomavirus.

was higher than the rate in the same grade in the birth FY one grade above.

3.2 | Scenario (1) (control): Cumulative human papillomavirus vaccination rate and lifetime relative risk of cervical cancer incidence and death when there was no resumption of governmental recommendation or commencement of the catch-up vaccination program and only an individual notification was provided

The calculated cumulative initial HPV vaccination rate when there was no resumption of a governmental recommendation for HPV vaccination nor the start of a catch-up vaccination program, and only mailed non-vaccine-promoting individual notifications are provided, was as follows: 29.31% for girls born in FY 2006, 33.97% for FY 2007, 36.98% for girls born in FY 2008, 38.20% for girls born in FY 2009, and 38.20% for girls born in FY 2010 to FY 2012 (Figure 2).

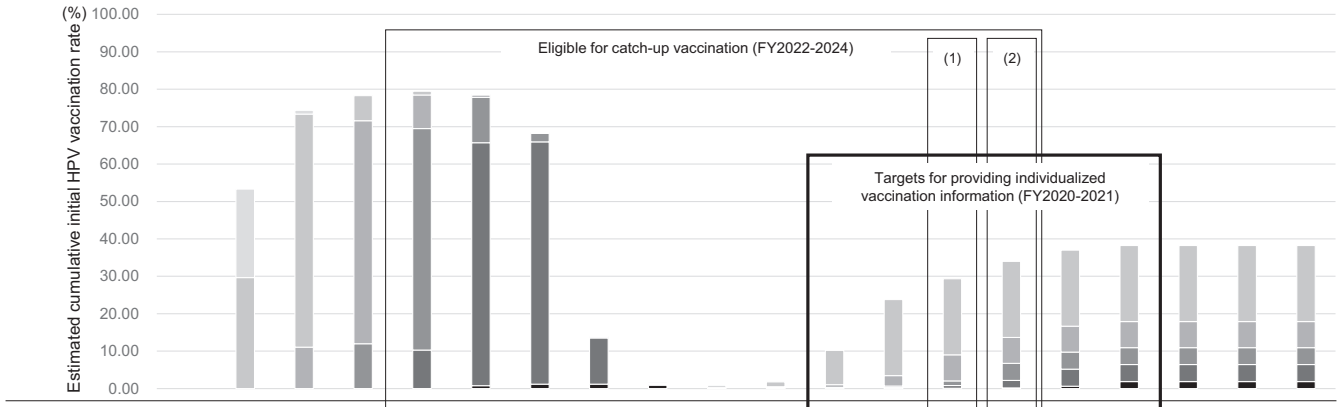
Figure 3 shows the lifetime relative risk of cervical cancer incidence and death calculated using the above-estimated vaccination rates. The relative risk for females born in FY 1997, the birth FY with the highest vaccination rate to date, was 0.535. The lowest risk achieved, 0.534, was for women born in FY 1998. The risks for women born between FY 2000 and FY 2003 were 0.917, 0.991, 0.995, and 0.991, respectively. For those born after FY 2004, the lowest risk value, 0.688, was for those born in FY 2011 and FY 2012.

3.3 | Scenario (2): Risks when the rates of routine and catch-up vaccinations spread evenly between FY 2022, FY 2023, and FY 2024, reach 50%, 70%, and 90% (respectively) in FY 2024 and only the bivalent and quadrivalent vaccines are used

We compared the control risk with the risk for a scenario wherein the vaccination rates of routine and catch-up vaccination spread evenly between FY 2022 and FY 2024, reaching 50%, 70%, and 90% (respectively) in FY 2024, and only the bivalent and quadrivalent vaccines are used (Figure 4). If the vaccination rate of females born in FY 2007 were to reach 90% during FY 2024, their risk (0.532) would be lower than the control risk (0.534) for those born in FY 1998. The risks for females born between FY 2000 and FY 2006 (leading up to FY 2007) was no lower under this scenario than the control risk for those born in FY 1998, even if their vaccination rates reached 90% in FY 2024.

3.4 | Scenario (3): Risks when the scenario was the same as Scenario 2 but using the bivalent and quadrivalent vaccines until FY 2022, then, starting in FY 2023, switching to only the 9-valent vaccine

We compared the control risk with the risk when the vaccination rates of routine and catch-up vaccination were spread evenly between FY 2022 and FY 2024, reached 50%, 70%, and 90% in



Birth FY	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
6th grade	-	-	-	-	-	0.75	1.18	1.17	0.89	0.04	0.03	0.02	0.03	0.08	0.17	0.61	1.83	1.83	1.83	1.83
7th grade	-	-	-	-	10.29	64.95	64.74	12.34	0.25	0.15	0.09	0.12	0.26	0.73	2.02	4.59	4.59	4.59	4.59	4.59
8th grade	-	-	-	11.95	59.19	12.14	2.28	0.23	0.05	0.03	0.07	0.15	0.36	1.24	4.52	4.52	4.52	4.52	4.52	4.52
9th grade	-	-	11.07	59.65	9.00	0.66	0.11	0.19	0.09	0.14	0.31	0.74	2.79	6.95	6.95	6.95	6.95	6.95	6.95	6.95
10th grade	-	29.66	62.27	6.66	0.98	0.05	0.04	0.10	0.24	0.47	1.24	9.18	20.31	20.31	20.31	20.31	20.31	20.31	20.31	20.31
11th grade	-	23.65	1.01	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Total	-	53.31	74.35	78.26	79.46	78.55	68.35	14.03	1.52	0.83	1.74	10.21	23.75	29.31	33.97	36.98	38.20	38.20	38.20	38.20

FIGURE 2 Cumulative initial HPV vaccination rate when there was no resumption of the governmental recommendation, after starting a catch-up vaccination program, and only information to individuals was provided by mail. Underline: HPV vaccination rates for the first vaccine dose were used for risk calculations for when there was no resumption of governmental recommendation, or the start of a catch-up vaccination program, and only individual notifications were provided by mail. Vaccination rates were assumed to be the same as those that occurred for each age group in FY 2020. (1) Females born in FY 2006 will be eligible for catch-up vaccination from FY 2023 to 2024. (2) Females born in FY 2007 will be eligible for catch-up vaccination in FY 2024. FY, fiscal year; HPV, human papillomavirus.

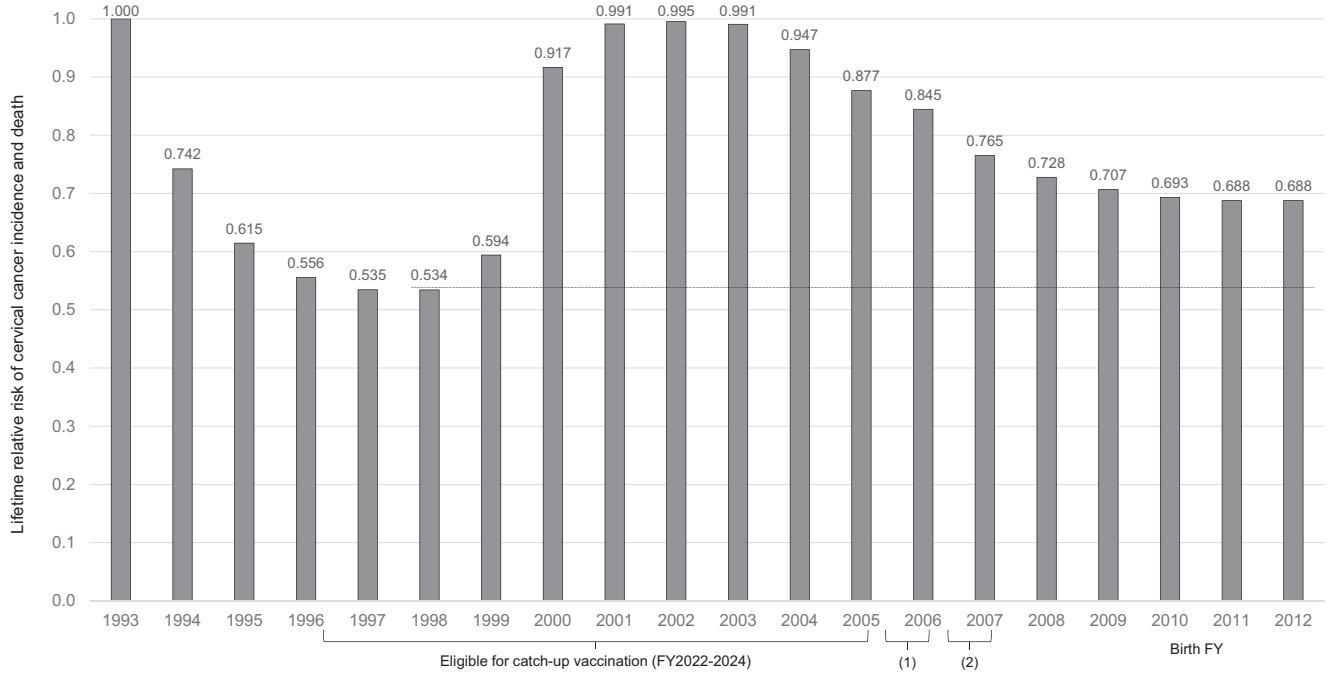


FIGURE 3 Scenario (1) (control): Cumulative HPV vaccination rate and lifetime relative risk of cervical cancer incidence and death when there was no resumption of governmental recommendation or the commencement of a catch-up vaccination program and only an individual notification was provided. (1) Females born in FY 2006 will be eligible for catch-up vaccination from FY 2023 to 2024. (2) Females born in FY 2007 will be eligible for catch-up vaccination in FY 2024. FY, fiscal year; HPV, human papillomavirus.

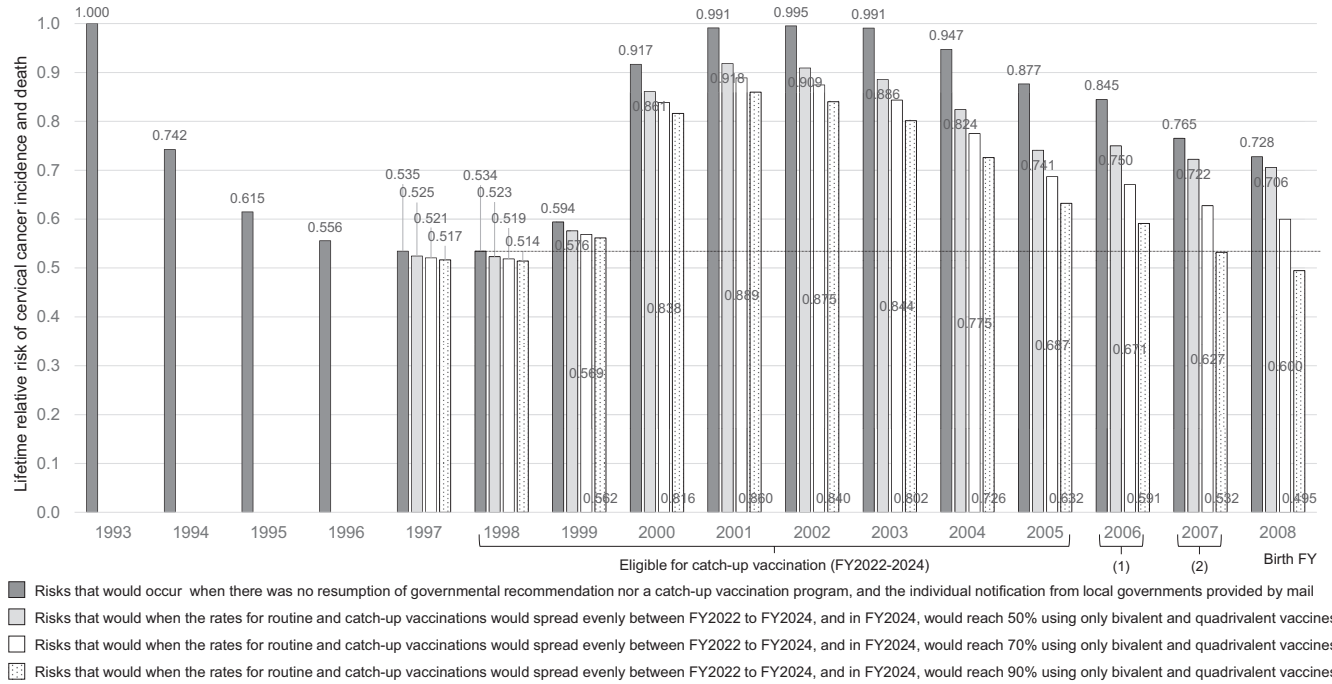


FIGURE 4 Scenario (2): Risks when the rates of routine and catch-up vaccinations are spread evenly between FY 2022, FY 2023, and FY 2024, reach 50%, 70%, and 90% (respectively) in FY 2024, and only the bivalent and quadrivalent vaccines are used. (1) Females born in FY 2006 will be eligible for catch-up vaccination from FY 2023 to 2024. (2) Females born in FY 2007 will be eligible for catch-up vaccination in FY 2024. FY, fiscal year.

FY 2024, using the bivalent and quadrivalent vaccines until FY 2022, then from FY 2023 onward, the 9-valent vaccine (Figure 5). If the vaccination rate of females born in FY 2006 reached 90% in FY 2024, the risk would be lower than the control risk for those born in FY 1998. The risk for women born in FY 2000 to FY 2005 is no lower than the control risk for those born in FY 1998, even if

the vaccination rate in FY 2024 reached 90%. In other words, the 9-valent vaccine that was introduced for routine vaccinations in FY 2023 did not have enough differential effect over the 2- and 4-valent vaccines to overcome the 8-year delay in cervical cancer control due to the suspension of the governmental recommendation for women and girls to have the HPV vaccination.

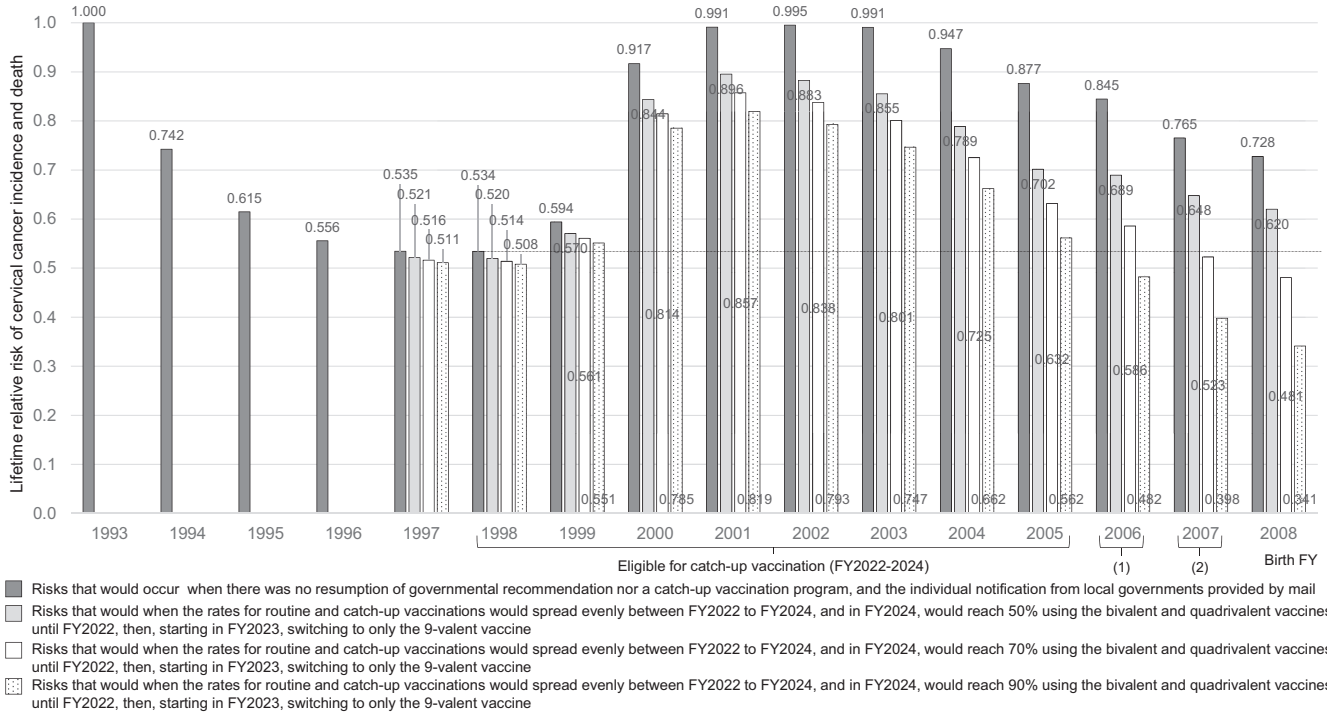


FIGURE 5 Scenario (3): Risks when the scenario was the same as Scenario (2) but using the bivalent and quadrivalent vaccines until FY 2022, then, starting in FY 2023, switching to only the 9-valent vaccine. (1) Females born in FY 2006 will be eligible for catch-up vaccination from FY 2023 to 2024. (2) Females born in FY 2007 will be eligible for catch-up vaccination in FY 2024. FY, fiscal year.

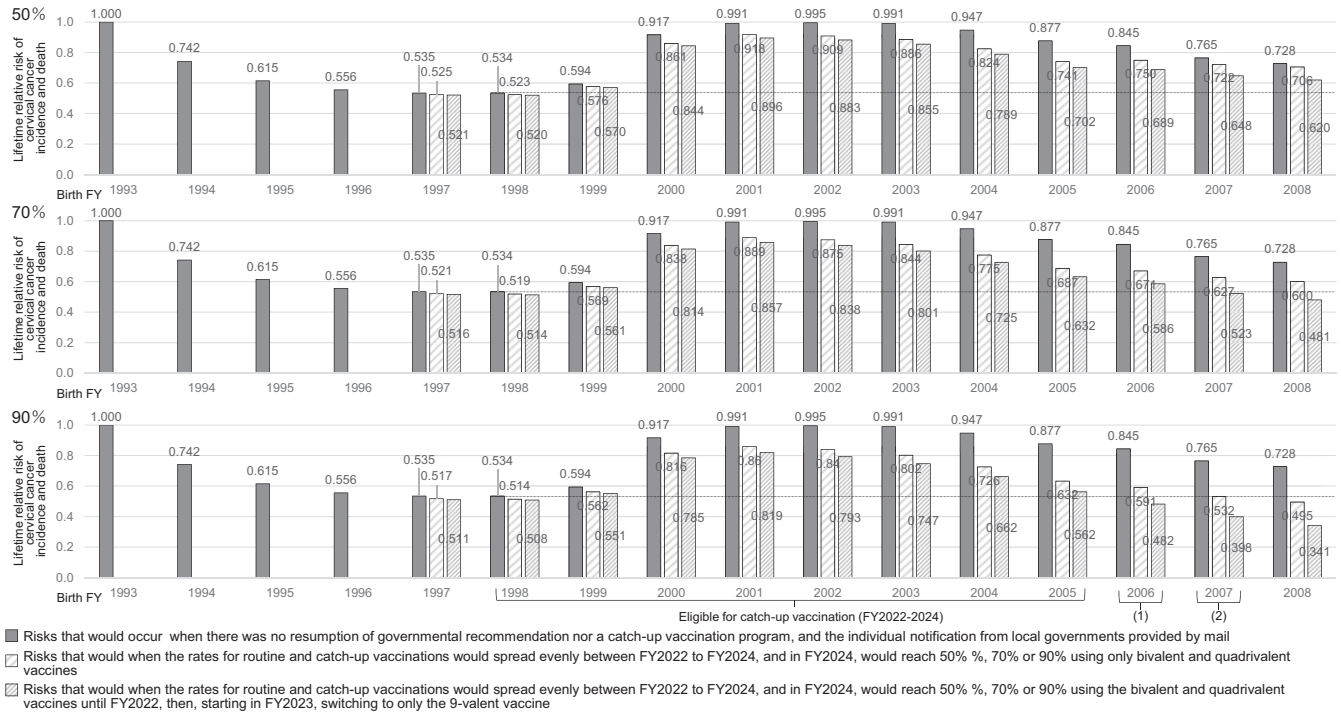


FIGURE 6 Scenario (3): Lifetime relative risk of cervical cancer incidence and death: comparison of the risks if use of the bivalent and quadrivalent vaccines continued until FY 2022; then from FY 2023 the 9-valent vaccine was used. (1) Females born in FY 2006 will be eligible for catch-up vaccination from FY 2023 to 2024. (2) Females born in FY 2007 will be eligible for catch-up vaccination in FY 2024. FY, fiscal year.

3.5 | Scenario (3): Lifetime relative risk of cervical cancer incidence and death—Comparison of the risks if use of the bivalent and quadrivalent vaccines continued until FY 2022, then from FY 2023 the 9-valent vaccine was used

We compared the control risk with the assumed risk as if the bivalent and quadrivalent vaccines were the only ones to be used versus the risk if the 9-valent vaccine was used from FY 2023 onward (Figure 6). For all assumed vaccination rates, the risks by birth FY were lower when the 9-valent vaccine was introduced. The introduction of the 9-valent vaccine was able to reduce the risk by 10% or more when compared with the risk derived from the continued to use of only the bivalent and/or quadrivalent vaccines, if the HPV vaccination rates reached the assumed rates, as follows: 50% for females born in FY 2007 or later, 70% for females born in FY 2006 or later, and 90% for females born in FY 2005 or later.

3.6 | Scenario (4): Lifetime relative risk of cervical cancer incidence and death when the vaccination rates of routine vaccination were spread evenly from 6th to 10th grade, reached an assumed rate in 10th grade, and bivalent and quadrivalent vaccines were used until FY 2022, then the 9-valent vaccine was used from FY 2023 onward

For females born in FY 2009 or later, their ending FY for subsidized routine vaccination will be FY 2025, as they pass the age of 16. We compared the control risk for girls born in FY 1998 with the risk when the vaccination rates of routine vaccination spread evenly from 6th to 10th grade and reached our assumed rate in 10th grade, when the bivalent and quadrivalent vaccines were used until FY 2022, and the new 9-valent vaccine will be used from FY 2023 onward (Figure 7). In a scenario where the vaccination rate of females born in FY 2009 to FY 2012 reached 60% in FY 2024, the risk would be lower than for those born in FY 1998, our "control risk" group. In addition, if the vaccination rate for females born in FY 2011 and FY 2012, who are now able to receive the 9-valent vaccine starting in the sixth grade, reaches 80%, which is equivalent to the 79.46% rate achieved for girls born in FY 1997, the risk for the FY 2011/2012-born girls will be lower than for girls born in FY 1997.

4 | DISCUSSION

In Japan, the organizations currently responsible for collecting vaccination rate data are public health centers and local governments, and the retention period for vaccination records is stipulated to be 5 years. Some local governments have already deleted many of the vaccination records we needed, and they cannot even confirm as accurate the vaccination records they do have. A national database for vaccination data is being established but is not yet in operation. Therefore, precise nationwide HPV vaccination rates by birth FY are not yet available, requiring us to make reasonable estimations of those numbers for our study. We accept that this is a clear weakness of our work.

In the present study, we have explored the possible consequences of various scenarios following the 2013 suspension of the governmental recommendation for the HPV vaccination. Importantly, we have looked at the potential effects of the recent approval and introduction into Japan of the 9-valent vaccine by estimating the latest vaccination rates and lifetime relative risk of cervical cancer incidence and death. We predict that even if a 90% vaccination rate were to be achieved by FY 2024 with the 9-valent vaccine among females born between FY 2000 and FY 2005, the risk would remain higher than for the vaccination generation. Therefore, for females born between FY 2000 and FY 2005, it will be necessary to significantly improve the cervical cancer screening rate to compensate for this increased risk. In addition, our efforts to raise awareness of cervical cancer prevention for the vaccine-suspension generation should be increased.

The results of our study are in line with a recent Danish research paper, which reported that HPV vaccination of women aged 20 to 30 did not reduce the incidence rate of cervical cancer compared to unvaccinated women of the same age, although the incidence rate of cervical cancer was significantly reduced when girls were vaccinated before age 20 and were the most protected if vaccinated when 16 years or younger.[16] The failure of the delayed vaccine to protect 20–30-year-old women who have already been infected with a latent virus that can hide from the immune system is sadly understandable. The results obtained from our previous calculations are also similar to those reported by Simms KT.[6] Therefore, we believe that our estimate calculations were performed appropriately.

In birth FYs where the sexual experience rate has not yet increased, the introduction of the 9-valent vaccine might have more of an effect on reducing cervical cancer risk. Girls born in FY 2007 or later can receive the 9-valent vaccine during the period of the target age for routine vaccination. The effect is particularly large for girls born in FY 2009 or later. If an HPV vaccination rate of 60% with the 9-valent vaccine is reached by FY 2024, the cervical cancer risk will be lower than the control risk for those born in FY 1998 who received the bivalent and quadrivalent vaccines.

We now need to come to terms with the reality that HPV vaccination rates have plummeted to crisis levels in Japan due to policy decisions made based on fear and weak evidence. Those decisions, and the needlessly prolonged delay in their reversal, have already caused real harm to females in the vaccine-suspension generation, who could have been protected by routine vaccination.[17,18]

Future measures against cervical cancer will need to be fine-tuned depending on the circumstances of each local government. At the national level, the Japanese Government needs to look back on its vaccine administration failures and build a future system that will not repeat those mistakes.

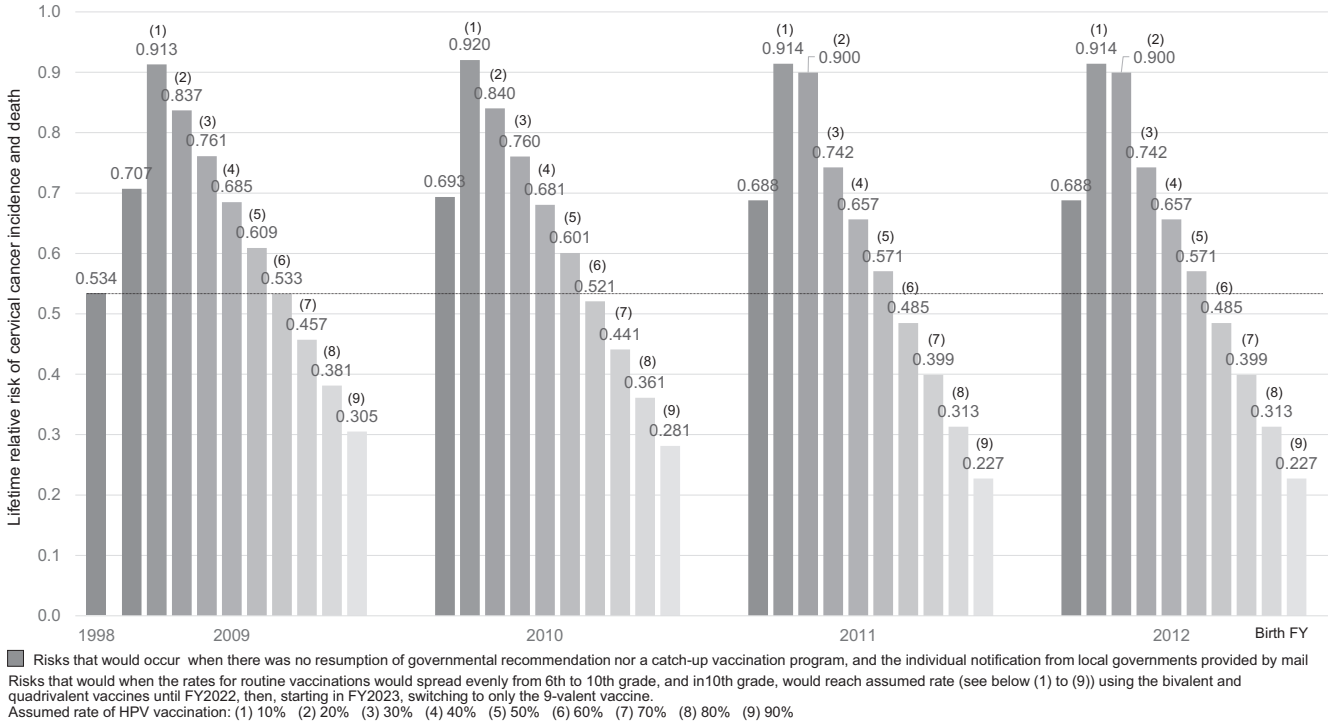


FIGURE 7 Scenario (4): Lifetime relative risk of cervical cancer incidence and death when the vaccination rates of routine vaccination are spread evenly from 6th to 10th grade, reached an assumed rate in 10th grade, and bivalent and quadrivalent vaccines were used until FY 2022; then the 9-valent vaccine was used from FY 2023 forward. FY, fiscal year.

AUTHOR CONTRIBUTIONS

Asami Yagi: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; validation; writing – original draft; writing – review and editing. **Satoshi Nakagawa:** Methodology; validation. **Yutaka Ueda:** Conceptualization; funding acquisition; supervision; writing – review and editing. **Emiko Oka:** Validation. **Sayaka Ikeda:** Validation. **Mamoru Kakuda:** Validation. **Eiji Kobayashi:** Validation. **Yuri Ito:** Methodology; validation. **Kayoko Katayama:** Methodology; validation. **Kei Hirai:** Conceptualization; validation. **Tomio Nakayama:** Conceptualization; validation. **Tadashi Kimura:** Conceptualization; supervision.

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CONFLICT OF INTEREST STATEMENT

AY and YU received a lecture fee from Merck Sharp and Dohme (MSD). The remaining authors do not have competing interests to declare.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

Approval of the research protocol by an Institutional Reviewer Board: This study was approved by the Ethics Committee of the Osaka University Hospital.

Informed Consent: N/A.

Registry and Registration No. of the study/trial: N/A.

Animal Studies: N/A.

ORCID

Asami Yagi https://orcid.org/0000-0002-3222-5963
Sayaka Ikeda https://orcid.org/0000-0001-7948-8990
Yuri Ito https://orcid.org/0000-0002-1407-2393
Tomio Nakayama https://orcid.org/0000-0002-3354-5096

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209-249.
2. World Health Organization. Cervical cancer. Accessed June 17, 2023. https://www.who.int/health-topics/cervical-cancer#tab=tab_1
3. Yagi A, Ueda Y, Kakuda M, et al. Epidemiologic and clinical analysis of cervical cancer using data from the population-based Osaka cancer registry. *Cancer Res*. 2019;79:1252-1259.
4. Tanaka S, Palmer M, Katanoda K. Trends in cervical cancer incidence and mortality of young and middle adults in Japan. *Cancer Sci*. 2022;113:1801-1807.
5. Tanaka Y, Ueda Y, Egawa-Takata T, Yagi A, Yoshino K, Kimura T. Outcomes for girls without HPV vaccination in Japan. *Lancet Oncol*. 2016;17:868-869.

6. Simms KT, Hanley SJB, Smith MA, Keane A, Canfell K. Impact of HPV vaccine hesitancy on cervical cancer in Japan: a modelling study. *Lancet Public Health*. 2020;5:e223-e234.
7. World Health Organization. Global Advisory Committee on Vaccine Safety Statement on Safety of HPV vaccines 17 December 2015.
8. Ministry of Health, Labour and Welfare. The 23rd Welfare Science Council Vaccination and Vaccine Subcommittee Side-Reaction Study Group. 2016. Accessed June 17, 2023. https://www.mhlw.go.jp/file/05-Shingikai-10601000-Daijinkanboukouseikagakuka-Kouseikagakuka/0000147016.pdf
9. Ministry of Health, Labour and Welfare. The 72nd Welfare Science Council Vaccination and Vaccine Subcommittee Side-Reaction Study Group. 2021. Accessed June 17, 2023. https://www.mhlw.go.jp/content/10601000/000853334.pdf
10. Nakagawa S, Ueda Y, Yagi A, Ikeda S, Hiramatsu K, Kimura T. Corrected human papillomavirus vaccination rates for each birth fiscal year in Japan. *Cancer Sci*. 2020;111:2156-2162.
11. Ministry of Health, Labour and Welfare. The 26th welfare science council vaccination and vaccine subcommittee side-reaction study group. 2021. Accessed June 17, 2023. https://www.mhlw.go.jp/content/10601000/000854570.pdf (In Japanese).
12. Yagi A, Ueda Y, Nakagawa S, et al. Can catch-up vaccinations fill the void left by suspension of the governmental recommendation of HPV vaccine in Japan? *Vaccines (Basel)*. 2022;10:1455.
13. Ministry of Health, Labour and Welfare. Report on regional public health services and health promotion services. Accessed June 17, 2023. https://www.e-stat.go.jp/ (In Japanese).
14. 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.
15. Kitamura K. The 5th survey on life and consciousness of men and women. *J Contemp Sex Educ*. 2011;7:1-6.
16. 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.
17. Sekine M, Yamaguchi M, Kudo R, et al. Suspension of proactive recommendations for HPV vaccination has led to a significant increase in HPV infection rates in young Japanese women: real-world data. *Lancet Reg Health West Pac*. 2021;16:100300.
18. Yagi A, Ueda Y, Ikeda S, et al. The looming health hazard: a wave of HPV-related cancers in Japan is becoming a reality due to the continued suspension of the governmental recommendation of HPV vaccine. *Lancet Reg Health West Pac*. 2021;18:100327.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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