Effectiveness of HPV vaccination against the development of high grade cervical lesions in young Japanese women

Yuki Shiko
Chiba University Hospital
Ryo Konno (kryo772007@yahoo.co.jp)
https://orcid.org/0000-0002-9403-1339
Hiroshi Konishi
Japan Cancer Society
Catherine Sauvaget
International Agency for Research on Cancer
Yasuo Ohashi
Chuo University
Tadao Kakizoe
Japan Cancer Society

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Abstract

Background Although more than 8 years have passed since HPV vaccination was implemented first, as an interim programme (Emergent vaccine promotion programme) in November 2010, followed by incorporating into the National Immunization Programme in April, 2013 and suspended in June 2013, limited studies have investigated the HPV vaccine effectiveness against high-grade cervical lesions in Japan.

Methods We collected the matched data of the results of cervical biopsy and history of vaccination from the Japan Cancer Society database. The subjects were women aged 20 to 29 years screened for cervical cancer between April, 2015 and March, 2017, and with information on HPV vaccination status. We estimated the relative risk of developing high-grade cervical lesions in a vaccinated group using Poisson regression as compared to an unvaccinated group.

Results Among the 34,281 women screened, 3,770 (11.0%) were vaccinated. The prevalence of CIN2+ was significant lower in the vaccinated women as compared to the unvaccinated women (Vaccine Effectiveness (VE) =76%; RR=0.24, 95% CI:0.10-0.60). High VE against CIN3+ was also observed (91%; RR=0.09, 95% CI:0.00-0.42).

Conclusion Women aged 20–29 years who received at least one dose of HPV vaccine had a significantly lower risk of high-grade cervical lesions than those not vaccinated. In Japan, HPV vaccination should be resumed in order to reduce the incidence of cervical cancer.

Background

The incidence rate of cervical cancer in developed countries is lower than that in developing countries. However, the estimated age-standardized incidence rate of cervical cancer in Japan is higher than other developed countries (14.7 per 10^5 person-years in Japan; 6.5 in USA; 8.4 in UK) [1], but it is comparable to that in low- and middle-income countries such as India (14.7) or in The Philippines (14.9) [1]. Moreover, the age-standardized mortality rate is also higher than the rates of countries of similar economical level (2.7 per 10^5 person-years in Japan; 1.9 in USA; 1.7 in UK) [1].

Persistent infection with human papillomavirus (HPV) can cause cervical lesions and cervical cancer [2, 3], while high efficacy of HPV vaccine has been demonstrated in clinical trials [4-7]. Bivalent, quadrivalent and nonavalent HPV vaccines are incorporated into National Immunization Programmes (NIPs) and they had already been introduced in 96

countries by June 2019 [8]. The nonavalent vaccine that can prevent infection by 90% of the oncogenic HPV strains has not yet been approved in Japan.

The Bivalent vaccine was licensed in Japan in October 2009, and an interim national programme (Emergent vaccine promotion programme) started in November 2010, followed by inclusion in the NIP and given for free to girls aged 12-16 years old from April 2013. However, after numerous media reports on adverse events following HPV vaccination [9], the Japanese Ministry of Health, Labor and Welfare (MHLW) suspended proactive recommendation for the vaccine in June 2013 as a precautionary measure [10]. Although a recent epidemiological study from a Japanese team reported that there was no causal association between the vaccine and reported symptoms or adverse events [11], MHLW is persisting in suspending the HPV vaccine proactive recommendation. If this suspension continues, both incidence and death rates from cervical cancer are likely to continue rising [12].

Numerous clinical trials [4-7] and epidemiological studies [13-19] showed strong efficacy and effectiveness of HPV vaccine. In Japan, years have passed since HPV vaccine started as an interim national programme, adolescent girls who have received the public HPV vaccine have attained the age of 20 years or older; 20 years old being the starting target age of the cervical cancer screening programme. Several studies reported the vaccine effectiveness against cervical cytological abnormalities [20, 21]. Our earlier study investigated 22,743 women who were screened for cervical cancer between April, 2015 and March, 2016. The vaccine effectiveness against histologically confirmed high-grade cervical lesions, CIN 2 or worse (CIN2+) was 71%, but CIN3+ could not be considered due to the limited sample size [22]. Because of the lack of national vaccine registry and national screening registry in Japan, we cannot use the national database in order to evaluate the vaccine effectiveness in the “real world”. In place of the national database, we used the maximum official data available as possible as in current Japan. We conducted the present study to investigate the effectiveness of HPV vaccine against histologically confirmed high-grade cervical lesions (CIN2+, CIN3+) in young women aged 20 to 29 years who underwent cervical cancer screening between April, 2015 and March, 2017.

Methods

Data sources

The Japan Cancer Society (JCS) with 46 branches among 47 prefectures nationwide, is the Japan's largest cancer screening organization, screening more than 11 million people every year. Some branches collect information on vaccination history, results of screening (cytology and if biopsy done, pathological results) and grade of cervical lesion. Pathological diagnosis is reported according to the WHO 2014 classification [23] and CIN classification. Women fill a self-reported questionnaire with information on vaccination history at the time of cervical cancer screening. In the present study, we collected the data from 26 branches of JCS. Among 26 branches, the 7 branches that did not inquire about vaccination history at screening were excluded. The study subjects were women aged 20 to 29 years who underwent cervical cancer screening in the FY 2015 (April 2015 to March 2016) and FY2016 (April 2016 to March 2017). We defined women who received at least one dose of HPV vaccine as vaccinated. The study outcomes are histologically confirmed diagnosis of CIN2 or worse (CIN2+) and CIN3 or worse (CIN3+).

Statistical analyses

The analysis was performed in two parts. In the first analysis, to evaluate the effectiveness of HPV vaccine against the high-grade precursor lesions of cervical cancer (CIN2+, CIN3+) for aged 20-29 and 20-22, we estimated the relative risk (RR) and associated 95% confidence interval (CI) for vaccinated group using Poisson regression as compared to the unvaccinated group. We adjusted for age as fixed effect and JCS branches as random effect. For CIN3+, RR and associated 95% CIs were estimated using exact Poisson regression for aged 20-29. Vaccine effectiveness (VE) was calculated as: (1-adjusted relative risk) × 100.

In the MHLW guidelines, the recommended screening interval of cervical cancer is 2 years; actually, however, the intervals of screening vary depending on the local governments responsible of the cancer screening organization. Therefore, some women might have undergone cervical cancer screening in both FY2015 and FY2016, i.e. within less than the 2-year interval of the recommended national guidelines. We defined this fact as “overlapping”. Therefore, a sensitivity analysis was performed after removing this overlapping in FY2016 (3024 women (15.6%) screened in both FY2015 and FY2016). Statistical analyses were performed using the SAS statistical software package, Version 9.4 (SAS Institute, Cary, NC, USA).

Results

The characteristics of the subjects are shown in Table1. Among the 37,305 women aged 20-29 years, 4,083 (10.9%) were vaccinated. The vaccination rates of 20 and 21 years who correspond to an interim national vaccination recipient were high at 62.7% and 44.6%, respectively, and 2.6% to 7.9% after 24 years. In the vaccinated group, the total number of cases of CIN2+ was only 7 (0.17%) with no CIN3+. In the unvaccinated group, the cases of CIN2+ and CIN3+ were 188 (0.57%) and 78 (0.23%), respectively.

After removal of overlapping, we included 34,281 women in the analyses (Table2). In the vaccinated group, the cases of CIN2+ were 5 (0.13%) and no CIN3+. In the unvaccinated group, the cases of CIN2+ and CIN3+ were 182 (0.59%) and 77 (0.25%), respectively.

The relative risk of developing high-grade cervical lesions according to the vaccination status is shown in Table3. Vaccine effectiveness against CIN2+ and CIN3+ was 67% (RR=0.33, 95% CI=0.15-0.73) and 91% (RR=0.09, 95% CI=0.00-0.41), respectively. High vaccine effectiveness against CIN2+ was also observed for those aged 20-22 years old (VE=77%; RR=0.23, 95% CI=0.06-0.82).

In the sensitivity analysis (without overlapping), the vaccine effectiveness against CIN2+ and CIN3+ in the age-group 20-29 was 76% (RR=0.24, 95% CI=0.10-0.60) and 91%

(RR=0.09, 95% CI=0.00-0.42), respectively. Vaccine effectiveness against CIN2+ was also observed for those aged 20-22 years old (VE=76%; RR=0.24, 95% CI=0.10-0.60). The effect of age was not significant in all analyses.

Discussion

In the present study, we compared the prevalence of histology confirmed high-grade cervical abnormalities (CIN2+, CIN3+) between an HPV-vaccinated group and unvaccinated group. As a result, the risk of high-grade cervical abnormalities was significantly lower in the vaccinated group as compared to the unvaccinated group.

Population-based studies are also conducted in many countries [13-19]. In Scotland, the risk for CIN3+ following bivalent vaccine at age 20 years was reduced by 86% in women who were vaccinated at the age of 12-13 years old [19]. In Sweden, the risk for CIN2+ and CIN3+ following quadrivalent vaccine was reduced by 75% and 84% in women who were vaccinated before the age of 16 years old [14]. These results were based on vaccination in women with 3 doses [14, 17], while our results were based on vaccination with at least one dose, because we did not have information on the number of doses. Several studies focused on the effectiveness of the number of doses received on CIN occurrence [24, 25]. In a case-control study from Australia, vaccine effectiveness for CIN2+ was observed in both 2- and 3-dose recipients (VE=46% in the 3-dose recipients, VE=21% in the 2-dose recipients) [25]. In the database linkage study from Australia, the vaccine effectiveness against high-grade was observed in the 3-dose recipients (hazard ratio=0.86, 95% CI: 0.78-0.94) and, women who were vaccinated before the age of 16 years old, trends of effectiveness were observed in less than 3-dose recipients [24]. A recent publication from India reported a rate of CIN1+ of 4.5% (5/132) in unvaccinated group, while there were no case (0/24) in vaccinated women (2- and 3-dose) [26]. These studies suggest that less than 3-dose regimens of HPV vaccine are effective against CIN.

In the recent reports from Denmark and Australia (with high coverage), one-dose regimen showed similar effectiveness than 3-dose regimen [27, 28].

Considering the results of these studies, it is reasonable to support that high effectiveness of vaccine was observed in the present study (although coverage was not so high). Moreover, distribution of HPV sub-types in Japanese women is also associated with high effectiveness in the present study. A previous study reported that prevalence of HPV-16/18 varied in accordance with age, prevalence of HPV-16/18 was highest in those aged 20-29 (53.8% and 90% in patients with CIN2/3 and cervical cancer, respectively) [29]. The HPV type distribution in Japanese women aged 20-25 enrolled in a clinical trial showed that HPV-16 was often found in HSIL cases (57.1%, 4/7) and CIN2+ cases (83.3%, 5/6) [30]. In short, detection rate of HPV-16/18 is high in young Japanese women, vaccination against HPV-16/18 is therefore considerably effective to prevent cervical cancer [31].

Several limitations of this study should be acknowledged. First, HPV vaccination status is self-reported and may be affected by recall bias. Japan has neither national vaccine registry nor national screening registry. Therefore, it is difficult to collect history of vaccination and screening results of individuals, and to link these data is even more difficult [32]. Deployment of the epidemiological surveillance at the national level is one of the most important challenges in the public health policy in Japan. Second, because screening uptake of cervical cancer in Japan is low, representativeness cannot be guaranteed, however we collected the linked data of 37,505 women, this is the largest study ever in Japan. Previous studies were based on limited sample size, and on cytology results solely [20, 21]. Our previous study using the data of 22,743 women from JCS showed the effectiveness of the vaccine against CIN2 + only [22]. This time, we can report the high effectiveness of vaccine against both CIN2+ and CIN3+.

In Japan, MHLW suspended proactive recommendation for the vaccine, as a result, uptake rate for HPV vaccine was plummeted from 70 percent to 0.3 percent [10]. Evidence of effectiveness and safety of vaccine has been accumulated, the recommendations have not yet been resumed. Additionally, screening uptake of cervical cancer younger than 30 is considerably low. Therefore, incidence rate is increasing especially among Japanese women aged 20-29 years old (5.1% per year between 1985 to 2012) [33].

In Ireland, uptake rate for HPV vaccine has also declined due to concerns about vaccine safety, however the uptake rate has recovered owing to efforts such as social media and governmental campaigns [34]. Since cervical cancer is a preventable disease [35], it is important to take steps to improve the HPV vaccination uptake rate in order to discontinue the increase in incidence and mortality from cervical cancer.

Conclusions

We showed the high vaccine effectiveness against high-grade cervical lesions in Japanese young women. We hope that HPV vaccination will be recommended actively again, therefore incidence and mortality rates from cervical cancer will stop increasing and will eventually decline.

Abbreviations

CIN: Cervical Intraepithelial Neoplasia; HPV: Human papillomavirus; HSIL: high-grade squamous intraepithelial lesion; JCS: The Japan Cancer Society; MHLW: Ministry of Health, Labor and Welfare; NIP: National Immunization Programme; VE: Vaccine Effectiveness.

Declarations

Ethics approval and consent to participate

Not applicable.

The appropriate research ethics committee granted an exemption of the requirement for ethics review, and deemed that informed consent was not required because the analysis used anonymized records from a pre-existing database (Japan Cancer Society).

Consent to Publish

All authors consented to publish.

Availability of data and materials

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

Competing interests

RK reports his personal lecture fee from Chugai Pharmaceuticals, Japan Vaccine Co Ltd, MSD, Mochida Co Ltd, Roche Diagnostics and BD, and grant for his institute from Chugai Pharmaceuticals, outside the submitted work. He is the Director of the Executive Board Members of the Japanese Expert Board for the Eradication of Cervical Cancer, which has received funding from Qiagen, MSD, Chugai Pharmaceuticals and GlaxoSmithKline, outside the submitted work. The other authors declare that they have no competing interests. YO reports personal fees from Statcom, personal fees from Sanofi, grants and personal fees from Eisai, personal fees from Chugai, personal fees from Taiho, personal fees from Shionogi, personal fees from Kowa, non-financial support from Yakult Honsha, non-financial support from Takeda, personal fees from Public Health Research Foundation, personal fees from Daiicchi-Sankyo, outside the submitted work. Those personal fees and funding have no influence on the manuscript. HK, CS and TK declare no competing of interests.

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Authors' contributions

YS analyzed the data and wrote the initial draft of the manuscript. RK conducted the study, RK, YO and CS contributed to the interpretation of data, and assisted in the preparation of the manuscript. HK and TK contributed to data collection and interpretation. All authors critically reviewed the manuscript. All authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Disclaimer

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References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M *et al*. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86. https://doi.org/10.1002/ijc.29210
2. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV *et al*. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189(1):12-9. https://doi.org/10.1002/(sici)1096-9896(199909)189:1%3C

12::aid-path431%3E3.0.co;2-f

3. zur Hausen H. Papillomaviruses in human cancer. Applied pathology. 1987;5(1):19-24. PubMed PMID: 3040050.
4. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med. 2007;356(19):1915-27.

https://doi.org/10.1056/nejmoa061741

5. Huh WK, Joura EA, Giuliano AR, Iversen OE, de Andrade RP, Ault KA *et al*. Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16-26 years: a randomised, double-blind trial. Lancet (London, England). 2017;390(10108):2143-59. https://doi.org/10.1016/s0140-6736(17)31821-4
6. Munoz N, Manalastas R, Jr., Pitisuttithum P, Tresukosol D, Monsonego J, Ault K *et al*. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24-45 years: a randomised, double-blind trial. Lancet (London, England). 2009;373(9679):1949-57.

https://doi.org/10.1016/s0140-6736(09)60691-7

7. Paavonen J, Naud P, Salmeron J, Wheeler CM, Chow SN, Apter D *et al*. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet (London, England). 2009;374(9686):301-14. https://doi.org/10.1016/s0140-6736(09)61248-4
8. Immunization, Vaccines and Biologicals. World Health Organization. https://www.who.int/immunization/monitoring_surveillance/en/. Accessed 20 Feb 2018.
9. Tsuda K, Yamamoto K, Leppold C, Tanimoto T, Kusumi E, Komatsu T *et al*. Trends of Media Coverage on Human Papillomavirus Vaccination in Japanese Newspapers. Clin Infect Dis. 2016;63(12):1634-8. https://doi.org/10.1093/cid/ciw647
10. Ministry of Health Labour and Welfare and Demographic and Health Statistics

    Division. Municipalities survey 2014. Tokyo. http://www.mhlw.go.jp/topics/bcg/other/5.html. Accessed 20 Feb 2019.

11. Suzuki S, Hosono A. No association between HPV vaccine and reported post-vaccination symptoms in Japanese young women: Results of the Nagoya study. Papillomavirus Res. 2018;5:96-103. https://doi.org/10.1016/j.pvr.2018.02.002
12. Simms KT, Steinberg J, Caruana M, Smith MA, Lew JB, Soerjomataram I *et al*. Impact of scaled up human papillomavirus vaccination and cervical screening and the potential for global elimination of

cervical cancer in 181 countries, 2020-99: a modelling study. Lancet Oncol. 2019;20(3):394-407. https://doi.org/10.1016/s1470-2045(18)30836-2

13. Brotherton JM, Gertig DM, May C, Chappell G, Saville M. HPV vaccine impact in Australian women: ready for an HPV-based screening program. Med J Aust. 2016;204(5):184-e1. https://doi.org/10.5694/mja15.01038
14. Herweijer E, Sundstrom K, Ploner A, Uhnoo I, Sparen P, Arnheim-Dahlstrom L. Quadrivalent HPV vaccine effectiveness against high-grade cervical lesions by age at vaccination: A population-based study. Int J Cancer. 2016;138(12):2867-74.

https://doi.org/10.1002/ijc.30035

15. Markowitz LE, Liu G, Hariri S, Steinau M, Dunne EF, Unger ER. Prevalence of HPV After Introduction of the Vaccination Program in the United States. Pediatrics. 2016;137(3):e20151968. https://doi.org/10.1542/peds.2015-1968
16. Mesher D, Soldan K, Howell-Jones R, Panwar K, Manyenga P, Jit M *et al*. Reduction in HPV 16/18 prevalence in sexually active young women following the introduction of HPV immunisation in England. Vaccine. 2013;32(1):26-32.

https://doi.org/10.1016/j.vaccine.2013.10.085

17. Pollock KG, Kavanagh K, Potts A, Love J, Cuschieri K, Cubie H *et al*. Reduction of low- and high-grade cervical abnormalities associated with high uptake of the HPV bivalent vaccine in Scotland. Br J Cancer. 2014;111(9):1824-30.

https://doi.org/10.1038/bjc.2014.479

18. Tabrizi SN, Brotherton JM, Kaldor JM, Skinner SR, Liu B, Bateson D *et al*. Assessment of herd immunity and cross-protection after a human papillomavirus vaccination programme in Australia: a repeat cross-sectional study. Lancet Infect Dis. 2014;14(10):958-66.
19. Palmer T, Wallace L, Pollock KG, Cuschieri K, Robertson C, Kavanagh K *et al*. Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study. BMJ. 2019;365:l1161. https://doi.org/10.1136/bmj.l1161
20. Ozawa N, Ito K, Tase T, Metoki H, Yaegashi N. Beneficial Effects of Human Papillomavirus Vaccine for Prevention of Cervical Abnormalities in Miyagi, Japan. Tohoku J Exp Med. 2016;240(2):147-51. https://doi.org/10.1620/tjem.240.147
21. Tanaka H, Shirasawa H, Shimizu D, Sato N, Ooyama N, Takahashi O *et al*. Preventive effect of human papillomavirus vaccination on the development of uterine cervical lesions in young Japanese women. J Obstet Gynaecol Res. 2017;43(10):1597-601. https://doi.org/10.1111/jog.13419
22. Konno R, Konishi H, Sauvaget C, Ohashi Y, Kakizoe T. Effectiveness of HPV vaccination against high grade cervical lesions in Japan. Vaccine. 2018;36(52):7913-5. https://doi.org/10.1016/j.vaccine.2018.05.048

23. R.J.Kurman, M.L.Carcangiu, C.S.Herrington, Young RH. WHO Classification of Tumours of Female Reproductive Organs, 4th ed.: IARC; 2014.
24. Brotherton JML, Malloy M, Budd AC, Saville M, Drennan KT, Gertig DM. Effectiveness of less than three doses of quadrivalent human papillomavirus vaccine against cervical intraepithelial neoplasia when administered using a standard dose spacing schedule: Observational cohort of young women in Australia. Papillomavirus Res. 2015;1:59-73. https://doi.org/10.1016/j.pvr.2015.05.005
25. Crowe E, Pandeya N, Brotherton JM, Dobson AJ, Kisely S, Lambert SB *et al*. Effectiveness of quadrivalent human papillomavirus vaccine for the prevention of cervical abnormalities: case-control study nested within a population based screening programme in Australia. BMJ. 2014;348:g1458. https://doi.org/10.1136/bmj.g1458
26. Basu P, Muwonge R, Bhatla N, Nene BM, Joshi S, Esmy PO *et al*. Two-dose recommendation for Human Papillomavirus vaccine can be extended up to 18 years - updated evidence from Indian follow-up cohort study. Papillomavirus Res. 2019;7:75-81. https://doi.org/10.1016/j.pvr.2019.01.004
27. Brotherton JM, Budd A, Rompotis C, Bartlett N, Malloy MJ, Andersen RL *et al*. Is one dose of human papillomavirus vaccine as effective as three?: A national cohort analysis. Papillomavirus Res. 2019;8:100177.

    https://doi.org/10.1016/j.pvr.2019.100177 [Epub ahead of print]

28. Verdoodt F, Dehlendorff C, Kjaer SK. Dose-related effectiveness of quadrivalent human papillomavirus vaccine against cervical intraepithelial neoplasia: A Danish nationwide cohort study. Clin Infect Dis.2019.https://doi.org/10.1093/cid/ciz239 [Epub ahead of print]
29. Onuki M, Matsumoto K, Satoh T, Oki A, Okada S, Minaguchi T *et al*. Human papillomavirus infections among Japanese women: age-related prevalence and type-specific risk for cervical cancer. Cancer Sci. 2009;100(7):1312-6.

    https://doi.org/10.1111/j.1349-7006.2009.01161.x

30. Konno R, Tamura S, Dobbelaere K, Yoshikawa H. Prevalence and type distribution of human papillomavirus in healthy Japanese women aged 20 to 25 years old enrolled in a clinical study. Cancer Sci. 2011;102(4):877-82. https://doi.org/10.1111/j.1349-7006.2011.01878.x
31. Konno R, Yoshikawa H, Okutani M, Quint W, P VS, Lin L *et al*. Efficacy of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical intraepithelial neoplasia and cervical infection in young Japanese women. Hum Vaccin Immunother. 2014;10(7):1781-94. https://doi.org/10.4161/hv.28712
32. Sauvaget C, Nishino Y, Konno R, Tase T, Morimoto T, Hisamichi S. Challenges in breast and cervical cancer control in Japan. The Lancet Oncology. 2016;17(7):e305-e12. https://doi.org/10.1016/s1470-2045(16)30121-8
33. Utada M, Chernyavskiy P, Lee WJ, Franceschi S, Sauvaget C, de Gonzalez AB *et al*. Increasing risk of uterine cervical cancer among young Japanese women: Comparison of incidence trends in Japan,

South Korea and Japanese-Americans between 1985 and 2012. Int J Cancer. 2019;144(9):2144-52. https://doi.org/10.1002/ijc.32014

34. Corcoran B, Clarke A, Barrett T. Rapid response to HPV vaccination crisis in Ireland. Lancet (London, England). 2018;391(10135):2103. https://doi.org/10.1016/s0140-6736(18)30854-7

35. WHO Director-General calls for all countries to take action to help end the suffering caused by cervical cancer. https://www.who.int/reproductivehealth/call-to-action-elimination-cervical-cancer/en/ Accessed 25 July 2019.

Tables

Table1 Information on vaccination status, CIN2+, CIN3+, among women aged 20-29 years (with overlapping)

Age at screening (year)	Vaccine(-)	Vaccine(+)		CIN2+		CIN3+	
				Vaccine(-)	Vaccine(+)	Vaccine(-)	Vaccine(+)
	n	n	%	n	n	n	n
20	522	878	62.7	4	1	1	0
21	1,860	1,496	44.6	6	1	3	0
22	1,569	489	23.8	8	1	2	0
23	2,517	217	7.9	17	1	8	0
24	2,985	214	6.7	11	1	4	0
25	3,035	149	4.7	17	0	6	0
26	5,367	189	3.4	34	1	14	0
27	3,849	128	3.2	20	0	7	0
28	6,820	184	2.6	50	0	22	0
29	4,698	139	2.9	21	1	11	0
Total	33,222	4,083	10.9	188	7	78	0

Table2 Vaccination status, CIN2+, CIN3+, among women aged 20-29 years (without overlapping)

Age at screening (year)	Vaccine(-)	Vaccine(+)		CIN2+		CIN3+	
				Vaccine(-)	Vaccine(+)	Vaccine(-)	Vaccine(+)
	n	n	%	n	n	n	n
20	514	869	62.8	4	1	1	0
21	1,822	1,436	44.1	5	1	3	0
22	1,435	399	21.8	8	0	2	0
23	2,367	197	7.7	17	1	8	0
24	2,710	189	6.5	11	1	4	0
25	2,740	115	4.0	17	0	6	0
26	4,998	175	3.4	33	1	14	0
27	3,428	108	3.1	20	0	7	0
28	6,354	165	2.5	48	0	22	0
29	4,143	117	2.8	19	0	10	0
Total	30,511	3,770	11.0	182	5	77	0

Table3. Relative risk of developing CIN2+ or CIN3+ lesions among vaccinated women as compared to the unvaccinated women

	CIN2+			CIN3+		
	RR(95%CI)		P-value	RR(95%CI)		P-value
Aged 20-29						
Unvaccinated	1.00	Reference		1.00	Reference	
Vaccinated	0.33	(0.15 , 0.73)	0.006	0.09	(0.00 , 0.41)	0.002
Age	1.04	(0.98 , 1.10)	0.233	1.06	(0.00 , 1.17)	0.246
Aged 20-29 (no overlapping)						
Unvaccinated	1.00	Reference		1.00	Reference	
Vaccinated	0.24	(0.10 , 0.60)	0.003	0.09	(0.00 , 0.42)	0.002
Age	1.03	(0.97 , 1.09)	0.360	1.06	(0.96 , 1.17)	0.246
Aged 20-22						
Unvaccinated	1.00	Reference				
Vaccinated	0.23	(0.06 , 0.81)	0.023			
Age	0.95	(0.51 , 1.76)	0.869			
Aged 20-22(no overlapping)						
Unvaccinated	1.00	Reference				
Vaccinated	0.24	(0.10 , 0.60)	0.003			
Age	1.03	(0.97 , 1.09)	0.306			