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SHORT REPORT

Realistic fear of cervical cancer risk in Japan depending on birth year

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ABSTRACT

Objective: In Japan, the possible adverse events upon HPV vaccination was widely reported in the media. MHLW announced the suspension of aggressively encouraging HPV vaccination in 2013, and inoculation rate has sharply declined. The aim of the present study was estimation of future cervical cancer risk.

Methods: The latest data on vaccination rate at each age in Sakai City were first investigated. The rate of experiencing sexual intercourse at the age of 12, 13, 14, 15, 16, 17 and throughout lifetime is assumed to be 0%, 1%, 2%, 5%, 15%, 25%, and 85% respectively. The cervical cancer risk was regarded to be proportional to the relative risk of HPV infection over the lifetime. The risk in those born in 1993 whom HPV vaccination was not available yet for was defined to be 1.0000.

Results: The cumulative vaccination rates were 65.8% in those born in 1994, 72.7% in 1995, 72.8% in 1996, 75.7% in 1997, 75.0% in 1998, 66.8% in 1999, 4.1% in 2000, 1.5% in 2001, 0.1% in 2002, and 0.1% in 2003. The relative cervical cancer risk in those born in 1994–1999 was reduced to 0.56–0.70, however, the rate in those born in 2000–2003 was 0.98–1.0, almost the same risk as before introduction of the vaccine.

Discussion: The cumulative initial vaccination rates were different by the year of birth. It is confirmed that the risk of future cervical cancer differs in accordance with the year of birth. For these females, cervical cancer screening should be recommended more strongly.

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Introduction

Worldwide, the frequency and the death rate of cervical cancer are the fourth highest among female cancers,[1] with estimated 530,000 people newly contracting this disease in 2012, making up 7.5% of cancer deaths among women.[2] In the United States, the estimated number of new cases of cervical cancer in 2016 is 12,900, with 4,120 of these cases leading to death.[3]

Most cervical cancers are known to be caused by persistent infection with human papillomavirus (HPV) including HPV types 16 and 18. While cervical cancers caused by HPV-16 and 18 infection are preventable with vaccination, the inoculation rate varies depending on the country[4] and remains low despite recommendation by the Centers for Disease Control and Prevention (CDC) in the United States. With regard to this, the American Society of Clinical Oncology (ASCO) has announced that the ASCO strongly supports efforts to markedly increase the proportion of boys and girls receiving the HPV vaccine in the United States and worldwide.[5] According to several studies, the obstacles to vaccination involve multiple possible factors, such as safety concerns about the vaccine, a lack of clear recommendations from health care providers, etc.[5] The issue of adverse events,

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although not markedly different from those of other vaccines, has made this problem worse worldwide.[6]

In Japan, the HPV vaccine was approved in 2009, after which an urgent promotion project for vaccination was initiated by the Ministry of Health, Labor and Welfare (MHLW) in 2010. HPV vaccinations were provided free of charge or at low cost for 13 to 16-year-old girls. From April 2013, periodical vaccination of 12 to 16-year-old girls was initiated, typically for 12-year-old girls. However, the occurrence of so-called serious adverse events upon HPV vaccination after initiating periodical vaccinations was widely reported in the media and a picture of a patient who exhibited symptoms was repeatedly broadcast. As a consequence, MHLW decided for the "suspension of aggressively encouraging vaccination" in June 2013.[7] As a result of this determination, the inoculation rate has sharply declined.[8]

Hanley et al. reported that, after the suspension of the governmental recommendation, the completion rate of HPV vaccination plummeted to just 0.6% in Sapporo, Japan in 2014[9]. Sekine et al. reported that the vaccination rates of the 12 to 16-year-olds in Niigata City, Japan, in 2014 and 2015 were 3.5% and 0.19% respectively.[10] The news of Japan's suspension of the HPV vaccine recommendation has traveled globally through online media and social media networks, being applauded by anti-vaccination groups but not by the global scientific community. Larson HJ described that the longer the uncertainty around the Japanese HPV vaccine recommendation persists, the further the public concerns are likely to travel.[11] The World Health Organization (WHO) stated that policy decisions based on weak evidence, leading to lack of use of safe and effective vaccines, can result in real harm.[12]

Cervical cancer patients number 8,000 people a year in Japan, and 3,500 die per year.[13] Furthermore, a marked increase in the incidence rate of cervical cancer in 20 to 49-year-olds has been seen.[13,14] This is assumed to be a result of a decline in the age of initial incidence of HPV infection due to a decline in the age of first sexual intercourse, in addition to low screening rate. Among 22 developed countries, the cervical cancer screening rate in Japan is the lowest at 37.7%, compared with that of 85.0% in the United States and more than 65.0% in all European countries.[15] A greater decline in cervical cancer screening rate is observed in young women and is 10.2% in 20 to 25-year-olds in Japan.[16] Although the WHO points out that the benefit of HPV vaccine is particularly great in countries having a low cervical cancer screening rate.[12]

We previously predicted that if aggressive encouragement of vaccination were not resumed going forward, the significant difference in the HPV infection rate would be observed according to the year of birth, and it would vary significantly in accordance with the year of restart of the governmental recommendation, using an assumed inoculation rate.[17] In the previous study, all female children were hypothesized to be vaccinated at the youngest targeted age. However, all the girls did not undergo vaccination at the youngest targeted age in practice. Moreover, the most serious public and medical concern should be future cervical cancer risk caused by infection of HPV without vaccination. The lifetime risk of cervical cancer does not correlate with the risk of HPV-16 and 18 infection at the age of 20. The aim of the present study was estimation of the lifetime cervical cancer risk by the year of birth, based on the latest real data on vaccination rate.

Results and discussion

Figure 1 shows the vaccination rate and the resulting change in cervical cancer relative risk that could actually occur in the future and was already being determined, confirming that our previous prediction is now becoming a reality and severity. Figure 2

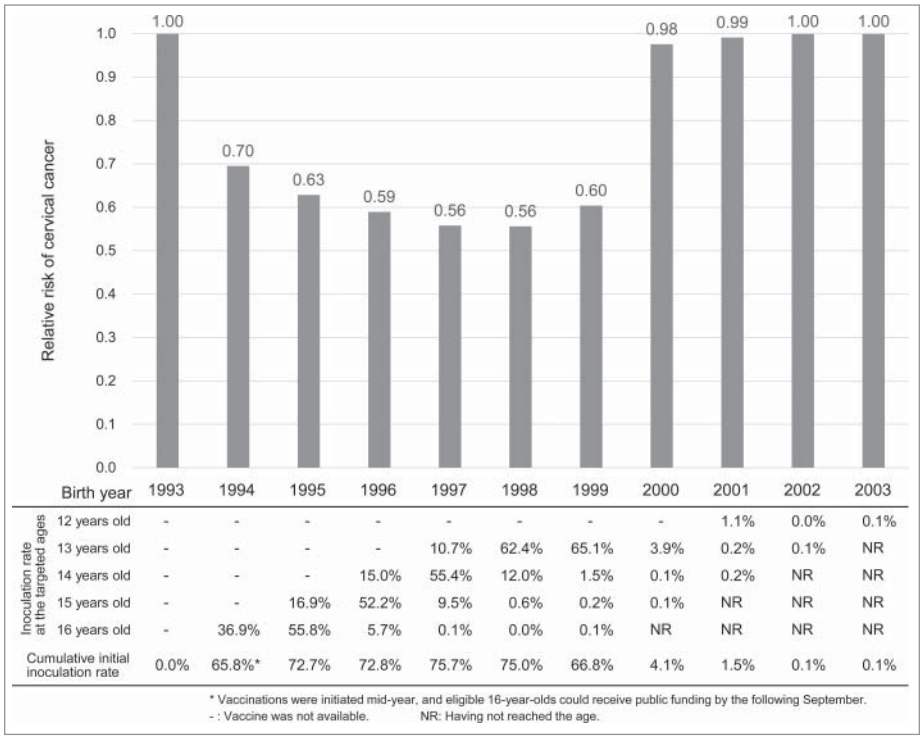

Figure 1. Prediction of the relative risk of cervical cancer. The relative cervical cancer risk was calculated based on the real vaccination rates in Sakai City. The statistical data of the HPV vaccination rates were provided from the Sakai City Government to our study team.

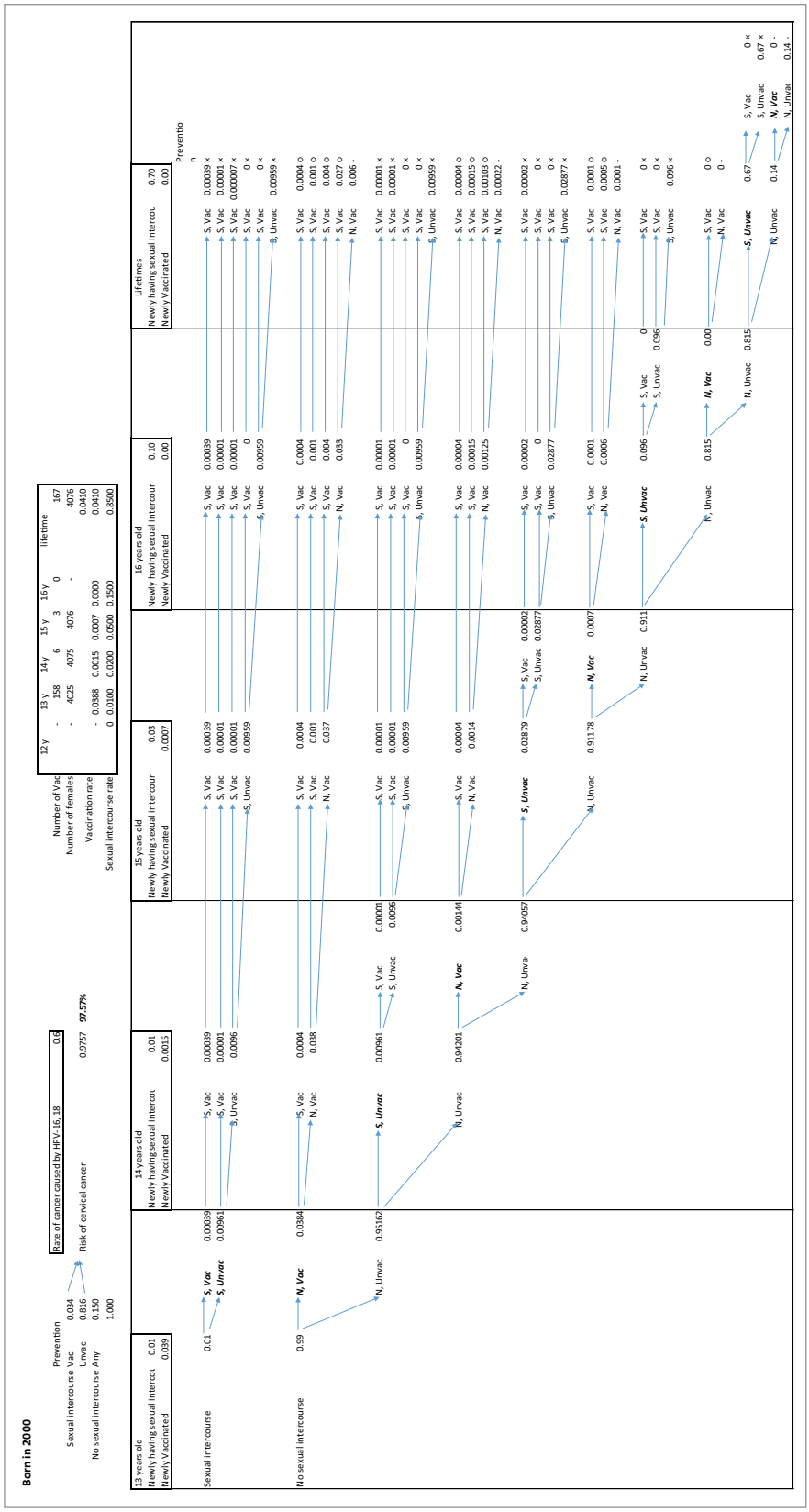

Figure 2. A sample of the risk calculation. S: having experienced sexual intercourse; N: not having experienced HPV vaccine; Vac: having received HPV vaccine; Unvac: not having received HPV vaccine.

demonstrates a sample of risk calculation. The initial vaccination rates of the youngest children every year were 10.8% (age 13) in 2010, 62.7% (age 13) in 2011, 65.4% (age 13) in 2012, 1.1% (age 12) in 2013, 0.1% (age 12) in 2014, and 0.1% (age 12) in 2015. It is clear that after the suspending of encouragement by MHLW, the vaccination rate significantly decreased and has currently almost ceased. Furthermore, the cumulative initial vaccination rates were 0.0% in 1993, 65.8% in 1994, 72.7% in 1995, 72.8% in 1996, 75.7% in 1997, 75.0% in 1998, 66.8% in 1999, 4.1% in 2000, 1.5% in 2001, 0.1% in 2002, and 0.1% in 2003.

The future cervical cancer risk in those born in 1993 was defined to be 1.0000. As a result, it was found that the relative risk in those born in 1994 was 0.70, that in those born in 1995 was 0.63, that in those born in 1996 was 0.59, that in those born in 1997 was 0.56, that in those born in 1998 was 0.56, that in those born in 1999 was 0.60, that in those born in 2000 was 0.98, that in those born in 2001 was 0.99, that in those born in 2002 was 1.0, and that in those born in 2003 was 1.0. It was clear that those born between 1994 and 1999 were part of the generation in which the prevention of future cervical cancer by HPV vaccine would be achievable to some extent, while those born after 2000 would be exposed to the same risk as before introduction of the vaccine. For these females, cervical cancer screening should be recommended more strongly.

The real inoculation rates showed how the reporting of possible adverse events in the media and the suspension of encouragement by MHLW influenced girls of the targeted age. From the above, at present, it is confirmed that the cumulative initial vaccination rates were different by the year of birth, leading to the realistic fear of differences in the risk of developing cervical cancer depending on the year of birth. It is a very unfortunate prediction that the different risks of cervical cancer depending on the year of birth will be caused by the governmental decision. The change in cervical cancer relative risk could actually occur in the future and was already being determined. In fact, Ozawa et al. demonstrated the significant reduction of the rate of abnormal cervical cytology among the vaccinated women aged 20–24 compared with those who had not received HPV vaccine in Japan.[18]

It is necessary for us to face the reality that the risk of the HPV infection and cervical cancer increases every day for girls who refrain from vaccination and begin to have sexual intercourse without it. For these females, cervical cancer screening should be recommended more strongly. In regard to HPV vaccine, catch-up vaccinations for females who missed the opportunity of HPV vaccination due to the suspension of the governmental recommendation, and use of 9-valent HPV vaccines (currently, only bi- and quadrivalent HPV vaccines are licensed in Japan) should be considered.[19]

There are some limitations in the present study. We used the data from Sakai City in this study; however, the vaccination situation will vary depending on the local government, and it appears that there are local governments which face a much worse reality than Sakai City. Moreover, we hypothesized that HPV infection risk is proportional to the rate of having sexual intercourse without HPV vaccination at every age and over the lifetime, and that the relative risk of cervical cancer could be determined by the relative risk of HPV infection over the lifetime. HPV infection risk is not regulated only by the rate of experiencing of sexual intercourse without vaccination, and cervical cancer risk is different by the type of HPV. Uncertainty of these hypotheses was minimized by demonstrating the relative risk compared with the risk of those born in 1993 whom HPV vaccination was not available yet for. One more limitation is assumption of the rates of having experienced sexual intercourse at each age, which are not derived from official data.

In conclusion, the risk of future cervical cancer differs in accordance with the year of birth. This is a problem that must be overcome not only in Japan but in all countries where the HPV inoculation rate is not increasing.

Methods

The lifetime risk of cervical cancer was estimated using the latest real data on vaccination rate at each age (2010 through 2015) in Sakai City, Osaka, a government-designated city with a population of 839,128 (2012), regarding the situation on vaccinations. In Sakai City, public funding was initiated in October 2010 and 13 to 16-year-olds were vaccinated. Because vaccinations were initiated mid-year, eligible 16-year-olds could receive public funding by the following September. Periodical vaccinations were initiated from 2013 and 12 to 16-year-olds were vaccinated. The statistical data of the HPV vaccination rates were provided from the Sakai City Government to our study team after approval of the Institutional Review Board of Osaka University Hospital.

Calculation to estimate the lifetime risk of cervical cancer was based on the following hypothesis:

1) The rate of having experienced sexual intercourse at the age of 12, 13, 14, 15, 16, and 17 is assumed to be 0%, 1%, 2%, 5%, 15%, and 25%, respectively. The lifetime rate is assumed to be 85%.
2) HPV infection risk is calculated based on the rate of having sexual intercourse without HPV vaccination at every age and over the lifetime.
3) The relative risk of cervical cancer is proportional to the relative risk of HPV infection over the lifetime.
4) Protective effect against HPV infection is provided by a one-time vaccination (because only the data of the first vaccination was provided)
5) Cervical cancer is caused by HPV infection. The rate of cancer caused by HPV type 16/18 infection is 60%, and 40% by other types, not including infections of HPV type 16/18 in combination with other types.
6) Even if inoculated, the incidence rate of cervical cancer caused by types other than HPV type 16/18 does not change.
7) During the analysis period, the population according to each year of birth does not change.
8) If the vaccine does not exist, the incidence rate of cervical cancer does not change over the course of the analysis period.
9) The presence of vaccination and sexual activity are independent of each other, with sexual activity not changing during the analysis period.

Abbreviations

ASCO	the American Society of Clinical Oncology
CDC	the Centers for Disease Control and Prevention in the United States
HPV	human papilloma virus
MHLW	the Ministry of Health, Labor and Welfare
WHO	World Health Organization

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