Cervical Cancer Protection in Japan

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In Japan, government subsidies for human papillomavirus (HPV) vaccination of girls aged 13–16 commenced in 2010. By early 2013, vaccination had become a widely accepted national immunization program. However, in June of 2013, the Ministry of Health, Labor, and Welfare (MHLW), the government's lead agency, suspended its recommendation for vaccination in response to reports of adverse vaccine events. The rate of HPV vaccination quickly dropped from 70% to almost zero, where it has lingered for eight years. In 2020, a new 9-valent HPV vaccine was licensed in Japan. The momentum seemed to be building for the resumption of HPV vaccinations, yet Japanese mothers remain widely hesitant about vaccinating their daughters, despite the well-proven safety and efficacy of the HPV vaccines.

Keywords: HPV vaccine ; cervical cancer ; government suspension of recommendation

1. Introduction

Cervical cancer is one of the most common cancers for women. In 2020, an estimated 600,000 women were diagnosed with cervical cancer worldwide, and about 341,000 deaths were attributed to it ^[1]. On a global scale, Japan has been classified as having a moderate age-standardized incidence rate of cervical cancer; India, Nigeria, and other countries belong to this moderate group as well. Interestingly, China, Korea, Russia, and Brazil have a lower incidence rate. The World Health Organization (WHO) has noted that the burden of cervical cancer typically falls most heavily on women who lack proper access to health services, mainly those in low-and middle-income countries ^[2], thus, it is disconcerting that among the most developed countries of the world, Japan's incidence rate of cervical cancer has been accelerating since 2000 (Age-adjusted rate: 28.0 in 1976, 9.1 in 2000, 14.1 in 2012, Annual percent change in 2000–2012: 3.8 (95% CI: 2.7–4.8)) ^[3], a trend not seen in any other advanced country. In Japan, 10,978 women were diagnosed with cervical cancer in 2018; in 2019, 2921 died from it ^{[4][5]}. Modern changes in sexual lifestyles and an increasing rate of smoking among women have clearly contributed to this national trend for increasing cervical cancer morbidity and mortality. Because Japan's human papillomavirus vaccination (HPV) vaccination program was only started in 2010, the bulk of these cancers are occurring in an extended generation of unvaccinated women.

It is well established that the most critical risk factor for cervical cancer is having experienced a persistent infection with one of the high-cancer-risk versions of HPV ^[6]. Persistent infection can lead to developing precancerous lesions that, if undetected and untreated, can progress to invasive cervical cancer. HPV has retrospectively been detected in most cervical cancers in Japan ^{[Z][8]}. The most frequent types attributed to causing cervical cancers are the HPV 16 and 18 strains, which together account for almost 60% of cervical cancers in Japan, which is significantly lower than the global average of 71% for HPV 16/18 ^{[9][10]}. Heavy smoking, long-term use of oral contraceptives, and promiscuous sexual experiences at a young age are contributing risk factors ^{[11][12][13]}.

Most cervical cancers are primarily preventable by an effective HPV vaccination. Secondary prevention approaches include early and consistent screening for and treatment of precancerous lesions. Almost inexplicably, although Japan has in hand all the technical, medical, policy, and fiscal tools with which to eliminate cervical cancer, they are almost totally failing to do so.

Among its many problems is cervical cancer screening, which in Japan is recommended for all women over the age of 20. Incredibly, the screening rates for young women within three key age groups, of 20–24, 25–29, and 30–39, are only 10%, 10–20%, and 10–30%, respectively ^[14]. Forty-two-point-four percent of Japanese women aged 20–69 had a Pap smear in the past two years, while 60.7% of target women had Pap smear in the past three years on average across OECD countries ^[15]. Furthermore, Japan's once enviable 70% HPV vaccination rate has fallen to almost zero ^[16], making Japan an outlier among the developed nations.

2. Politics, Policies, and Events Related to HPV Vaccinations

We would like to share some relevant background information, some insights on the current states of HPV vaccinations and cervical screening in Japan, and give some consideration as to what directions Japan is now moving. We begin by noting that the quadra-valent HPV vaccine was approved in 2006 in the United States of America, the European Union, and Australia, and by 2020, it had been approved in more than 130 countries ^[127]. The new broader-spectrum 9-valent vaccine has already been approved in more than 80 countries ^[18]. In 2018, the Director-General of WHO called for a global action to eliminate cervical cancer. In 2020, the World Health Assembly adopted its Global Strategy to accelerate the elimination of cervical cancer as a public health problem, which has since been adopted by many countries ^[2].

Table 1 shows a brief history of HPV vaccination in Japan. Here are some of the high points. In October of 2009, the bivalent HPV vaccine was the first to be cautiously licensed in Japan; licensing the quadra-valent form followed two years later, in July 2011, a full five years after it had been widely accepted elsewhere. Subsidies from local and national government programs for HPV vaccination of girls aged 13–16 commenced flowing in November of 2010. By April of 2013, both the bi-valent and quadra-valent HPV vaccines were being used routinely for vaccinating girls aged 12–16 as part of the National Immunization Program.

2009	October	The bi-valent HPV vaccine was licensed.
2010	November	Subsidies from local and national governments for an HPV vaccination program for girls 13–16 commenced.
2011	July	The quadra-valent HPV vaccine was licensed.
	April	The national immunization program for girls aged 12–16 years commenced
2013	June	The VARRC ruled that "It is necessary to determine the frequency of pain occurrence whose relationship can be undeniably linked to HPV vaccination. HPV vaccination should not be actively recommended until proper information can be provided to the public." The VARRC announced the suspension of its recommendation for vaccination (Notification by the Director-General of the Health Service Bureau of the MHLW).
2014	January and July	The VARRC evaluated the pathogenesis and causal relationship of the "diverse symptoms" reportedly experienced after HPV vaccination. The reported chronic pain and motor impairment were regarded as functional physical symptoms (a form of functional somatic syndrome).
2015	August	The "Guide for the Management and Treatment of Symptoms that Occur after HPV Vaccine Injection" was published. An organization of cooperative medical institutions from all 47 prefectures agreed to provide treatment for any girl suffering from symptoms after HPV vaccination in any community throughout Japan. The MHLW announced three measures for patients with symptoms, mainly of pain or movement disorders.
	September	The result of the adverse events follow-up survey was released. The suspension of governmental recommendation was continued. The MHLW and the Ministry of Education, Culture, Sports, Science, and Technology issued their "Improvement of the Consultation and Support System for Persons with Symptoms after HPV Vaccination". Relief (subsidies for medical expenses, etc.) based on the Immunization Law and the Pharmaceuticals and Medical Devices Agency Law, was implemented
	November	Symptom consultation services were established in the health and education departments of each prefecture.
	December	The VARRC evaluated the safety and efficacy of HPV vaccines in Japan and abroad.
2017	April	The conclusions of a nationwide epidemiological survey by a research team designated by the MHLW were reported to the VARRC (Key finding: Unvaccinated girls had a similar number of "diverse symptoms").
	November	The VARRC evaluated all available information on the safety and efficacy of the HPV vaccine in Japan and abroad and expressed its commitment to continue to provide close support to patients who presented with any of the diverse symptoms. The VARRC discussed ways to better inform the public about the HPV vaccine.
2018	January	An extensively revised informational leaflet was released by the MHLW to better inform the public about the HPV vaccine.
2019	August	The VARRC reported the results of a survey on the provision of HPV vaccine information.

Table 1. Timeline of the policies and events related to HPV vaccines in Japan.

2020	July	The "Parliamentary Association for the Resumption of Recommendation of HPV Vaccination" submitted a petition to the MHLW. The 9-valent HPV vaccine was licensed in Japan.
	October	MHLW's 'Leaflet to Inform the Public about the HPV Vaccine' was revised.
	December	The quadra-valent HPV vaccine was approved to prevent anal cancer for males.
2021	August	"Parliamentary Association for the Resumption of Recommendation of HPV Vaccination" submitted a petition to the MHLW again. The Japanese Society of Obstetrics and Gynecology submitted a petition to the MHLW to extend the period of routine vaccination.

Abbereviations: human papillomavirus, HPV; Vaccine Adverse Reactions Review Committee, VARRC; Ministry of Health, Labor, and Welfare, MHLW.

Those were the 'good old days' when vaccination rates for girls of targeted age groups approached 70% compliance. However, soon thereafter, the news media began to sensationalize reports regarding the occurrence of diverse symptoms after HPV vaccination, including chronic pain, motor impairment, and other symptoms. As a result, on the 14th of June 2013, Japan's Ministry of Health, Labor, and Welfare (MHLW) decided to temporarily suspend the national immunization program's recommendation for routine HPV vaccination while an investigation into the safety of the vaccine was conducted.

Such a safety study was carried out. In 2014, MHLW's advisory group, the Vaccine Adverse Reactions Review Committee (VARRC), assessed the pathogenesis and the causality of the "diverse symptoms" reported to have occurred after HPV vaccination, and they defined them as "functional somatic symptoms". Later that same year, the Japanese Pediatric Society submitted a request to the MHLW to resume its recommendation for HPV vaccinations, with no success. In 2015, positive results from an adverse vaccine events follow-up survey were released, but the suspension remained under "continued review". Next, the WHO Global Advisory Committee for Vaccine Safety (GACVS) noted that the MHLW's policy decisions were based on weak circumstantial evidence, causing the public to fail to use a safe and effective vaccine, potentially resulting in real harm ^[19]. In April 2016, a group of 17 academic societies, comprising the Japanese Expert Council on Promotion of Vaccination, published its "Views of Relevant Academic Groups on Promoting HPV Vaccination", which stated that "the suspension of the governmental recommendation is an extremely alarming situation, and the Japanese government should resume its proactive support for HPV vaccination" ^[20].

A year later, in April 2017, a nationwide epidemiological survey, led by a research team designated by the MHLW, concluded that "the diverse symptoms" occurred equally among unvaccinated girls of the same age groups and were therefore not specific to vaccinated girls ^[21]. The details of their findings are described in the next section.

In response to this last finding, in 2017 the VARRC discussed how to provide better information to the public to overcome their deeply entrenched HPV vaccine hesitancy. The following year, 2018, a HPV vaccine information leaflet developed by the MHLW was released; an evaluation of its results was reported in 2019 [22][23].

Most recently, in 2020, a 9-valent HPV vaccine was licensed in Japan. Combined with the pro-vaccine effort driving the COVID-19 vaccination program, momentum seems to be building for the resumption of HPV vaccinations as well. However, eight long years have now passed since the recommendation was suspended, and during those eight years, almost no one was vaccinated, leaving large numbers of Japanese girls and women at future risk of HPV-driven cancers and cancer deaths.

3. Future Prospects for Discussion

3.1. After a Resumption of the Governmental Recommendation?

Eight years have passed since the government's recommendation was discontinued in 2013. During this time, the population of mothers with daughters eligible for HPV vaccination has been almost completely replaced. What are now the attitudes toward HPV vaccination of this new generation of mothers?

Following the suspension of governmental recommendation, we have been periodically conducting internet surveys of the mothers, which were done in March 2014, May 2015, March 2016, and December 2019, and compared the results of these surveys ^[24]. The respondents were mothers who had HPV-unvaccinated daughters who were aged 12–16 at the time of their responses. The results showed that at least 90% or more of the mothers knew something about the HPV vaccine throughout the four surveys: 95.0% (190/200), 97.5% (2008/2060), 89.8% (1796/2000), and 91.7% (1416/1545), respectively. Similarly, the percentage of mothers who knew about the 2013 news reports regarding so-called adverse

events remained high over the course of the four surveys: 83.0% (166/200), 80.9% (1666/2060), 78.7% (1573/2000) and 85.9% (1328/1545), respectively. The percentages of mothers who replied they would "inoculate" if the MHLW restarted their recommendation was 22.5% (45/200), 21.0% (433/2060), 12.2% (244/2000), and 17.8% (275/1545). The percentages were significantly higher during the 1st and 2nd surveys and became significantly lower for the 3rd survey (p < 0.05, p < 0.05, respectively). At any point in time, only about 20% of mothers would "inoculate" solely based on whether the MHLW would restart their recommendation.

Most Japanese mothers are concerned about vaccinating their daughters against HPV, so there is still hope for a turnaround. We must plan now to quickly take effective measures to increase the vaccination rate, once the long-promised governmental recommendation is resumed. As part of that preparation, we have been investigating the effectiveness of providing different informational leaflets to girls of HPV vaccination age and/or to their parents ^[25]. In July 2019, Isumi City (population 38,000) started sending an informational/educational leaflet addressing the risks of cervical cancer. Their leaflet was sent to 139 girls whose birth year was 2003 and who were 16 at the time. Their cumulative vaccination rate reached 10.1% (14/139) by December 2019, which was significantly higher than the 0.0% for girls born in 2002 who did not receive the leaflet (p < 0.001). This was proof that an increase in HPV vaccination rate could be achieved (among the targeted girls born in 2003) by a leaflet sent to individuals by a local government entity.

We have found that, even under the suspension of governmental recommendation, if their family doctor provided information using an information leaflet explaining the need for cervical cancer prevention, that act led to an increase in the number of vaccinations ^[26]. Among the 53 mothers who said they would impose certain preconditions before being willing to encourage their daughters' HPV vaccination, 21 (39.6%) became more willing to vaccinate their daughters immediately after receiving such an explanation. Mothers requiring no other preconditions, other than the resumption of the governmental recommendation, were more likely to be willing to be vaccinated after receiving their doctor's explanation (*p* = 0.02). Seven of the 21 mothers (33.3%) returned to the clinic to get their daughter vaccinated during the study period. Despite the small number of subjects observed, the study suggests that efforts to re-establish HPV vaccine acceptance should be focusing on mothers who are less likely to impose preconditions on their daughter's vaccination.

The challenges Japan faces as a nation in reviving its national HPV vaccination program are immense. How can we possibly achieve the WHO's lofty goal of 90% HPV vaccination by age 15 ^[2]? According to one marketing theory, when the penetration (acceptance) rate of a product or service reaches 16.0% and overcomes the next chasm of penetration, demand will accelerate rapidly. This marketing theory is useful in considering the re-promotion of the HPV vaccine ^[27]. Under this theory, the adopter categories by which a new product penetrates the market can be divided into five groups, including Innovators, Early adopters, Early majority, Late majority, and Laggards.

According to the "Chasm Theory", there is a large chasm between the early market, consisting of Innovators and Early adopters, and the mainstream market, which consists of the Early and Late majorities, that cannot be easily crossed. The leaflet intervention by Isumi City resulted in a 10% vaccination rate, and the vaccination rate, if and when the recommendation is resumed, may be about the same. As the report by Ugumori et al. implies, to cross that chasm, first, medical workers will need a firmer understanding of the HPV vaccine so that they can confidently recommend vaccination to the targeted population of girls and their parents. That population will be expected to pass on that recommendation to their peers, resulting in the widening dissemination of the HPV vaccine among the majority.

3.2. Women Who Missed Their Opportunity of HPV Vaccination

If the governmental recommendation is finally resumed in 2022, it will be the women born between 2000 and 2005 that have a very low vaccination rate because they have surpassed the targeted age (12–16) for the routine free vaccination program. When the future risk of cervical cancer incidence in women born in 1993 is considered to be 1 (these girls were never vaccinated because they were over 16), for receiving HPV vaccination when public subsidies started in 2010, the risk for the women born in 2000 is 0.916, 0.990 for women born in 2001, 0.998 for women born in 2002 to 2003, and 0.999 for women born in 2004 to 2005 ^[27]. These women are between the ages of 17 and 22, the age range where sexual experiences increase. The cumulative rate of first intercourse among Japanese women is 30% at age 18, over 50% at age 19, and reaches 70% at age 22 ^[28].

The introduction of catch-up vaccinations has been somewhat effective, although it can never be as effective as the original preventive effect due to the increasing rate of sexual experience. In Sweden, the incidence rate ratio for the comparison of the vaccinated population with the maximally unvaccinated population was significantly reduced to 0.47 (95% CI, 0.27 to 0.75) among women who had been vaccinated between the ages of 17 to 30 ^[29]. In order to reduce their risk, it would be desirable for them to receive the 9-valent vaccine, free of charge and as soon as possible, although it has not yet been introduced into the routine vaccination system.

Women who lost their opportunity to be vaccinated also lost the opportunity to know how to prevent cervical cancer. We analyzed two internet surveys, conducted in 2015 and 2020, to evaluate the differences in their understanding of the means of preventing cervical cancer in young Japanese women ^[30]. We compared non-vaccinated women aged 18–19 years during the golden period of pro-vaccination policies and the period when the recommendation was suspended. Even though none of the women in either group were HPV-vaccinated, 98.8% of the pro-vaccination generation knew about the HPV vaccine, while only 60.3% of the women under the suspension of recommendation were aware of the vaccine (*p* < 0.001). The answer yes to the question "Did you ever talk with your family about cervical cancer?" was also significantly lower (25.0%) compared to 44.6% of the pro-vaccination generation (*p* < 0.001).

For those who missed their routine vaccination opportunity, we must promote providing them with catch-up vaccination opportunities, and we must encourage them to undergo routine cervical cancer screening. To avoid burdening them unfairly with the consequences of the suspension of the government recommendation, every measure must be taken to reduce their risk.

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