HPV (Human Papillomavirus) Vaccination for Preventing Cervical Cancer
~ Its Benefits/Risks and Current Status in Japan ~

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Where is Wakayama?

Wakayama
1 h from Osaka
1.5h from Kyoto

Population: 300,000 in city
1,000,000 in prefecture
1. WHAT IS CERVICAL CANCER?

2. WHAT IS HPV (Human Papilloma-Virus)?

3. HOW HPV INFECTION CAUSES CERVICAL CANCER?

4. HOW WE PREVENT CERVICAL CANCER?

5. CURRENT STATUS OF HPV VACCINATION IN JAPAN
Cervical cancer is the 4th most common cancer in women worldwide, with nearly 300,000 estimated related deaths annually in the world.

Invasive cervical cancer is generally treated by radical surgery or CCRT consisting of radiotherapy and chemotherapy.

Patients who undergo radical surgery or CCRT are likely to suffer from undesirable treatment-related adverse symptoms or lose their fertility, which results in a lowered quality of life, even if their disease is cured.
In Japan, 10,000 cases of cervical cancer are newly diagnosed every year, and nearly 3,000 women die of the disease every year. Both the incidence and mortality have increased and are now increasing.
The incidence of cervical cancer in younger ages such as twenties and thirties has increased in Japan, and the mortality has also increased. Such situations in young women of reproductive (child-bearing) ages are serious issues.
• Considering the current situations, to increase the survival rate of cervical cancer patients as well as to protect the health of young women, strategic prevention of cervical cancer is an important and continuing global challenge.

• My talk today will focus on the prevention of cervical cancer, and discuss the current issues on HPV vaccination.
What is HPV?

• HPV is a DNA virus from the papilloma virus family.

• HPV infection is related to various diseases in humans.

• About 15 types of HPV (HPV16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -68, -73, and -82) are oncogenic and defined as high-risk HPV, which can cause cervical cancer as well as other HPV-related cancers such as of the vulva, vagina, penis, anus, and oropharynx.

• HPV is transmitted by sexual contact.

• HPV infections are very common and generally asymptomatic. It is estimated that 50-80% of healthy sexually-active individuals are at risk of HPV infection within their lifetime.

• Nearly all patients with cervical cancer show evidence of HPV infection.

• HPV16 and HPV18 are the most oncogenic, and these 2 types are responsible for about 70% of invasive cervical cancer.
Approximately 90% of women infected initially by HPV may eliminate the infection within 2 years. In contrast, in the remaining 10% of women, persistent HPV infection may occur, and some of those could develop high-grade precancerous lesions and some may develop invasive cancer.

HPV infection is necessary for the development of cervical cancer, but other factors, such as smoking, immune suppression, and long-term oral contraceptive use, may increase the risk of development.

Over 70% of CIN1 lesions regress, while 10 to 30% CIN3 lesions progress to invasive cancer. Invasive cancer develops over some years or longer.
Strategies for Preventing Cervical Cancer

Strategies for preventing cervical cancer consist of two major steps: Primary prevention is the prevention of HPV infection by “Vaccination”. Secondary prevention is the early detection of persistent HPV infection and precancerous lesions by screening using PAP cytology or HPV test.

Both primary and secondary prevention strategies are indispensable to prevent cervical cancer, reaching a global consensus.
Cervical Cancer is Preventable through Screening and Vaccination

Dr. Papanicolaou invented Pap test (cytology) for cervical cancer screening

Dr. Harald zur Hausen awarded for Nobel Prize in 2008 for his discovery of "HPV causing cervical cancer"
Cervical Cancer Screening in Women aged 20-69

In Japan, the proportion of women undergoing PAP screening is only 35 to 40% of targeted women, which is lower than those in Western countries, at 50 to 80%.

Limited Effectiveness of Cytology Screening

• It is difficult to more effectively reduce the number of deaths from cervical cancer only through the screening (PAP cytology), mainly due to its relatively lower sensitivity (55 to 80%).

• The importance of HPV-DNA testing has been recognized, and its role is shifting from cytology alone to cytology plus HPV cotesting, which shows high sensitivity and specificity, and now to a new paradigm in which HPV testing alone may become a primary screening tool.

• In Japan, the screening system using cytology in combination with the HPV test has not yet been established.
Efficacy and Safety of HPV Vaccine
HPV Vaccines - WHO position in 2014

WHO recognizes the importance of cervical cancer and other HPV-related diseases as global public health problems and reiterates its recommendation that HPV vaccines should be included in national immunization programs.

HPV vaccines have excellent safety and efficacy profiles.


Up to now, over 65 countries have introduced HPV vaccine in their national immunization programs for girls aged 9-14 years, and in some countries also for boys.
Vaccine-Type HPV Prevalence Declined in Females aged 14-19 Years After Introduction of the HPV Vaccine

HPV vaccination has led to marked reductions in the prevalence of vaccine-preventable HPV types in Australia. Interestingly, this was observed not only in vaccinated women but also in unvaccinated women, suggesting a “herd-immunity effect”.

The incidence of high-grade precancerous lesions in vaccinated generations has decreased to less than 50% during 7-8 years following the introduction of a national HPV vaccination program.
Summary for Impact of HPV Vaccination

• Marked decrease in the HPV infection rates in younger women or girls in several countries where national HPV vaccination programs had been introduced since 2007-2008, with a 3-dose coverage rate of over 70% of the targeted population.

• The incidence of pre-cancerous lesions (CIN3) in vaccinated generations has decreased to less than 50% during 7-8 years following the introduction of a HPV vaccination program.

• These findings suggest that the incidence of invasive cervical cancer in younger women must markedly decrease over the next several to 10 years, leading to a subsequent decrease in the mortality rate due to cervical cancer in the near future.
Current Status of HPV Vaccination in Japan
Active recommendation has been suspended since June 2013. Discussion continues at MHLW Adverse Events Review Committee.

- Tentative Public Funding Program started
- Cervarix launched
- Gardasil launched
- National immunization program (NIP) for HPV started
- Media reports on chronic pain and movement disorder cases following HPV vaccination
- MHLW committee decided to suspend active promotion
- JSOG released a statement on active recommendation of HPV vaccine
- HPV vaccination status to date in Japan
- JSOG released a statement on active recommendation of HPV vaccine
The case of a girl who suffered from severe symptoms such as body pain and movement disorder was made public in many newspapers, which was followed by coverage by major media, leading to public fears about vaccine’s safety.

Josei Jishin (March 12, 2013)

Asahi Shimbun (March 8, 2013)

FNN Super News (March 12, 2013)

Tokyo Shimbun (March 15, 2013)
HPV Vaccination Coverage By Birth Cohort Year in Japan


Rapid drop in vaccination coverage after suspension of active recommendation despite continuation of national program.
<table>
<thead>
<tr>
<th>Date</th>
<th>Discussions at AERC</th>
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<tbody>
<tr>
<td>May 16</td>
<td>Concluded that no evidence to stop vaccination. Need to gather more information.</td>
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<td><strong>Jun 14</strong></td>
<td><strong>Active promotion of HPV vaccination suspended</strong></td>
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<tr>
<td>Oct 28</td>
<td>Continue suspension</td>
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<tr>
<td>Dec 16</td>
<td>Reviewed all reported cases</td>
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<td>Dec 25</td>
<td>Investigation results (AE cases, papers and data from foreign health authorities) reported and discussed</td>
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<td>Jan 20</td>
<td>Suggested “psychosomatic reaction” causes symptoms</td>
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<td>Feb 26</td>
<td>Hearing from experts on treatments of psychosomatic reactions (functional somatic symptoms)</td>
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<td>Jul 4</td>
<td>Summarized information on functional somatic symptoms</td>
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<td>Oct 29</td>
<td>Discussed follow-up survey on all adverse event cases</td>
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<tr>
<td>Sep 17</td>
<td>Results of follow-up survey reported</td>
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<td>Nov 27</td>
<td>Discussed <strong>epidemiological study</strong> plan</td>
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WHO (GACVS), CDC, and EMA confirmed HPV vaccine safety

World Health Organization (WHO) Statement on safety of HPV vaccines by the Committee (GACVS)¹: 2015

*The GACVS has systematically investigated safety concerns raised about HPV vaccines and has issued several reports in this regard. To date, it has not found any safety issue that would alter its recommendations for the use of the vaccine.

*GACVS: Global Advisory Committee on Vaccine Safety

Centers for Disease Control and Prevention (CDC) ACIP Meeting Summary Report² : 2015

A large body of published and preliminary data from many sources demonstrate the safety of HPV vaccines. Safety monitoring and evaluation will continue for all HPV vaccines.

European Medicines Agency (EMA) Scientific conclusion of safety reviews³ : 2015

EMA confirms that the evidence does not support a causal link between the vaccines and development of CRPS* or POTS**. Therefore there is no reason to change the way the vaccines are used or amend the current product information.

*CRPS: Complex regional pain syndrome
**POTS: Postural orthostatic tachycardia syndrome
Global Advisory Committee on Vaccine safety (GACVS) Statement on Safety of HPV vaccines (17 December 2015)

The circumstances in Japan, where the occurrence of chronic pain and other symptoms in some vaccine recipients has led to suspension of the recommendation for routine use of vaccine in the national immunization program, warrants additional comment.

Review of clinical data by the national expert committee led to a conclusion that symptoms were not related to the vaccine, but it has not been possible to reach consensus to resume HPV vaccination.

As a result, young women are being left vulnerable to HPV-related cancers that otherwise could be prevented.

As GACVS has noted previously, policy decisions based on weak evidence, leading to lack of use of safe and effective vaccines, can result in “real harm”.
Japanese academies require resumption of recommendation of vaccine for cervical cancer prevention

Tomoyuki Fujii, MD, PhD
Chairperson of the Executive Board
Japan Society of Obstetrics and Gynecology (JSOG)


Over 2 years have passed since June 2013 when the Ministry of Health, Labour, and Welfare suspended recommendations for HPV vaccination. During this period, institutions led by the ministry, including the Investigative Committee on Adverse Reactions, have thoroughly collected data, performed analyses, conducted follow-up surveys, and organized discussions among specialists to address various symptoms that were reported after HPV vaccination. At the 8th meeting of the Investigative Committee on Adverse Reactions, which took place in February 2014, chronic pain and motor impairment were regarded as functional, physical symptoms (functional somatic syndrome). Furthermore, at the committee’s 10th meeting held in July 2014, the incidence of adverse events among a cumulative total of 8,998,030 females, who had been vaccinated in Japan within the period between the initiation of sales of the vaccine and the end of March 2014, was examined, and it was reported that the total number of adverse events, such as chronic pain and motor impairment, was 17%, this is equivalent to 2.0 per 100,000 vaccinations. Although subsequent studies did not provide scientific or epidemiologic evidence to confirm the causal relationship for those suffering from symptoms after HPV vaccination in any community throughout Japan by this April, including systems for referral to advanced and specialized medical institutions (27 facilities), through cooperation with prefectoral medical associations and the Ministry of Health, Labour, and Welfare. It should also be noted that the “Guidelines for the Management and Treatment of Symptoms that Occur after HPV Vaccine Injection” was published by the Japan Medical Association and Japanese Association of Medical Sciences on August 19 of this year to specify important points regarding early management by physicians in charge of vaccination and community-based medical institutions, covering medical interviews, consultations, and treatment, as well as the importance of approaches to support patients’ daily lives, including rehabilitation, and communication with their families and schools. The availability of appropriate treatment systems and guidelines facilitates the establishment of environments enabling those who desire vaccination to undergo it with a sense of security.

As the second step, the JSOG has also been engaged in activities to establish systems for mutual trust-based vacc-

• Many obstetricians and pediatricians worry about increase of cervical cancer in the future in Japan.
• The Japan Society of Obstetrics and Gynecology (JSOG) released a statement that they strongly demands the immediate resumption of recommendations for HPV vaccination, with the aim of eradicating cervical cancer.
• Expert Council on Promotion of Vaccination composed of 17 academies relating vaccination (including JSOG) released the Promotion of HPV vaccination.
Summary for Current Issues on HPV Vaccine in Japan

• The safety of the HPV vaccine remains a subject of intense controversy and debate in Japan, despite global scientific evidence pointing to the vaccine’s safety.

• The Investigative Committee concluded that various post-vaccination symptoms are functional somatic symptoms.

• The incidence rate of such adverse events was very low: 176 cases, equivalent to 0.005% of all vaccine recipients (3.3 million) in Japan.

• Studies did not provide any scientific or epidemiologic evidence to confirm the causal relationship between these symptoms and HPV vaccine.
What should we do against this difficult situation?

- It is of concern that if the suspension of vaccine recommendation continues, young Japanese generations will be deprived of the benefits of vaccines for cancer prevention.

- Who in Japan should take responsibility for those cervical cancer deaths that could have been prevented? Of course, we should. We must continue to appeal it to the government.

- As is the case in Japan, incorrect rumors about adverse events as well as broadcasting them by “non-scientific” media may lead to public fears, antipathy, and strong resistance to vaccination.

- A surveillance system of adverse events is the most important. Assessment of the real causal relationship of all suspected events by scientific and epidemiologic analyses is essential.

- Finally, we should support the girls complaining of the symptoms with appropriate approach including cognitive behavior therapy (rehabilitation, counseling, encouraging). (Ushida T et al, Pain Res Manag 2016)
Acknowledgement

I thank Prof. Beisler, Prof. Janni, and all staff of J SPS for holding this worthwhile symposium.

Thank you for your attention!