JSPS Japanese-German Symposium May 19-20, 2017, in Ulm

HPV (Human Papillomavirus) Vaccination for Preventing Cervical Cancer

～Its Benefits/Risks and Current Status in Japan～

Kazuhiko Ino

Professor and Chairman
Department of Obstetrics and Gynecology
Wakayama Medical University
Japan

Where is Wakayama?

Wakayama

1 h from Osaka
1.5h from Kyoto

Population: 300,000 in city
1,000,000 in prefecture

Today's Talk

1 WHAT IS CERVICAL CANCER ?

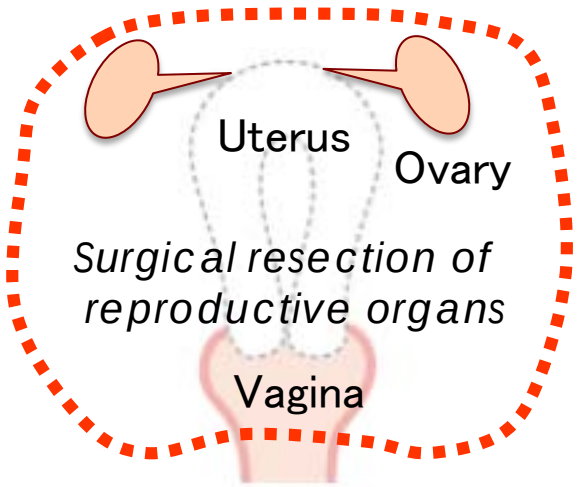
2 WHAT IS HPV (Human Papilloma-Virus) ?

3 HOW HPV INFECTION CAUSES CERVICAL CANCER ?

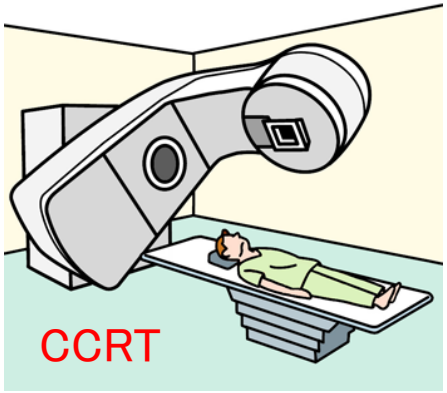
4 HOW WE PREVENT CERVICAL CACER ?

5 CURRENT STATUS OF HPV VACCINATION IN JAPAN

Cervical cancer



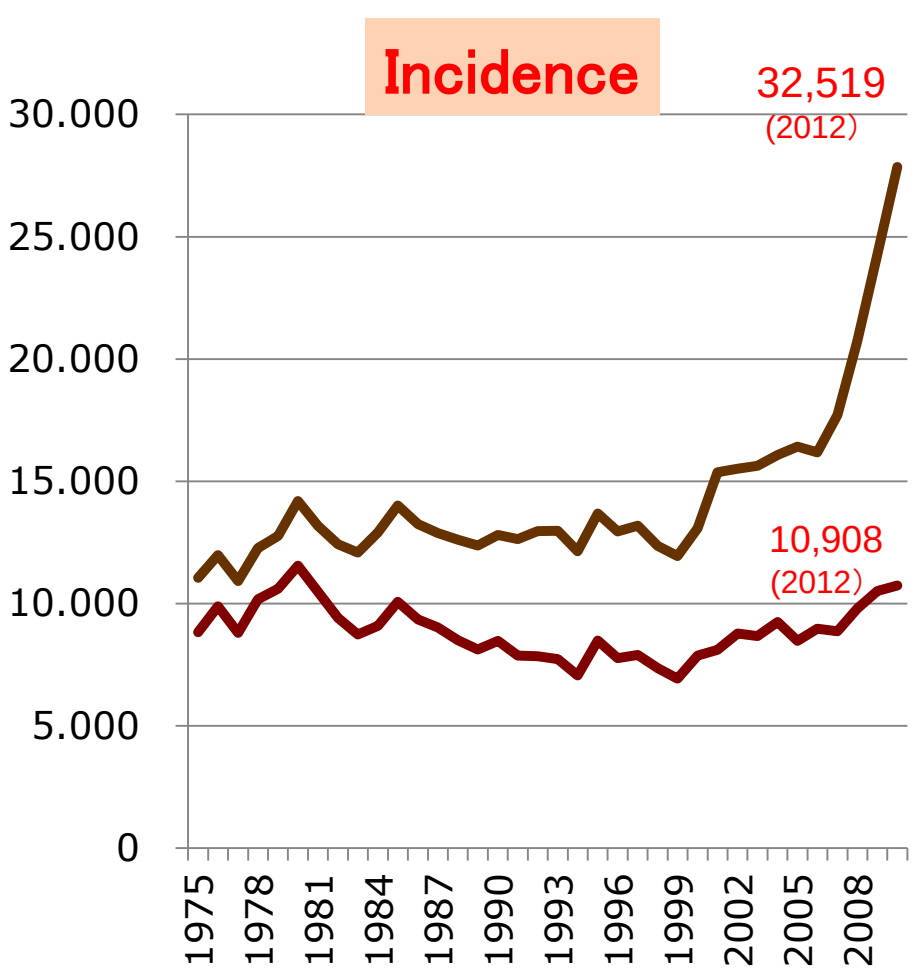
Radical hysterectomy

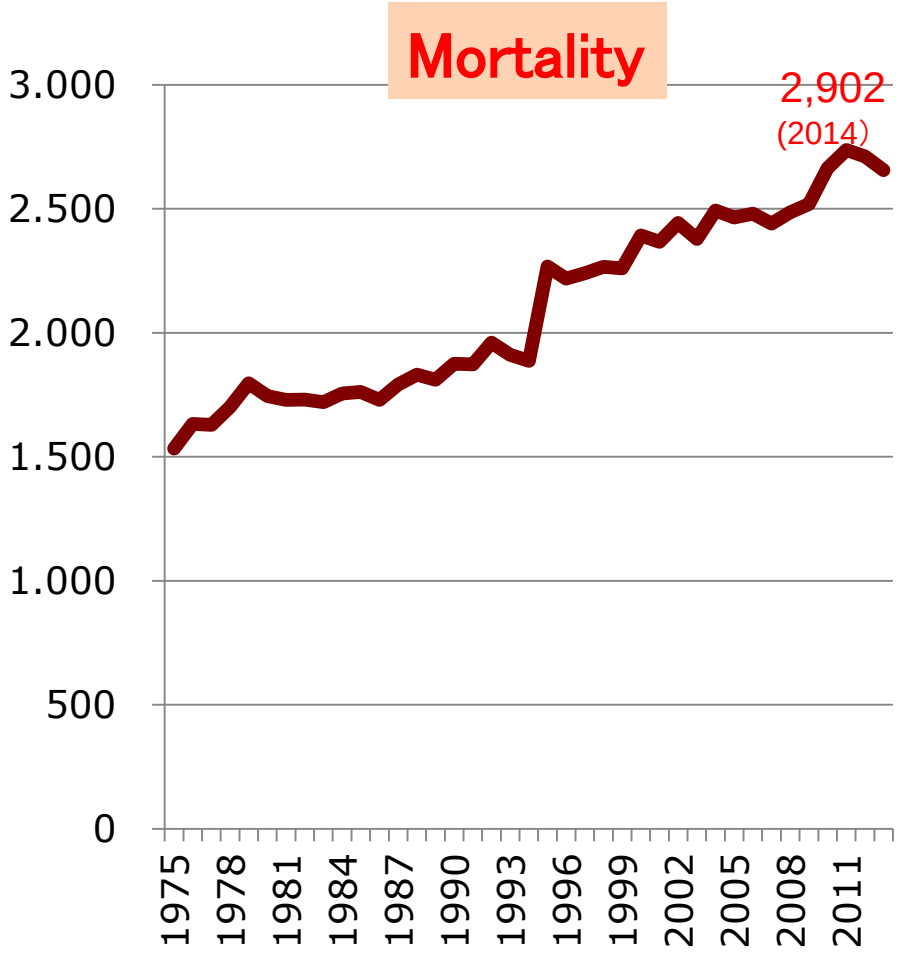


Radiotherapy
Chemotherapy

- 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.

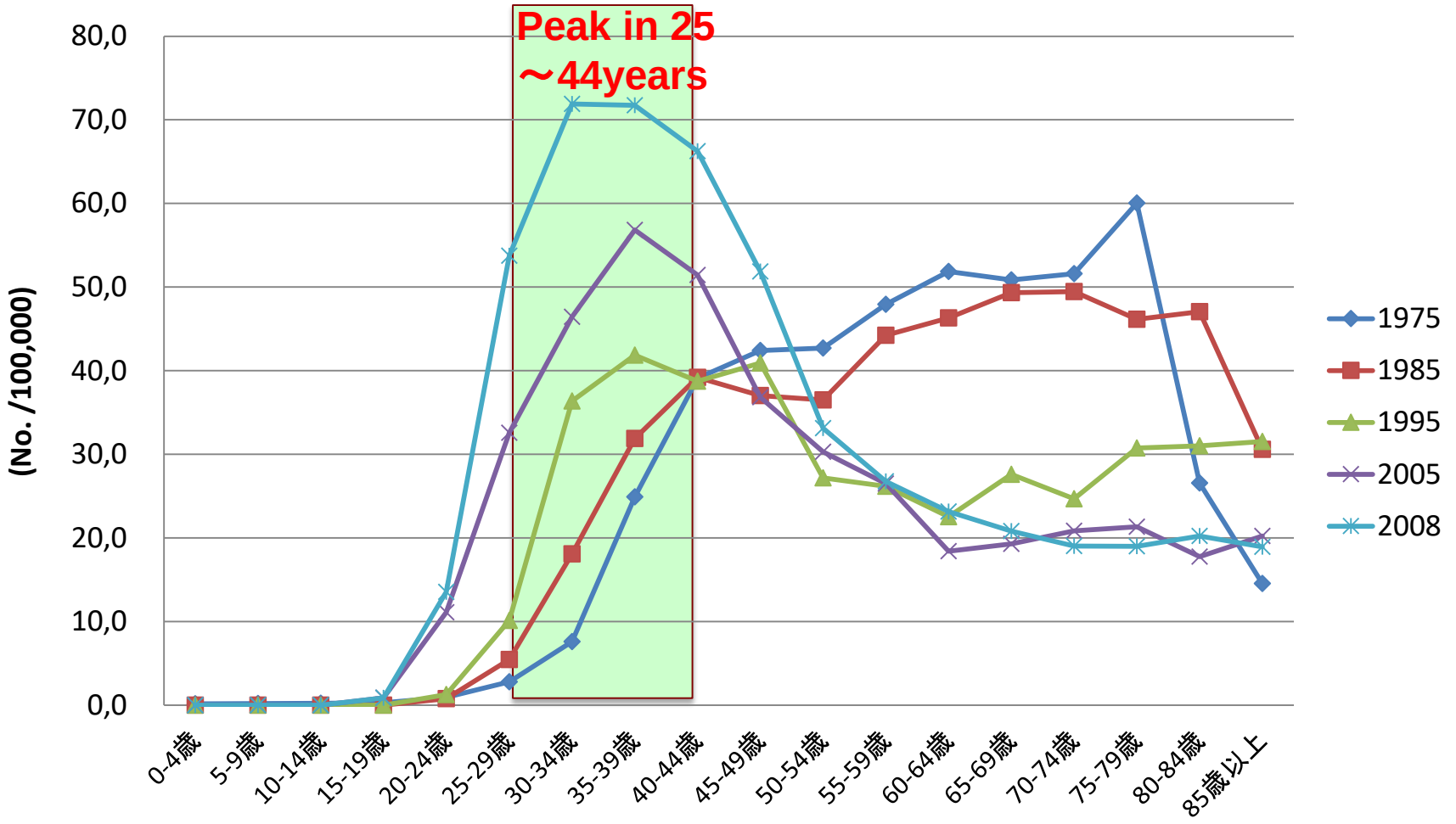
Annual incidence and mortality of cervical cancer in Japan





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.

Age-specific morbidity rates of cervical cancer in Japan

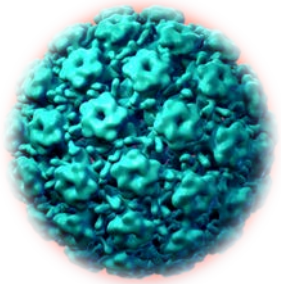


The incidence of cervical cancer in younger ages such as twenties and thirties has increased in Japan, and the mortality has also increased. Such situations in young women of reproductive (child-bearing) ages are serious issues.

- 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.

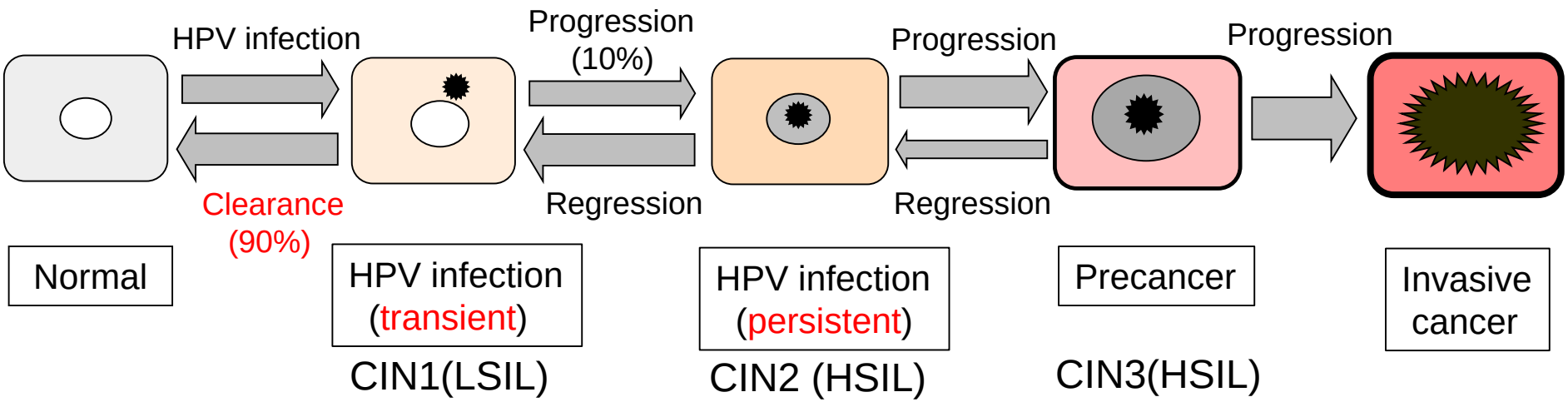
- My talk today will focus on the prevention of cervical cancer, and discuss the current issues on HPV vaccination.

What is HPV?



- HPV is a DNA virus from the papillomavirus 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.

HPV Infection and Cervical Carcinogenesis

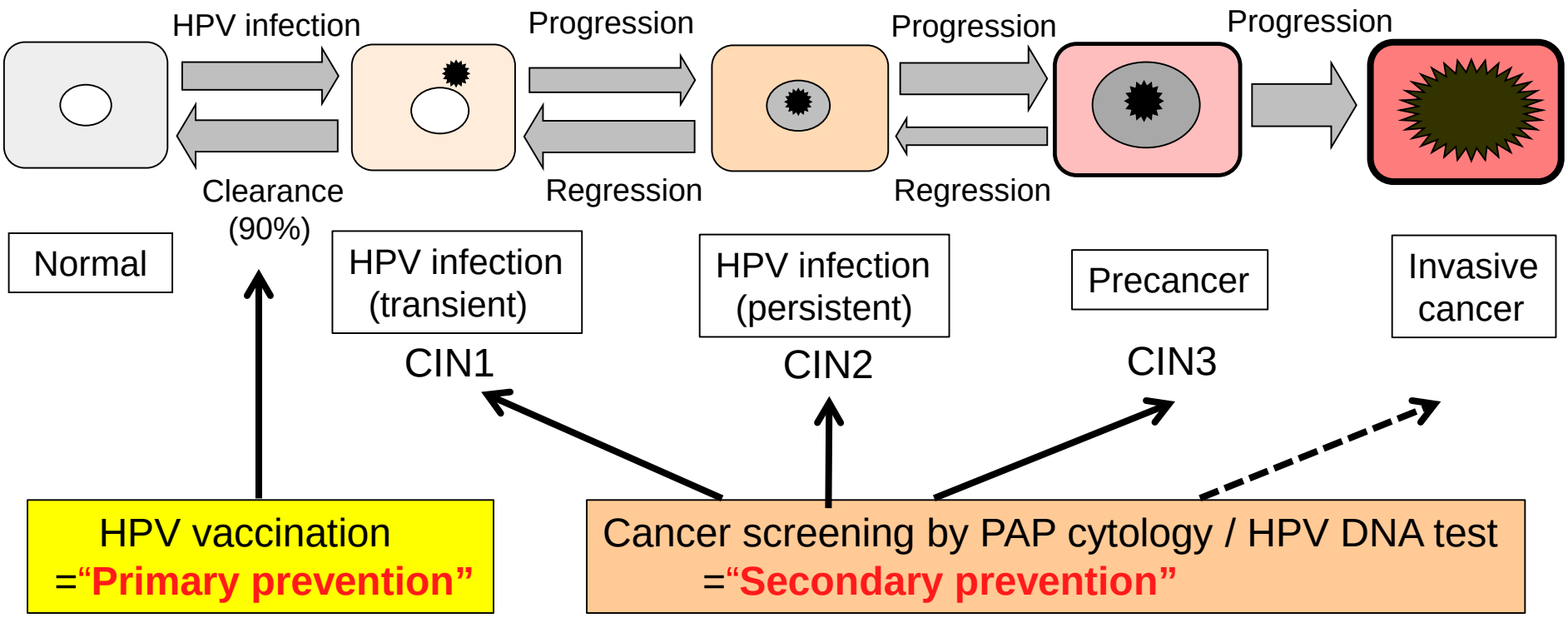


- Approximately 90% of women infected initially by HPV may eliminate the infection within 2 years. In contrast, in the remaining 10% of women, persistent HPV infection may occur, and some of those could develop high-grade precancerous lesions and some may develop invasive cancer.

- 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% CIN 3 lesions progress to invasive cancer. Invasive cancer develops over some years or longer.

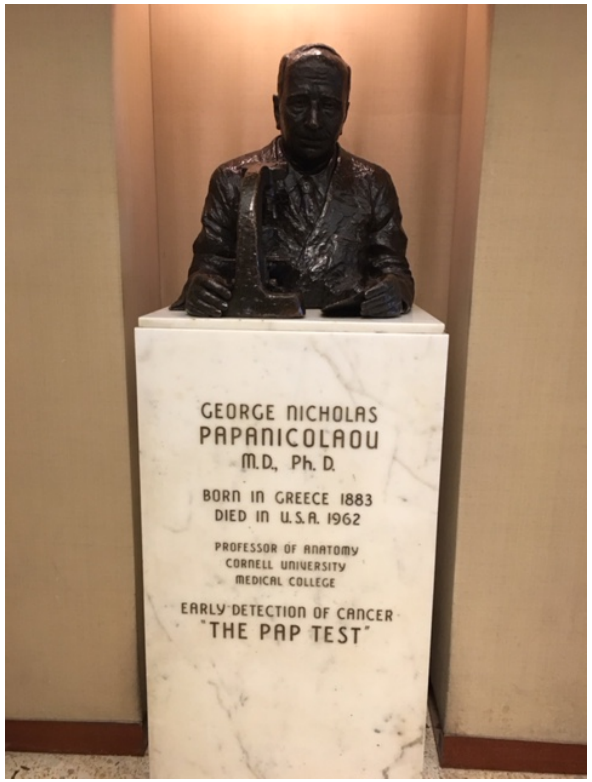
Strategies for Preventing Cervical Cancer



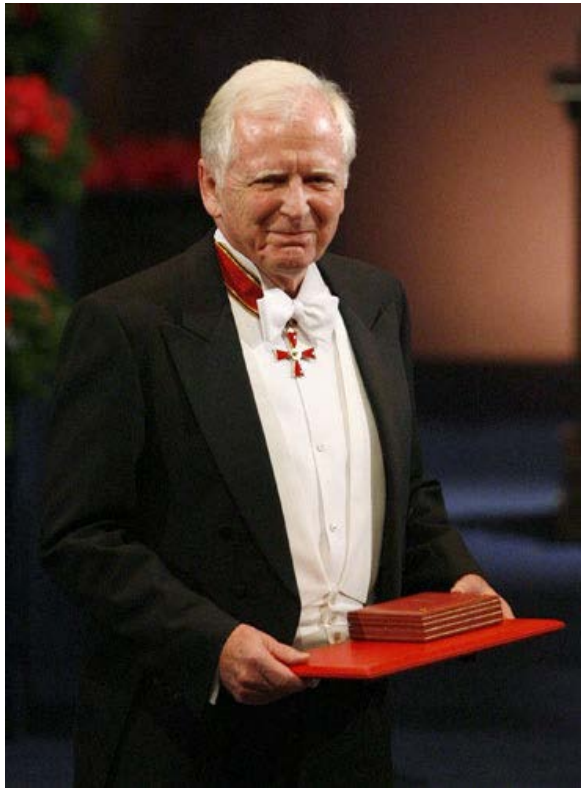
- Strategies for preventing cervical cancer consist of two major steps: Primary prevention is the prevention of HPV infection by "Vaccination". Secondary prevention is the early detection of persistent HPV infection and precancerous lesions by screening using PAP cytology or HPV test.

- Both primary and secondary prevention strategies are indispensable to prevent cervical cancer, reaching a global consensus.

Cervical Cancer is Preventable through Screening and Vaccination

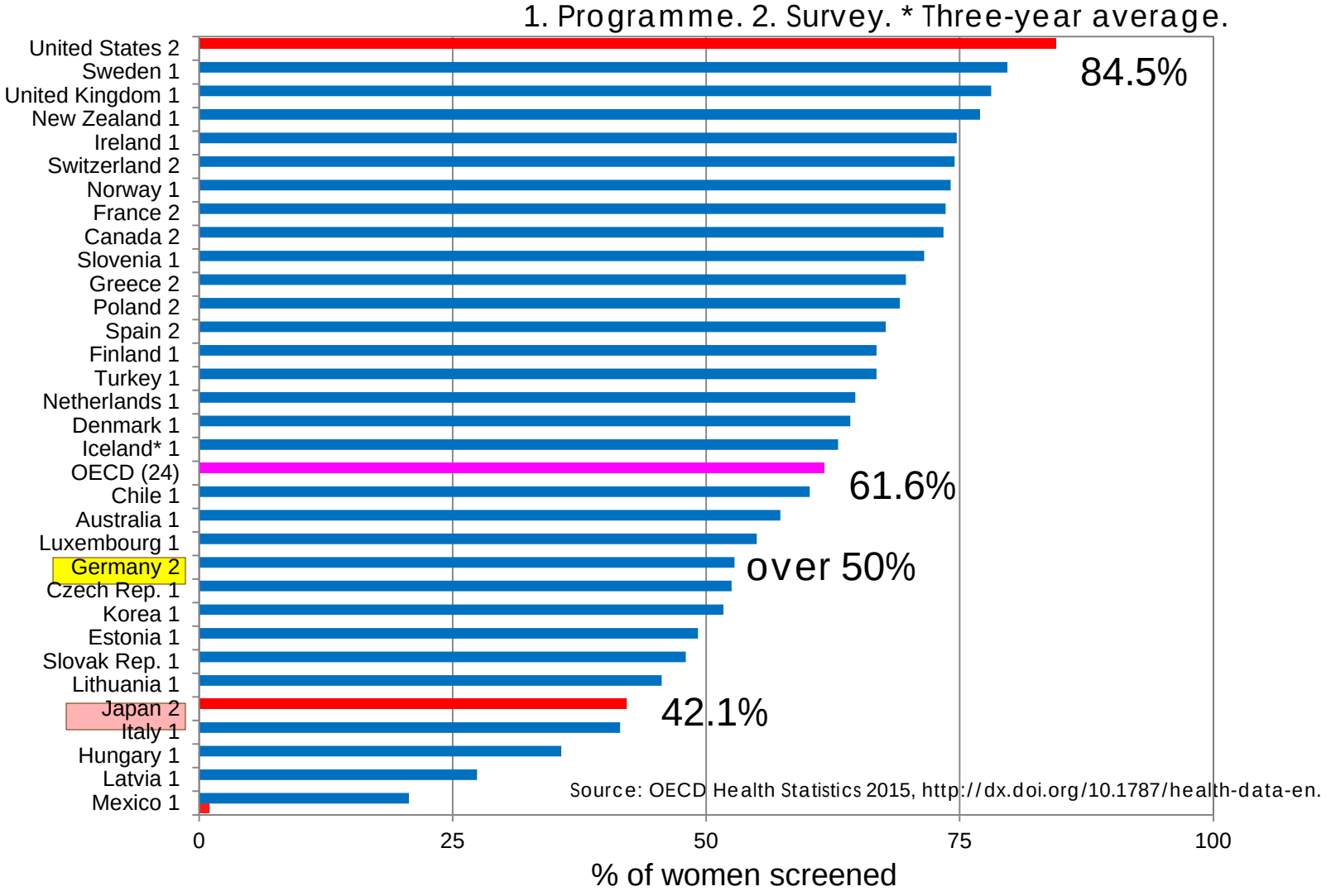


Dr. Papanicolaou invented Pap test (cytology) for cervical cancer screening



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



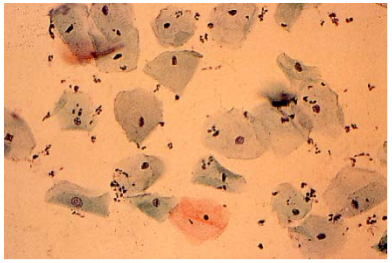
In Japan, the proportion of women undergoing PAP screening is only 35 to 40% of targeted women, which is lower than those in Western countries, at 50 to 80%.

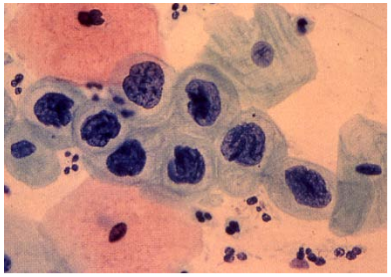
Limited Effectiveness of Cytology Screening

- 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

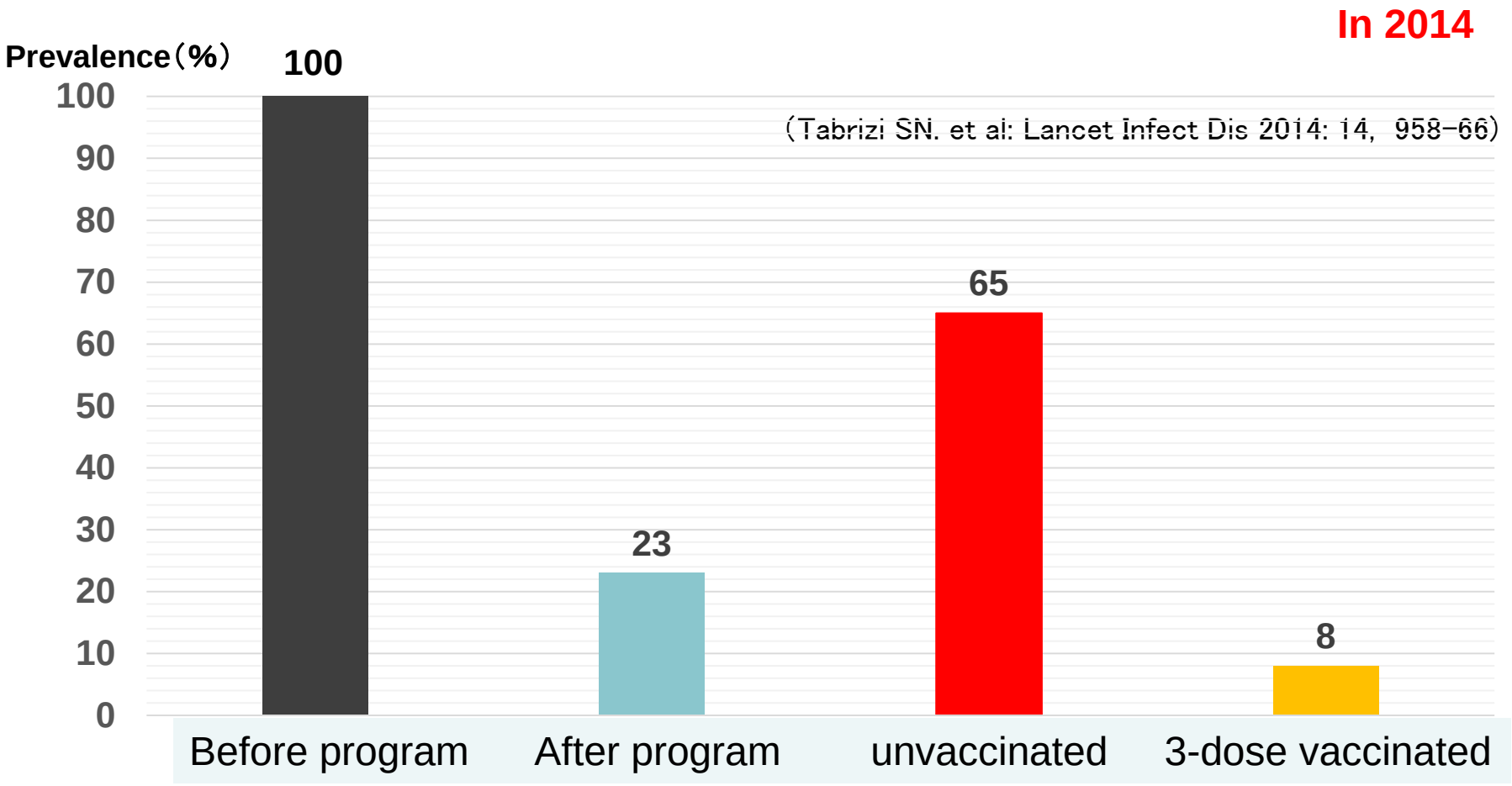
WHO recognizes the importance of cervical cancer and other HPV-related diseases as global public health problems and reiterates its recommendation that **HPV vaccines should be included in national immunization programs.**

HPV vaccines have excellent safety and efficacy profiles.

WHO position paper The Weekly Epidemiological Record (WER) No. 43, 2014, 89, 465–492

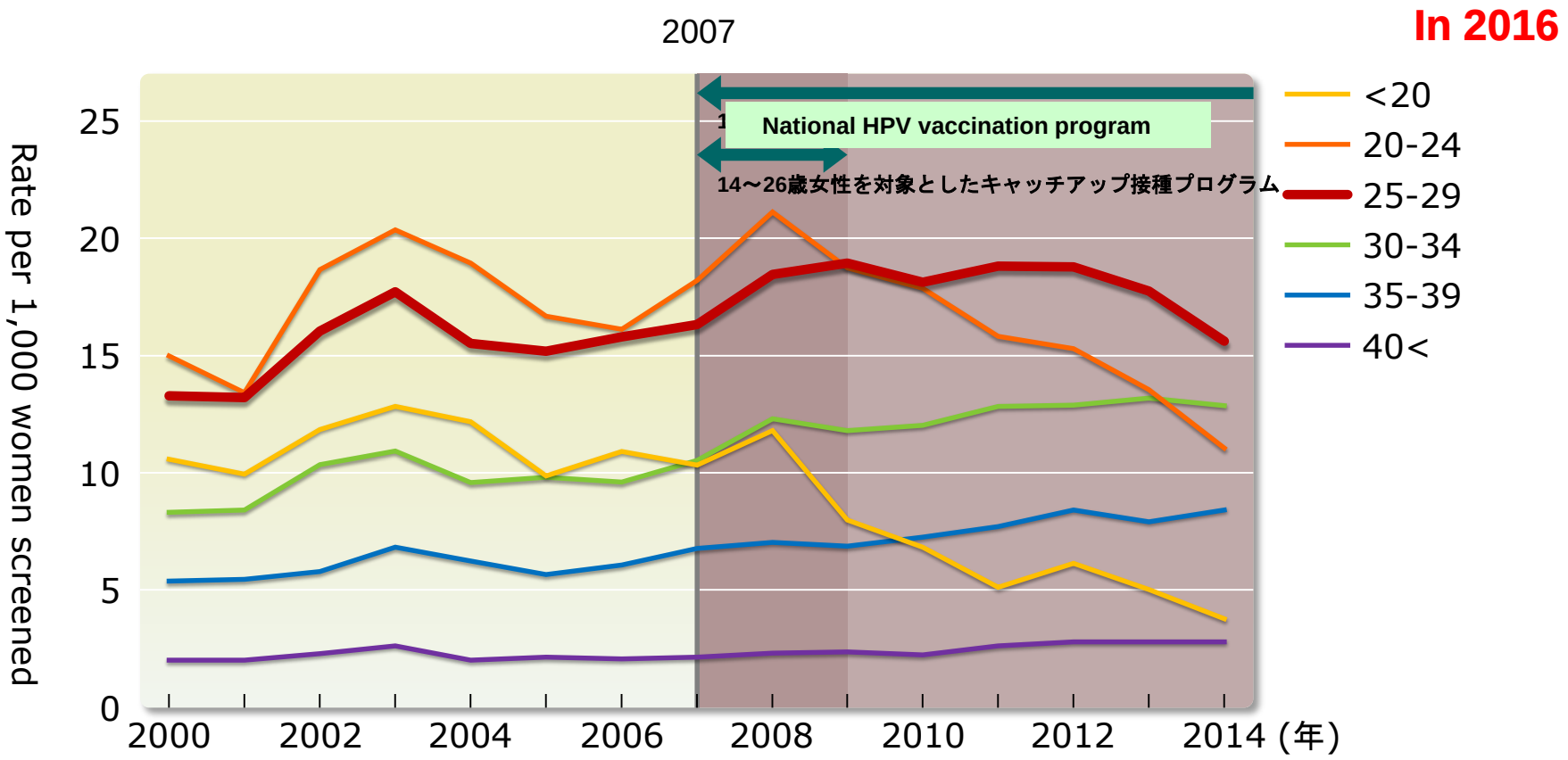
Up to now, over 65 countries have introduced HPV vaccine in their national immunization programs for girls aged 9-14 years, and in some countries also for boys.

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” .

Decline in Precancer Now up to Age of 30 Years



Brotherton JM et al. *Med J Aust*. 2016; 204(5):184-184e1.

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.

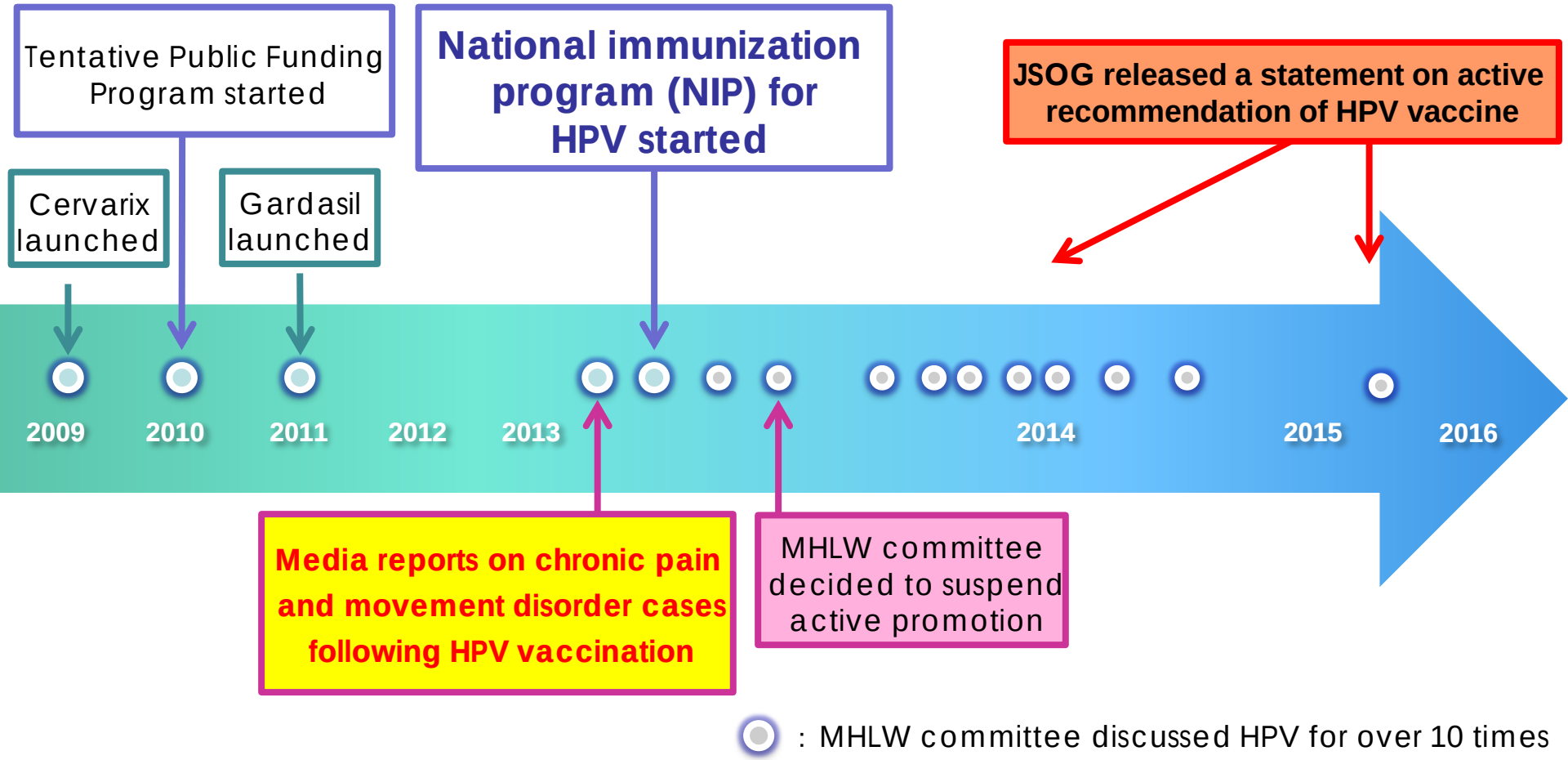
- The incidence of pre-cancerous lesions (CIN3) in vaccinated generations has decreased to less than 50% during 7-8 years following the introduction of a HPV vaccination program.

- 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

HPV vaccination status to date in Japan

Active recommendation has been suspended since June 2013.
Discussion continues at MHLW Adverse Events Review Committee.



The Beginning of Adverse Event Issue in Japan

The case of 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.

Asahi Shimbun (March 8,2013)

子宮頸がんワクチン
中学生が重い副反応
杉並区、補償へ

子宮頸がんワクチン「サーバリックス」を接種した東京都杉並区の女子中学生（14）が、歩行障害などの重い症状が出て、1年3カ月にわたり通学できない状況だったことが、7日の区議会で明らかになった。無料接種を行った区は「接種の副反応」と認め、補償する方針だ。補償額は未定。

サーバリックスは3回の接種が必要。区側によると、女子中学生は12歳だった2011年10月に区内の医療機関で2回目の接種をした。その直後、接種した左腕がしびれ、腫れて痛む症状が出た。症状は脚や背中にも広がり入院。今年1月には通学できる状態になったが、割り算ができないなど症状が残っているという。

厚生労働省は8月末

接種した延べ663万5千人のうち956人に副反応が起きているという。失神が多いが「四肢の運動能力低下」「歩行不能」などで未回復の例もあり、副反応の発生率はインフルエンザワクチンの10倍程度という。

杉並区は10年7月、子宮頸がんワクチンの接種を全額無料化。現在は全国1700以上の自治体で、国の補助を受けた接種事業が行われている。国は定期接種を進める医議決定をしている。（斎藤智子）

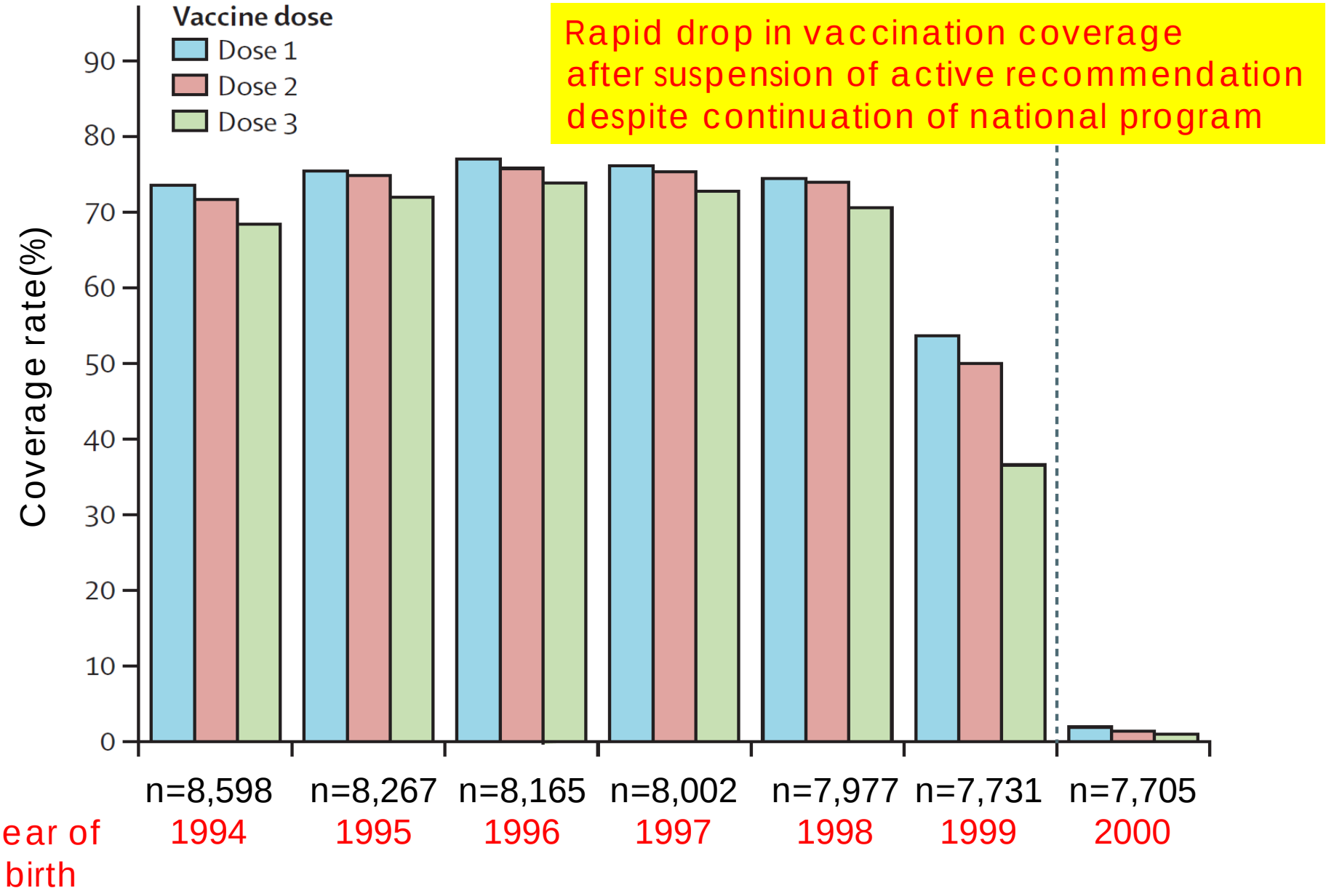
Josei Jishin (March 12, 2013)

Tokyo Shimbun (March 15, 2013)

FNN Super News (March 12, 2013)

HPV Vaccination Coverage By Birth Cohort Year in Japan

(Hanley et al. Lancet 385: 2015)



Committee has discussed over 10 times but no resolution

Date		Discussions at AERC
2013	May 16	▸ Concluded that no evidence to stop vaccination. Need to gather more information.
	Jun 14	▸ **Active promotion of HPV vaccination suspended**
	Oct 28	▸ Continue suspension
	Dec 16	▸ Reviewed all reported cases
	Dec 25	▸ Investigation results (AE cases, papers and data from foreign health authorities) reported and discussed
2014	Jan 20	▸ Suggested "**psychosomatic reaction** " causes symptoms
	Feb 26	▸ Hearing from experts on treatments of psychosomatic reactions (**functional somatic symptoms**)
	Jul 4	▸ Summarized information on functional somatic symptoms
	Oct 29	▸ Discussed follow-up survey on all adverse event cases
2015	Sep 17	▸ Results of follow-up survey reported
	Nov 27	▸ Discussed **epidemiological study** plan

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 Report[2] : 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 reviews[3] : 2015

*CRPS: Complex regional pain syndrome
**POTS: Postural orthostatic tachycardia syndrome

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.

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

THE JOURNAL OF
Obstetrics and Gynaecology Research
doi:10.1111/jog.12912 J. Obstet. Gynaecol. Res. 2015

Declaration to demand the resumption of recommendations for human papillomavirus (HPV) vaccination for cervical cancer prevention

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

J Obstet Gynaecol Res 41 : 1859–1860, 2015

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).[1] Furthermore, at the committee's 10th meeting held in July 2014, the incidence of adverse events among a cumulative total of 8 898 000 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 176; this is equivalent to 2.0 per 100 000 vaccinations.[2] Although subsequent studies did not provide scientific or epidemiologic evidence to confirm the causal relation-

treatment 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 prefectural medical associations and the Ministry of Health, Labour, and Welfare.[5] It should also be noted that the "Guidelines for the Management and Treatment of Symptoms that Occur after HPV Vaccine Injection"[6] 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 vac-

Vaccine
evier.com/locate/vaccine

Commentary

Consensus statement from 17 relevant Japanese academic societies on the promotion of the human papillomavirus vaccine

CrossMark

Vaccine 35 : 2291–2292, 2017

- 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 JSPS for holding this worthwhile symposium.

Thank you for your attention !