Prevention of Cervical Cancer: Era of HPV Testing and Vaccination

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Abstract

The incidence and mortality of cervical cancer in young women of reproductive ages have recently increased, which is a serious issue worldwide. This chapter will focus on the prevention of cervical cancer with HPV testing and vaccination. It is recognized that strategies for preventing cervical cancer consist of two major steps: preventing infection of oncogenic human papillomavirus (HPV)-16 and HPV-18 by HPV vaccination and secondary prevention by screening using HPV testing and/or cytology. Current cervical cancer screening strategies using cytology combined with HPV testing have been successfully introduced, with shifting from cytology alone to cytology plus HPV cotesting and now to a new paradigm in which HPV testing alone may become a primary screening tool. HPV vaccination is a "primary prevention" tool, and both the bivalent and quadrivalent HPV vaccines have excellent safety and efficacy profiles. Recently, a 9-valent vaccine, targeted against HPV-6, HPV-11, HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58, has been developed, which may possibly protect against over 80% of invasive cervical cancers. Further evidence on the 9-valent HPV vaccine should be accumulated worldwide, and its application is expected as a new strategy. Finally, the WHO recognizes the prevention of cervical cancer and other HPV-related diseases as global public health problems and strongly recommends the HPV vaccination programs. Both HPV vaccination and cancer screening tests are indispensable for cervical cancer prevention.

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I. Konishi (ed.), *Precision Medicine in Gynecology and Obstetrics*,
Comprehensive Gynecology and Obstetrics, DOI 10.1007/978-981-10-2489-4_5

The complete eradication of this malignant disease in the world will be realized in the near future by the further development and widespread application of these two strategies.

Keywords
Cervical cancer • Cervical intraepithelial neoplasia (CIN) • Cytology • Human papillomavirus (HPV) • HPV testing • HPV vaccine

5.1 Introduction

Cervical cancer is the fourth most common cancer in women worldwide, with approximately 500,000 estimated new cases annually and nearly 300,000 estimated related deaths in the world [1]. In Japan, over 11,000 cases of cervical cancer are newly diagnosed every year, and more than 3000 women die of the disease, which causes the second greatest number of deaths among gynecologic malignancies. Furthermore, over the last two decades, there has been an increasing trend in cervical cancer mortality among young Japanese women below the age of 50 years [2]. In fact, the incidence rate of cervical cancer in those of younger ages such as in their 20s and 30s has recently increased in Japan, and the mortality of these patients has also increased in parallel. Such situations associated with cervical cancer in young women of reproductive (childbearing or child-rearing) ages are serious issues to share and solve, drawing social attention not only in Japan but also in other developed and developing countries.

Invasive cervical cancer is generally treated by surgery or radiotherapy with/without chemotherapy. While concurrent chemoradiotherapy (CCRT) has been frequently selected for FIGO stage IIB–IVB advanced disease, most patients with stage IA2 through IIB disease are treated with radical hysterectomy in Japan [3]. Despite the generally good prognosis of patients with FIGO stage I–II cervical cancer, significant numbers of patients develop recurrence, and the prognosis of patients with recurrence, metastatic disease, or advanced disease is still poor. Furthermore, most patients who undergo radical surgery or CCRT are likely to suffer from undesirable treatment-related adverse symptoms and/or lose their fertility due to hysterectomy, ovariectomy, or irradiation to the reproductive organs, which results in a lowered quality of life (QOL) even if their disease is cured. In addition, over 9000 patients with precancerous lesions such as cervical intraepithelial neoplasia (CIN)2/3 or microinvasive carcinoma (FIGO stage IA1) are treated with cervical conization every year in Japan, resulting in the possibility of complications on subsequent pregnancy, such as an increased risk of preterm birth, as well as a marked psychological burden for affected women even if their fertility is preserved.

Considering these current situations, to increase the survival rate of cervical cancer patients and improve the posttreatment QOL as well as to protect the health of young women, fundamental and strategic prevention of cervical cancer is an important and continuing global challenge, which could lead to the eradication of this

disease worldwide in the future. This chapter will focus on the prevention of cervical cancer and discuss recent advances, current issues, and future perspectives on HPV testing/cytology and HPV vaccination.

5.2 Prevention of Cervical Cancer: Primary and Secondary Prevention

It is generally recognized based on large-scale global evidence that strategies for preventing cervical cancer consist of two major steps (Fig. 5.1). Primary prevention is the prevention of infection by oncogenic human papillomavirus (HPV), which is directly involved in cervical carcinogenesis and causes nearly all cervical cancers, by HPV vaccination of adolescent girls aged 9–14 years. In contrast, secondary prevention is the early detection of persistent HPV infection into cervical epithelial cells and subsequent precancerous lesions by screening using HPV testing and/or the Papanicolaou (PAP) test (cytology) in women older than 20 years old. Both primary and secondary prevention strategies are indispensable to prevent invasive cervical cancer effectively, reaching a global consensus.

Two highly effective and safe HPV vaccines are available. HPV vaccination is now performed in over 65 countries in the world as the national governmental programs, and its active introduction is strongly recommended by the World Health Organization (WHO) [4] not only in developed countries but also in developing or resource-limited countries where the availability of cytology/HPV testing is limited. More than 200 million HPV vaccinations have been performed worldwide with no significant safety issues, and its effectiveness has been confirmed in countries with high vaccination rates. In contrast, cervical cancer screening systems using HPV testing combined with the PAP test (cytology) have started in some developed countries, but their criteria and methodologies are still diverse among the countries, and have yet to be established worldwide, although their effectiveness has been confirmed.

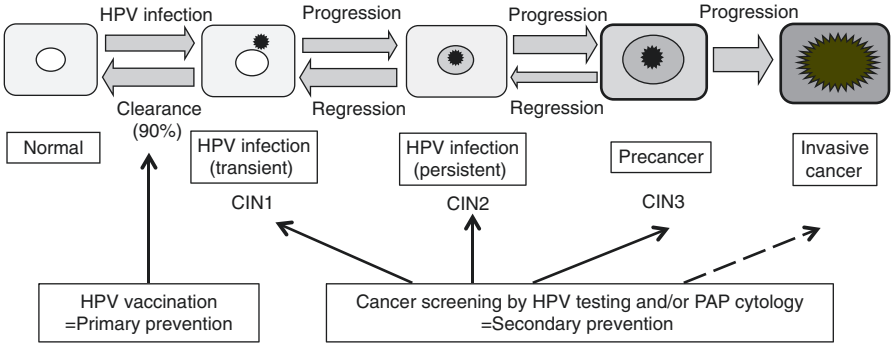

Fig. 5.1 HPV infection and cervical carcinogenesis: role of primary and secondary prevention against progression to invasive cancer

5.3 HPV Infection and Cervical Carcinogenesis

HPV has many types, and its infection is related to various diseases in humans. About 15 types of HPV (HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-68, HPV-73, and HPV-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 common and generally asymptomatic, and it is estimated that 50–80% of healthy sexually active individuals are at risk of HPV infection within their lifetime. However, approximately 90% of women infected initially (incidentally) by HPV may eliminate the infection from their cervical epithelial cells within 2 years, and most women with this transient infection never develop cancer. 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 subsequently develop invasive cancer (Fig. 5.1).

Nearly all patients with invasive cervical cancer show evidence of HPV infection. HPV-16 and HPV-18 are the most oncogenic, and these two types are responsible for about 70% of cervical squamous cell carcinomas worldwide. In Japan, HPV-16/HPV-18 were detected in 24% of CIN1, 36% of CIN2/3, and 67% of invasive cervical cancer [5]. More importantly, the detection rate of HPV-16/HPV-18 in invasive cervical cancers varies according to the age and is the highest in patients aged 20–29 years (90.0%) [5]. The next most frequently detected HPV types in cervical cancer are HPV31, HPV-33, HPV-35, HPV-45, HPV-52, and HPV-58. HPV infection with these high-risk types 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.

Invasive cervical cancer results from the progression of precancerous lesions named CIN or squamous intraepithelial lesion (SIL). CIN is histologically graded into CIN1, CIN2, and CIN3, although most CIN1 and some CIN2 regress. The results of a PAP test are presented according to the Bethesda system, based on cytologic findings: atypical squamous cells of undetermined significance (ASC-US) and low-grade squamous intraepithelial lesions (LSIL) show transient HPV infection (CIN1), while high-grade squamous intraepithelial lesions (HSIL) show persistent HPV infection with cellular atypia (CIN2–3) (Fig. 5.1). In fact, over 70% of ASC-US or CIN1 lesions regress, while 10–30% CIN3 lesions progress to invasive cancer. After screening using cytology, women with abnormal results (ASC-US, LSIL, HSIL, AGC, or more) need colposcopy and biopsy to determine the histological diagnosis and subsequent management/treatment.

Usually, invasive cancer develops from CIN slowly over some years or longer. This long natural history from HPV infection to the development of cervical cancer provides the opportunity for screening to detect this process in precancerous stages and allows the treatment of preinvasive lesions before they become cancerous, which could prevent invasive cancer effectively.

5.4 Limited Effectiveness of Cytology Screening

Historically, cervical cancer screening was conducted using the PAP test (cytology) alone until HPV testing became available. Programs since the 1960s using annual screening with Papanicolaou-stained cervical cytology smears have been successful, and actually, it has contributed to a significant decrease in the mortality rate due to cervical cancer. However, it is now difficult to more effectively reduce the number of deaths from cervical cancer only through this screening measure, mainly due to its relatively lower sensitivity (the percentage of "true-positive" cases that are detected by the screening test). Previous studies showed that the sensitivity for detecting high-grade lesions on a single conventional PAP test is approximately 55–80% [6], and failures to prevent invasive cervical cancer can be attributed to false-negative PAP smears as well as to poor follow-up of abnormal results [7]. False-negative results occasionally occur, especially in pregnant women or in patients with glandular abnormality or precancerous/cancerous lesions of adenocarcinoma. Additionally, in Japan, the proportion of those undergoing such examinations is only 30–40% of targeted women >20 years old, which is lower than those in Western countries, at approximately 70–80%. Recently, the liquid-based cytology technique was developed to improve the sensitivity of screening. Up to now, there has been no evidence that liquid-based cytology significantly reduces the number of deaths compared with the conventional PAP smear test, although there is actually one advantage that the HPV test can be simultaneously conducted on the same preparation for the examination of liquid-based cytology.

5.5 HPV Testing

In consideration of the limitations of cytology, efforts have focused on enhancing the sensitivity of screening to reduce false-negative results and developing new molecular/virological tests to detect high-risk HPV as well as to reduce unnecessary colposcopic examinations. Since 2000, various HPV-DNA tests have been developed, and now some are commercially available for the detection of HPV in cervical specimens [8]. Most of these tests generate a pooled result ("high-risk HPV-positive" or "high-risk HPV-negative") to detect nucleic acids of the 12 HPV types altogether (HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, and HPV-59; some tests also detect HPV-66 and HPV-68). In contrast, HPV genotyping tests that distinguish individual HPV types are also available. HPV infections are particularly common in young women, and the majority clear their infection within 2 years; therefore, the challenge of incorporating HPV testing into cervical screening programs is to balance increasing sensitivity to detect CIN2/3 and minimizing overdiagnosis/treatment of women with transient HPV infections and cervical abnormality that may regress.

Actually, previous studies demonstrated that, compared with cytology, HPV-DNA testing was more sensitive for identifying women who have CIN2/3, with

sensitivities of 84–97%, and that the combination of HPV testing and cytology led to an almost 100% sensitivity. In contrast, it has been noted that HPV-DNA testing generally has a lower specificity compared with cytology. Among women ≥30 years old, cytology had a specificity of 97% compared with 94% for HPV testing. The specificity of HPV-DNA testing is likely be lower among women younger than 30 years old, who have more transient HPV infection.

Now, HPV testing has been approved for use in the following: (1) as a second test (triage) following a cytology result of ASC-US; (2) for primary screening combined with the PAP test for women aged 30 years or older or primary screening by the HPV test alone may be considered; and (3) HPV genotyping tests that distinguish highly oncogenic HPV types, especially HPV-16 and HPV-18, for the further triage of women with a positive pooled result or for risk stratification in patients with CIN1/2.

A recent major clinical trial, "ATHENA HPV Study," demonstrated that incorporating screening with HPV and triage of HPV-positive women by a combination of genotyping for HPV-16/HPV-18 and cytology provided a good balance between maximizing sensitivity (benefit) and specificity by limiting the number of colposcopies (potential harm) [9]. Furthermore, the study showed that primary HPV screening in women ≥25 years is as effective as a hybrid screening strategy that uses cytology if 25–29 years and cotesting if ≥30 years [10]. Further analysis of HPV genotyping from the ATHENA trial supported the identification of HPV-16 in primary screening for all women and demonstrated that the identification of HPV-18 is also warranted with a significant contribution to adenocarcinoma in situ (AIS) and cancer [11].

5.6 Current Cervical Cancer Screening Guidelines Using HPV Test and PAP Cytology

Table 5.1 demonstrates the current cervical cancer screening guidelines in the USA [8, 12]. All normal-risk women should begin cervical cancer screening at age 21. Between the ages of 21 and 29 years, women should be screened using cytology every 3 years. HPV testing is used following an abnormal cytology result. Primary HPV testing can be considered starting at age 25 every 3 years. For women aged 30–65 years, screening can be done using cytology alone every 3 years or HPV cotesting (cytology plus simultaneous HPV test) every 5 years. The guidelines support the discontinuation of screening in women older than 65 years who have three consecutive normal cytology results or two consecutive negative cotest results within the previous 10 years, with the most recent test performed within the past 5 years.

In Japan, the screening system using cytology in combination with the HPV test has not yet been established and is still under investigation by clinical trials. At this time, the guideline proposed by the Japan Association of Obstetricians and Gynecologists in 2012 (Fig. 5.2) is applied for cancer screening targeting women aged 30 years or older in some local areas or cities. According to this guideline,

Table 5.1 Current cervical cancer screening guidelines (2012) in the U.S. [8]

Age (years)	Screening recommendations
21	Initiation of screening
21–29	Cytology every 3 years, or primary HPV testing can be considered starting at age 25 every 3 years; if primary HPV testing is positive, test for HPV16 and HPV18 and refer to colposcopy if positive, or cotesting if negative
30–65	Cytology every 3 years and HPV testing for triage of ASC-US, or HPV cotesting every 5 years and test for HPV16 and HPV18 if normal cytology but HPV-positive, or primary HPV screening every 3 years as indicated above
Discontinuation of screening	Women aged >65 who have 3 or more consecutive negative cytology tests or two consecutive negative cotests within 10 years with the most recent test performed within 5 years; women of any age who have a total hysterectomy and have no history of cervical cancer or precancer should not be screened

From the American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), American Society for Clinical Pathology (ASCP), U.S. Preventive Services Task Force (USPSTF), and American College of Obstetricians and Gynecologists (ACOG) with interim guidance from the Society of Gynecologic Oncology and ACOG

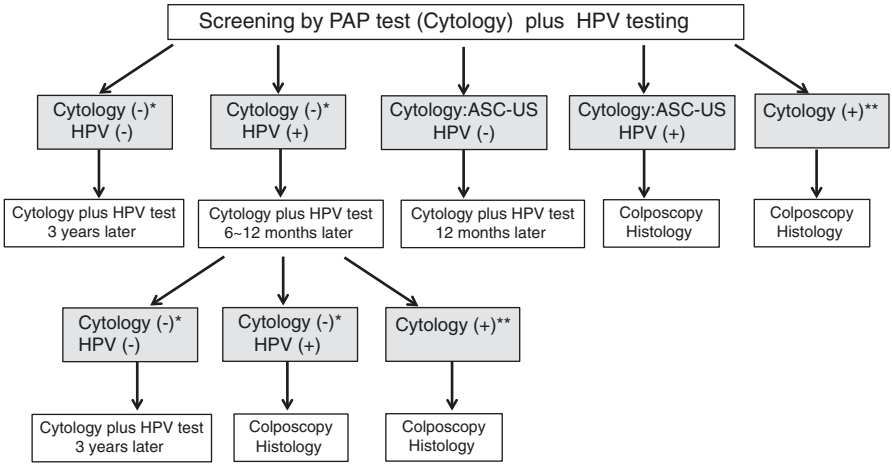

Fig. 5.2 Cervical cancer screening system by PAP test (cytology) in combination with HPV-DNA test in Japan: recommended in 2012 by the Japan Association of Obstetricians and Gynecologists. *Cytology (−): NILM. **Cytology (+): LSIL, HSIL, ASC-H, AGC, or more

women who are both cytology-negative and HPV-negative can be screened 3 years later. Women who are cytology-negative, but HPV-positive, are recommended to undergo cotesting again 6–12 months later. Women with cytology of ASC-US and HPV-positive or cytology of LSIL or more should undergo colposcopy and biopsy. Such studies are expected to establish the appropriate screening system in Japan.

5.7 HPV Vaccines

Two prophylactic vaccines are currently available in many countries worldwide for the primary prevention of cervical cancer and other HPV-related diseases [4, 13]. Both bivalent and quadrivalent vaccines are developed against two main oncogenic HPV genotypes, HPV-16 and HPV-18, responsible for 65–70% of invasive cervical cancer cases. The quadrivalent vaccine is also directed against low-oncogenic types, HPV-6 and HPV-11, that cause anogenital warts (condyloma). The quadrivalent vaccine was first licensed in 2006, followed by licensing of the bivalent vaccine in 2007. It is recommended that HPV vaccine should be administered before the onset of sexual activity (before the first exposure to HPV infection). Both vaccines are prepared from virus like particles that resemble HPV type-specific L1 protein, which contains no viral DNA and, therefore, is noninfectious. Immunologically, HPV vaccine can protect against HPV infecting cervical epithelial cells through humoral immunity mediated by neutralizing antibodies against HPV-16/HPV-18.

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. Both vaccines are used according to the three-dose immunization schedule at 0, 1(2), and 6 months. After a three-dose schedule, both vaccines are highly immunogenic, and antibody titers remain high for at least 8 years or more. Recent reports have shown that two doses of HPV vaccine in girls aged 9–14 years are non-inferior to three doses in terms of immunogenicity, suggesting the possibility of introducing a two-dose immunization program to such younger girls [4].

5.8 Efficacy of HPV Vaccination and Latest Evidence of HPV Vaccine Benefits

Both vaccines have been evaluated in large Phase III pre-licensed studies, where they can protect against HPV-16/HPV-18 infections at almost 100% in vaccine recipients not already infected with HPV (HPV-naive) and demonstrate high efficacy against HPV-16- or HPV-18-associated precancerous (CIN2/3) lesions in such HPV-naive individuals [14, 15]. It was also observed that the quadrivalent vaccine significantly decreased genital warts.

Recently, many beneficial effects have been reported in several industrialized countries where national HPV vaccination programs had been introduced early since 2007–2008, such as Australia, the UK (England and Scotland), or Denmark, with a three-dose coverage rate of over 70% of the targeted population. In these countries, actually, HPV vaccination has led to marked reductions in the prevalence of vaccine-preventable HPV types, HPV-16 and HPV-18 (and HPV-6/HPV-11 if quadrivalent). Interestingly, this was observed not only in vaccinated women but also in unvaccinated women, suggesting a “herd-immunity effect” [16].

Furthermore, in these countries, there have been some reductions in the prevalence of other HPV types (HPV-31, HPV-33, and HPV-45) that are not specifically targeted by the vaccine, suggesting a "cross-protection effect" [17].

Consistent with such a marked decrease in the HPV infection rates in younger women or girls, HPV vaccination has shown a major impact on the incidence of high-grade cervical abnormalities. In fact, the incidence of CIN3 or AIS in vaccinated generations has decreased to less than 50% during 7–8 years following the introduction of a national HPV vaccination program [18–20]. These findings strongly 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 this disease in the near future.

5.9 Global Consensus on Safety of HPV Vaccine

The WHO Global Advisory Committee for Vaccine Safety (GACVS) has repeatedly reviewed the evidence on the safety of HPV vaccines and concluded that both HPV vaccines continue to have an excellent safety profile [4].

As a local adverse event, both vaccines are associated with relatively high rates of injection site reactions, particularly pain, but these are usually of short duration and resolve spontaneously. Systemic adverse events following immunization (AEFI), although it has not yet been confirmed whether they are related to vaccination, include pyrexia (fever), headache, dizziness, myalgia, arthralgia, and gastrointestinal symptoms (nausea, vomiting, abdominal pain). In a comparison of the bivalent and quadrivalent vaccines, systemic reactions were reported at comparable rates. Postvaccination syncope, possibly the vasovagal reflex, has been reported at relatively higher rates but can be minimized and its complications avoided with appropriate care.

There have been no clinically relevant differences reported between vaccinated and unvaccinated groups with regard to new-onset chronic disease, including autoimmune disease, neurological disorders, or immune-mediated diseases. A few case reports showed a link between vaccination and the onset of these chronic conditions; however, a well-conducted population-based study demonstrated no association between HPV vaccine and such conditions [4]. It was also confirmed that Guillain-Barré syndrome and acute disseminated encephalomyelitis (ADEM) after vaccination were within the expected range in a general population. In a large cohort study in Denmark and Sweden, there was no causal relationship between exposure to HPV vaccine and the incidence of autoimmune, neurological, or venous thromboembolic adverse events [21].

Recently, the European Medicines Agency (EMA) confirmed that evidence does not support a causal link between HPV vaccine and the development of two syndromes, complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS), in girls and young women aged 10–19 years [22].

5.10 Current Issues in Japan on Suspension of Recommendation of HPV Vaccination

Over 3 years have passed since June 2013 when the Ministry of Health, Labour, and Welfare (MHLW) of Japan suspended recommendations for HPV vaccination because of reported cases of suspected adverse events such as chronic pain and motor impairment postvaccination. The Investigative Committee of the MHLW thoroughly and repeatedly analyzed the data and concluded that various postvaccination symptoms including persistent pain or motor impairment are functional physical symptoms (functional somatic syndrome). They also showed that the incidence rate of such adverse events was very low: 176 cases, equivalent to 0.005% of all vaccine recipients (3,380,000) in Japan. Subsequent studies did not provide any scientific or epidemiologic evidence to confirm the causal relationship between these symptoms and HPV vaccine; nevertheless, the suspension of recommendations for vaccination has continued, consequently decreasing the vaccination rate to nearly 0% in Japan [23]. It is of marked concern that if the suspension of vaccine recommendations continues, young Japanese generations will be deprived of the benefits of vaccines for cancer prevention.

The Japanese MHLW in cooperation with the Japan Society of Obstetrics and Gynecology (JSOG) organized 85 cooperative medical institutions covering all areas in Japan to provide treatment for those suffering from any symptoms after HPV vaccination. Furthermore, "Guidelines for the management and treatment of symptoms that occur after HPV vaccine injection" was published in August 2015. Based on this situation, the JSOG published their declaration to demand the immediate resumption of recommendation for HPV vaccination in August 2015 [24]. Furthermore, the Expert Council on Promotion of Vaccination consisting of 15 Japanese academic associations including JSOG also published a statement for the promotion of HPV vaccination in April 2016.

GACVS (WHO) made the following additional comments in December 2015 on such Japanese situations [25]: "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 a consensus to resume HPV vaccination. As a result, young women in Japan are being left vulnerable to HPV-related cancers that otherwise could be prevented. Policy decisions based on weak evidence, leading to a lack of use of safe and effective vaccines, can result in real harm."

As is the case in Japan, public concern and incorrect rumors about adverse events as well as broadcasting them by "nonscientific" media may lead to strong resistance to increasing vaccine coverage. A thorough surveillance system of adverse events following vaccination is the most important, but it should be complemented by assessment of the real causal relationship of all suspected adverse events by scientific and epidemiologic analyses.

5.11 Conclusions and Future Perspectives

Current cervical cancer screening strategies as a "secondary prevention" using cytology combined with HPV testing have been successfully introduced, but further efforts are needed for improving the efficiency and effectiveness and preventing increased costs. The importance of HPV testing has been recognized, and its role in cervical screening is shifting from cytology alone to cytology plus HPV cotesting and now to a new paradigm in which HPV testing alone may become a primary screening tool.

HPV vaccination is a "primary prevention" tool, and both the bivalent and quadrivalent HPV vaccines have excellent safety and efficacy profiles. However, vaccination cannot eliminate the need for screening with cytology and/or HPV testing later in life, since both vaccines can protect against HPV-16/HPV-18 infection, but not protect against all high-risk HPV types. Recently, in February 2015, the US Advisory Committee on Immunization Practices (ACIP) recommended 9-valent HPV vaccine [26], a newly developed vaccine targeted against HPV-6, HPV-11, HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58, as one of three HPV vaccines that can be used for routine vaccination. As HPV-16/HPV-18 are responsible for 65–70% and the five additional types (HPV-31, HPV-33, HPV-45, HPV-52, HPV-58) for about 15%, the 9-valent HPV vaccine may possibly protect against over 80% of invasive cervical cancers. Additionally, it has been reported that approximately 40–50% of CIN2/3 are caused by HPV-16/HPV-18 and 25% by HPV-31, HPV-33, HPV-45, HPV-52, or HPV-58. Further evidence on the 9-valent HPV vaccine should be accumulated worldwide, and its application is expected as a new strategy.

Finally, the WHO recognizes the prevention of cervical cancer and other HPV-related diseases as global public health problems and strongly recommends that HPV vaccines should be included in national immunization programs. Both HPV vaccination and cancer screening tests are indispensable for cervical cancer prevention, with a global consensus. The complete eradication of this malignant disease in the world will be realized in the near future by the further development, improvement, and widespread application of these two strategies.

Disclosure Statement The author has no conflict of interest.

References

1. GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012. International Agency for Research on Cancer, World Health Organization. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx
2. Motoki Y, Mizushima S, Taguri M, Takahashi K, Asano R, Kato H, Asai-Sato M, Katayama K, Okamoto N, Hirahara F, Miyagi E. Increasing trends in cervical cancer mortality among young

Japanese women below the age of 50 years: an analysis using the Kanagawa population-based Cancer Registry, 1975-2012. Cancer Epidemiol. 2015;39(5):700–6. doi:10.1016/j.canep.2015.08.001.
3. Yamagami W, Aoki D. Annual report of the committee on gynecologic oncology, the Japan Society of Obstetrics and Gynecology. J Obstet Gynaecol Res. 2015;41:1861–9.
4. Human papillomavirus vaccines: WHO position paper, October 2014. Wkly Epidemiol Rec. 2014;89(43):465–91. http://www.who.int/wer
5. Onuki M, Matsumoto K, Satoh T, Oki A, Okada S, Minaguchi T, Ochi H, Nakao S, Someya K, Yamada N, Hamada H, Yoshikawa H. Human papillomavirus infections among Japanese women: age-related prevalence and type-specific risk for cervical cancer. Cancer Sci. 2009;100(7):1312–6. doi:10.1111/j.1349-7006.2009.01161.x.
6. Nanda K, McCrory DC, Myers ER, Bastian LA, Hasselblad V, Hickey JD, Matchar DB. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. Ann Intern Med. 2000;132(10):810–9.
7. Spence AR, Coggin P, Franco EL. Process of care failures in invasive cervical cancer: a systematic review and meta-analysis. Prev Med. 2007;45:93–106. doi:10.1016/j.ypmed.2007.06.007.
8. Burd EM. Human papillomavirus laboratory testing: the changing paradigm. Clin Microbiol Rev. 2016;29(2):291–319. doi:10.1128/CMR.00013-15.
9. Cox JT, Castle PE, Behrens CM, Sharma A, Wright Jr TC, Cuzick J, Athena HPV Study Group. Comparison of cervical cancer screening strategies incorporating different combinations of cytology, HPV testing, and genotyping for HPV 16/18: results from the ATHENA HPV study. Am J Obstet Gynecol. 2013;208(3):184.e1–11. doi:10.1016/j.ajog.2012.11.020.
10. Wright TC, Stoler MH, Behrens CM, Sharma A, Zhang G, Wright TL. Primary cervical cancer screening with human papillomavirus: end of study results from the ATHENA study using HPV as the first-line screening test. Gynecol Oncol. 2015;136(2):189–97. doi:10.1016/j.ygyno.2014.11.076.
11. Monsonego J, Cox JT, Behrens C, Sandri M, Franco EL, Yap PS, Huh W. Prevalence of high-risk human papilloma virus genotypes and associated risk of cervical precancerous lesions in a large U.S. screening population: data from the ATHENA trial. Gynecol Oncol. 2015;137(1):47–54. doi:10.1016/j.ygyno.2015.01.551.
12. Saslow D, Solomon D, Lawson HW, Killackey M, Kuasingam SL, Cain J, Garcia FA, Moriarty AT, Waxman AG, Wilbur DC, Wentzensen N, Downs Jr LS, Spitzer M, Moscicki AB, Franco EL, Stoler MH, Schiff-man M, Castle PE, Myers ER, ACS-ASCCP-ASCP Cervical Cancer Guideline Committee. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. CA Cancer J Clin. 2012;62:147–72. doi:10.3322/caac.21139.
13. Bailey HH, Chuang LT, duPont NC, Eng C, Foxhall LE, Merrill JK, Wollins DS, Blanke CD. American Society of Clinical Oncology statement: human papillomavirus vaccination for cancer prevention. J Clin Oncol. 2016;34(15):1803–12. doi:10.1200/JCO.2016.67.2014.
14. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med. 2007;356(19):1915–27.
15. Paavonen J, Naud P, Salmerón J, Wheeler CM, Chow SN, Apter D, Kitchener H, Castellsague X, Teixeira JC, Skinner SR, Hedrick J, Jaisamrarn U, Limson G, Garland S, Szarewski A, Romanowski B, Aoki FY, Schwarz TF, Poppe WA, Bosch FX, Jenkins D, Hardt K, Zahaf T, Descamps D, Struyf F, Lehtinen M, Dubin G, HPV PATRICIA Study Group. 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, randomized study in young women. Lancet. 2009;374(9686):301–14. doi:10.1016/S0140-6736(09)61248-4.
16. Tabrizi SN, Brotherton JM, Kaldor JM, Skinner SR, Liu B, Bateson D, McNamee K, Garefalakis M, Phillips S, Cummins E, Malloy M, Garland SM. 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. doi:10.1016/S1473-3099(14)70841-2.
17. Mesher D, Panwar K, Thomas SL, Beddows S, Soldan K. Continuing reductions in HPV 16/18 in a population with high coverage of bivalent HPV vaccination in England: an ongoing cross-sectional study. BMJ Open. 2016;6(2):e009915. doi:10.1136/bmjopen-2015-009915.
18. Crowe E, Pandeya N, Brotherton JM, Dobson AJ, Kisely S, Lambert SB, Whiteman DC. 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. doi:10.1136/bmj.g1458.
19. Pollock KG, Kavanagh K, Potts A, Love J, Cuschieri K, Cubie H, Robertson C, Cruickshank M, Palmer TJ, Nicoll S, Donaghy M. 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. doi:10.1038/bjc.2014.479.
20. Baldur-Felskov B, Munk C, Nielsen TS, Dehlendorff C, Kirschner B, Junge J, Kjaer SK. Trends in the incidence of cervical cancer and severe precancerous lesions in Denmark, 1997-2012. Cancer Causes Control. 2015;26(8):1105–16. doi:10.1007/s10552-015-0603-7.
21. Arnheim-Dahlström L, Pasternak B, Svanström H, Sparén P, Hviid A. Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. BMJ. 2013;347:f5906. doi:10.1136/bmj.f5906.
22. European Medicine Agency (EMA). HPV vaccines: EMA confirms evidence does not support that they cause CRPS or POTS. 2015. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/11/news_detail_002436.jsp&mid=WC0b01ac058004d5c1
23. Hanley SJ, Yoshioka E, Ito Y, Kishi R. HPV vaccination crisis in Japan. Lancet. 2015;385(9987):2571. doi:10.1016/S0140-6736(15)61152-7.
24. Fujii T. Declaration to demand the resumption of recommendations for human papillomavirus (HPV) vaccination for cervical cancer prevention. J Obstet Gynaecol Res. 2015; 41(12):1859–60.
25. The World Health Organization, Global Advisory Committee on Vaccine Safety. Statement on safety of HPV vaccines. 2015. http://www.who.int/vaccine_safety/committee/GACVS_HPV_statement_17Dec2015.pdf?ua=1
26. Joura EA, Giuliano AR, Iversen OE, Bouchard C, Mao C, Mehlsen J, Moreira Jr ED, Ngan Y, Petersen LK, Lazcano-Ponce E, Pitisuttithum P, Restrepo JA, Stuart G, Woelber L, Yang YC, Cuzick J, Garland SM, Huh W, Kjaer SK, Bautista OM, Chan IS, Chen J, Gesser R, Moeller E, Ritter M, Vuocolo S, Luxembourg A, Broad Spectrum HPV Vaccine Study. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med. 2015;372(8):711–23. doi:10.1056/NEJMoa1405044.