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Comparison of Preventive Care for Cervical Cancer Between Japan And Western Countries: A Review

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Abstract

The aim of this review is to promote the prevention of cervical cancer in Japan. Cervical cancer due to human papillomavirus (HPV) infection is a preventable cause of death, although HPV infection is very common and anyone who has had sexual intercourse can become infected. Cervical cancer is a serious disease that can significantly affect women's lives; it can not only deprive women of their fertility but also lead to death if left untreated.

Keywords: Cervical cancer; HPV infection; Sexual intercourse

Introduction

Every year, 10,000 Japanese women are newly diagnosed with cervical cancer [1,2], and 2,700 die from it [2]. Moreover, in contrast with the situation in other developed countries, where there has been a reduction in the incidence of HPV infection, the cervical cancer prevalence and mortality rates have tended to increase among young women in their twenties and thirties in Japan.

Efforts to slow the rate of cervical cancer in Japan seem to have had limited success. It has been reported that the cervical screening rate among nurses is only 15% and that this is positively correlated to their level of knowledge [3]. Without a basic knowledge of the disease and the importance of screening, it is unlikely that healthcare providers would be able to adequately educate their patients about the symptoms of HPV infection and the importance of cervical cancer screening. The objectives of this review are to consider the reasons for the aforementioned issues and the measures that can be taken to improve the situation.

What is HPV?

HPVs are extremely common DNA viruses [4]. HPV is transmitted though contact with the skin and mucous membranes, often through sexual intercourse [5]. HPV received its name because of the fact that it can form a wart called a papilloma. More than 100 different genotypes of HPV (approximately 40 of which affect the genital area) [6] have been identified so far, and a number has been assigned to each type based on the order in which it was discovered [7]. HPVs are classified into high or low risk [8]. There are at least 13 types of high-risk HPV, including genotype 16 (HPV16), which is highly carcinogenic [9,10]. HPVs can lead to abnormal tissue changes [6] and cause other cancers [4,11], in addition to cervical cancer, and laryngeal papillomas that may require surgical intervention [6].

Cervical Cancer

All sexually active women have the potential to suffer from cervical cancer [4]. The US Centers for Disease Control predicts [12] that at least 80% of all sexually active people will be infected with HPV at some point in their lives. However, most infected individuals do not develop cervical cancer [13] because 90% of the infection is discharged by the immune system within two years [10]. If the infection persists, the infected abnormal cells in the cervix can change to exhibiting precancerous characteristics (dysplasia) in 4% and proceed to cervical cancer in 0.15% of infected individuals after more than 10 years [14,15]. HPV can infect the same individual repeatedly because immunity to it is hardly induced. If a precancerous state of cervical cells is identified and treated before it progresses, cervical cancer is preventable [16].

Approximately 99% of cervical cancers are caused by sexual exposure to high-risk types of HPV [17]. HPV16 and HPV18 infections account for 70% of cervical cancers worldwide [4] and for 50%–70% of cervical cancers diagnosed in Japan [18,19]. Other risk factors for cervical cancer include smoking, immunosuppression, being overweight, long-term use of birth control pills, sexual activity at an early age, and having many sexual partners [20,21]. Cervical cancer can be divided into two types: squamous cell carcinoma (90%) and adenocarcinoma (10%). Adenocarcinoma, having increased in prevalence/incidence recently, is more difficult to treat and to identify through cervical cancer screening [22].

Symptoms

Most cervical cancers cause no symptoms in the early stage of development [10] and go unnoticed by patients. Even if cervical cancer progresses, it is asymptomatic in most cases. The following symptoms of cervical cancer indicate that it may already have progressed: vaginal bleeding after sexual intercourse, abnormal discharge, irregular bleeding except menses, and pelvic pain [23]. Progression tends to be more rapid in younger patients. A hysterectomy is required once the cancer has progressed; as a result, it deprives women of their fertility and the possibility of childbirth. More severe symptoms such as leg swelling, fatigue, and weight loss may be present at advanced stages and may be life threatening. Even if the cervical cancer is not deadly, women can experience various types of mental and physical burden during the course of treatment, including anxiety about metastasis and recurrence, and surgery complications such as polycystic ovary syndrome, urination, lymphedema, and failure to perform sexual intercourse [4].

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Treatment

If abnormal cells of the cervix, such as precancerous lesions, are discovered at an early stage, they can be treated simply through conization, surgery to remove a narrow range of the cervix in a conical shape with a laser or electric scalpel [24]. Although the risk of miscarriage [25] and premature birth increases after treatment [26], fertility can be preserved. If the results of cervical biopsies show that abnormal lesions extend beyond the surface (epithelium) of the cervix, further treatment such as a hysterectomy is required. If the cancer has spread to surrounding organs (such as the ovaries) and the lymph nodes, it is necessary to excise these organs and glands as well. The main treatments for advanced cervical cancer are surgery, radiation therapy, and chemotherapy. The treatment method is selected according to the patient's condition, considering aspects such as age, general health, treatment complications, and the stage and location of the cancer. The more advanced the cancer is, the larger the scale of treatment required, and post-surgical complications often occur. Therefore, early detection is extremely important [27].

History

Cervical cancer had been presumed to be a sexually transmitted disease, because it was a common disease among prostitutes, multiparous women, and women who became sexually active at a young age. In 1983, Dr. Harald zur Hausen discovered that cervical cancer is caused by HPV16 infection in the cervix, and he won the Nobel Prize in Physiology or Medicine in 2008 for this discovery. Other types of high-risk HPV were discovered in the early 1990s [28], enabling the development of the HPV vaccine and sensitive diagnostic methods, such as the polymerase chain reaction [29].

Epidemiology

Cervical cancer is the second most common cancer among women. It is estimated that, in 2012, 445,000 women in the world suffered from cervical cancer, and 270,000 women died from it, representing one death every two minutes. More than 80% of cases of cervical cancer occur in developing countries [14]. In most developed countries, promoting the prevention of cervical cancer tends to decrease the incidence of this cancer. In 2013 in Japan, approximately 10,000 individuals developed cervical cancer [1], and 2,700 died from it [2]. The age-adjusted prevalence of cervical cancer in Japan is 10.9 per 100,000 individuals, representing the seventh highest prevalence rate among the 31 developed countries [30]. It has been estimated that one in 76 women have been diagnosed with cervical cancer at some point in their lives [31]. The incidence of cervical cancer rises for women in their twenties and forties, and it levels off for women older than 50 years. Concerning annual trends in cervical cancer mortality rates and prevalence, in contrast to other developed countries, those in Japan have tended to increase for young women in their twenties and thirties, making cervical cancer the most common cancer of these age groups [30,32].

Geographical, social, and cultural aspects

There are geographical differences in the HPV genotypes. Whereas 70% of cervical cancer cases worldwide are caused by HPV16 and HPV18, this value ranges from 50%–70% in Japan [4,18]. The prevalence of cervical cancer does not differ in cities versus rural areas [33]; instead, beliefs and the culture surrounding sexual behavior affect cervical cancer rates. To provide a historical and culture perspective, in Japan, the death penalty was executed in the 19th century for women but not men who had adulterous affairs. In addition, fewer and fewer Japanese practice Buddhism, which promotes sexual abstinence. Although traditionally the ideal Japanese women has been monogamous, the percentage of individuals who believe having sex before marriage to be disgraceful has decreased from 52% in 1978 to 22% in 2008 [34]. According to a Japanese sex survey conducted in 2013, 13.6% of women and 31.4% of men had had multiple sexual partners [34]. The average age of first intercourse in Japanese women (19.6 years old) has decreased by 3.6 years over the past 25 years [34]. The average age at first marriage has increased from 25.2 years in 1980 to 29.3 years in 2013 [31], coinciding with the social progress of women in Japan. The age of first intercourse positively correlates with education and income level [35]. At school, Japanese teenagers do not tend to learn about safer sex but, rather, about more scientific matters such as organs, hormones, and infections [36]. Even medical students are not given many opportunities to discuss sex. The Japanese get information about sexual relationships, medical services, and diseases from their friends, TV, and the internet, rather than their families, as the Japanese are not accustomed to discussing sex and often feel too ashamed or embarrassed to do so. These cultural phenomena may lead to a lack of education regarding safe sex [36].

Surveillance methods

As HPV infection is extremely common, and because it can take more than 10 years for symptoms to present after infection with potentially carcinogenic HPV, it is often difficult to ascertain by whom HPV-positive women were originally infected. This, in turn, makes it challenging to treat that particular individual. Thus, when developing public health initiatives, we should take into account the fact that all individuals with a history of sexual activity could potentially have been infected.

Policies and public health priorities

As mentioned earlier, cervical cancer is preventable, and public health priorities and funding clearly should be directed toward its prevention. The two primary methods of preventing cervical cancer are HPV vaccination (primary prevention) and regular screening (secondary prevention), which could prevent 93% of cervical cancers [12]. Current policies will be considered below.

HPV Vaccines

Vaccines have enabled the primary prevention of cervical cancer. This is a milestone in medical history. The World Health Organization [37] has recommended HPV vaccination, which is reported to be safe and effective [38-40] and has been used in more than 100 countries since 2006. The two existing HPV vaccines, Cervarix and Gardasil, are designed to protect against the two primary high-risk HPVs (HPV16 and HPV18). Cervarix also protects against two low-risk HPVs (HPV6 and HPV11). Both vaccines are also effective at preventing adenocarcinoma, whose prevalence/incidence increased recently and that is more difficult to identify through screening [22]. Girls/young women in Japan are inoculated intramuscularly, via three doses of the vaccine over a six-month period, without charge. The vaccine is recommended for girls between the ages of 11 and 16 years, as it is desirable to vaccinate prior to the initiation of sexual activity. Both vaccines have been estimated to remain effective for more than five years and to prevent the occurrence of over 90% of precancerous lesions [41,42]. Although the cost of the HPV vaccination is enormous (over $100 per dose), its cost-effectiveness (i.e., reduction in medical expenses because of the prevention of cervical cancer) is estimated to be large, especially for adolescent girls [43,44]. Vaccinating men is not

cost-effective [45] and is believed to have little additional impact on the reduction of cervical cancer rates for women [46].

Both vaccines were licensed in Japan in 2009, and they have been administered routinely, starting in 2013. However, approximately 600 cases of serious side effects including complex regional pain syndrome, were reported, and this quickly became an issue of social concern in Japan. Within only a few months after its license, the Japanese Ministry of Health, Labour and Welfare (MHLW) controversially suspended recommendation of the vaccine until the MHLW was able to provide citizens with appropriate information about the vaccine's safety and association with these side effects [47]. This was followed by a worldwide controversy. The Global Advisory Committee on Vaccine Safety concluded that the severity/frequency of adverse events following immunization with the HPV vaccine was not significantly greater than those of other vaccines and that HPV vaccination should be continued [48].

On the other hand, the number of adverse effects following Cervarix immunization has been reported to be considerably higher than other vaccines [49]. According to the Vaccine Adverse Event Reporting System [50], by January 2015, 220 women worldwide had died because of adverse effects related to the HPV vaccine. In the USA, 200 people reported adverse effects after receiving the HPV vaccine, and 49, including two deaths, were compensated [51]. The safety, validity and causal relationship between the vaccine and its complications are not clearly understood at this stage, and these aspects will take time to be evaluated in more detail. Cancer screening in Japan should therefore be a public health priority.

Cancer Screening

The implementation of widespread cervical cancer screening including cytology (pap smear) as an easy and non-invasive method of secondary prevention has been demonstrated to reduce the prevalence and mortality of cervical cancer through the detection of precancerous lesions [52]. In 2004 in Japan, the recommendation regarding the target age and frequency of screening for cervical cancer changed from once a year for women aged over 30 years to every two years for women aged over 20 years, based on the increasing tendency for women to have sexual intercourse at a younger age [53]. However, the rate of adherence to cervical cancer screening in Japan (37%) is the worst (and much lower) compared with those of other developed countries (70%–80%) (Figure 1) [54]. This is likely the primary explanation for the increase in the incidence and mortality rate of cervical cancer among young women in Japan. There is currently an urgent need to address this issue.

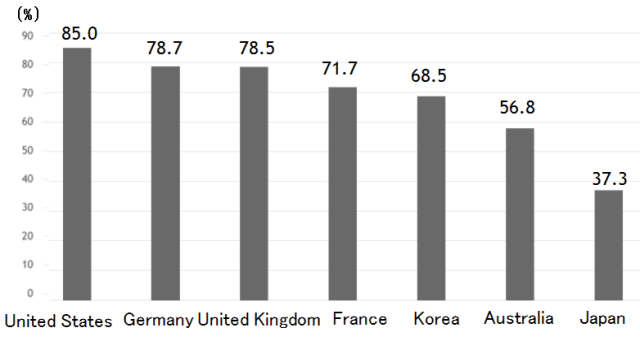

Figure 1: The adherence rates of cervical cancer screening during 2 years among women aged 20-69 in different countries.

Intervention and Prevention

To address the low rate of visits for cervical cancer screening in Japan, since 2009, the Japanese Government has offered free screening coupons each year to all women aged 20, 25, 30, 35, and 40 [55]. Although the utilization rate of free coupons has remained at only 20% overall and the adherence rate remains the worst among developed countries, the visit rate has improved slightly (24.5% per year and 37.5% per two years) [56]. This offer should thus be continued. Although the low adherence rate might be related to poor lifestyle, one-third of Japanese women do not even know about the free screening program [3]. This is true despite the fact that they receive invitation letters for cancer screening through small campaigns that disseminate information about health check-ups. Cervical cancer screening is implemented by a gynecologist at a specific type of hospital in Japan. Reported barriers to screening include embarrassment, busyness, laziness, poor access, fear of having cancer, fear of an unknown procedure, believing that screening is unnecessary because of a lack of symptoms, and believing oneself to be too young to have cancer [57]. Eliminating these barriers will likely be crucial to improving this situation.

Use of condoms represents another HPV prevention method [58]. Although HPV can infect the genital areas that are not protected by a condom during sexual intercourse [59], using a condom reduces the risk of infection [58] and also prevents other types of sexually transmitted infections. Additional important prevention factors include smoking cessation, avoiding use of the contraceptive pill, getting adequate sleep, proper nutrition, sex education, and having a fixed sexual partner.

Recommendations

It is true that, from a public health standpoint, vaccination plays a crucial role in HPV prevention because it protects society as a whole (herd immunity) in addition to individuals. However, providing evidence that clearly demonstrates the safety and efficacy of the newly introduced HPV vaccine proves challenging at this stage, and further research is required on an international scale. As soon and as carefully as possible, the MHWL should provide information concerning the HPV vaccine and associated policies to the Japanese population, who have been confused about and distrustful of the vaccine's safety. Furthermore, although current HPV vaccines targeting HPV16 and HPV18 are believed to protect against 80% of cervical cancers [60], the prevalence of infection with these particular HPV genotypes is lower in Japan than in Western countries [8,19]. The development and wider commercialization of new vaccines that are safer and cover other types of high-risk HPV are expected in the future. Moreover, it should be noted that screening will continue to be required after vaccination, because the HPV vaccines do not prevent infection with all high-risk HPV genotypes and receiving the vaccine does not treat pre-existing HPV infections [61].

The most urgent challenge in Japan is to increase the visit rate for cervical cancer screening. Some solutions will now be considered via a comparison with approaches used in other countries that have high rates of adherence. Firstly, educating teenagers at school and at home about the importance of prevention and providing a basic knowledge of cervical cancer is a priority. We must change the belief that we should visit hospitals only when we are sick. Media campaigns carried out via newspapers, television, and the internet would be effective ways to disseminate this information. It also would be simple and practical to place flyers concerning cervical cancer screening in women's restrooms. Moreover, unlike the family doctor/general practitioner system used in Western countries, patients in Japan generally consult a number of

different doctors and hospitals, and, because medical records are not unified among hospitals, medical practitioners may not always access to full patient information, including whether the patient has undergone cervical cancer screening and, if so, when this last occurred. Thus, it will be important for medical practitioners to deliberately collect this information from patients and, if needed, to educate the patient about cervical cancer and promote its screening. Secondly, women can receive screening free of charge in most Western countries, and the USA provides incentives, such as insurance discounts, to individuals who receive health check-ups [62]. Considering the importance of prevention, medical costs in Japan should be more highly supported. Thirdly, an increasing number of European countries have implemented screening for cervical cancer by female healthcare workers (e.g., nurses and midwives) to avoid the psychological burden experienced by female patients when exposing their genital areas in front of male doctors. It is vital to create an environment where women feel less embarrassed and more comfortable when undergoing gynecological screening. Fourthly, a call/recall system improved adherence to screening in the UK [63]. This system is expected to be adopted in Japan. Finally, there is a need to improve the screening implementation system so that women have a wider range of options in terms of more convenient times and locations to undergo screening.

It is expected that combining additional HPV-DNA tests with cytology, which detects 70%–80% of existing cervical cancers and rarely finds adenocarcinoma, will increase the accuracy of screening (sensitivity: 100%) [64]. Moreover, it will allow women to prolong the interval between screening visit if no abnormality is found [65]. However, as it can lead to over–diagnosis and overtreatment, further consideration about the selection of women who get involved for effective inspection is required.

References

1. Katanoda K, Hori M, Matsuda, T, Shibata A, Nishino Y, et al. (2015) An updated report on the trends in cancer incidence and mortality in Japan, 1958-2013. Jpn J Clin Oncol 45: 166-168.
2. Center for Cancer Control and Information Services (2013) National Cancer Center, Japan.
3. Yoshino Y, Ohta H, Kawashima, M, Koji Wada, Midori Shimizu, et al. (2012) The knowledge of cervical cancer and screening adherence among nurses at a university-affiliated hospital in Japan. Kitasato Med J 42: 6-14.
4. WHO (2015) Human papillomavirus (HPV) and cervical cancer.
5. Gavillion N, Vervaet H, Derniaux E (2010) Papillomavirus humain (HPV) : comment ai-je attrapé ça? Gynécologie Obstétrique & Fertilité, 38: 199-204.
6. National Health Service (2014) Cervical cancer vaccine.
7. De Villiers EM (1997) Papillomavirus and HPV typing. Clin Dermatol 15: 199-206.
8. Munoz N, Bosch FX, Sanjose S, Herrero R, Castellsagué X, et al. (2003) Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med 348: 518-27.
9. WHO (2006) IARC monographs on the evaluation of carcinogenic risks to humans, volume 90, human papillomaviruses. Lyon: International Agency for Research on Cancer.
10. Moscicki AB, Schiffman M, Kjaer S, Albero G, Giuliano AR, et al. (2006) Chapter 5: Updating the natural history of HPV and anogenital cancer. Vaccine 24: S42-51.
11. Cutts FT, Franceschi S, Goldie S, Castellsague X, Garnett G, et al. (2007) Human papillomavirus and HPV vaccines: a review. Bulletin of the World Health Organization 85: 649732.
12. CDC and Prevention (2014) Cervical Cancer is Preventable.
13. Center for Cancer Control and Information Services, Recommendation for screening.
14. Dunne EF and Park IU (2013) HPV and HPV-associated diseases. Infect Dis Clin North Am 27: 765-78.
15. WHO (2014) World Cancer Report 2014. World Health Organization.
16. Greenblatt RJ (2005) Human papillomaviruses: Diseases, diagnosis, and a possible vaccine. Clinical Microbiology Newsletter 27: 139-145.
17. OECD/European Union (2014) Screening, survival and mortality for cervical cancer. Health at a Glance. OECD Publishing.
18. WHO (2010) Human Papillomavirus (HPV).
19. Onuki M, Matsumoto K, Satoh T, Oki A, Okada S, et al. (2009) Human papillomavirus infections among Japanese women: age-related prevalence and type-specific risk for cervical cancer. Cancer Sci 100: 1312-1316.
20. Miura S, Matsumoto K, Oki A, Toyomi Satoh, Hajime Tsunoda, et al. (2006) Do we need a different strategy for HPVscreening and vaccination in EastAsia? Int J Cancer 119: 2713-27135.
21. Faridi R, Zahra A, Khan K, Idrees M (2011) Oncogenic potential of Human Papillomavirus (HPV) and its relation with cervical cancer. Virol J 3: 269.
22. Castells ague X, Munoz N (2003) Cofactors in human papillomavirus carcinogenesis role of parity, oral contraceptives, and tobacco smoking. J Natl Cancer Inst Monogr 31: 20-28.
23. Alsbeih G, Al-Harbi N, El-Sebaie M, Ismail Al-Badawi (2013) HPV prevalence and genetic predisposition to cervical cancer in Saudi Arabia. Infect Agent Cancer 4: 8-15.
24. Divakar H (2008) Asymptomatic uterine fibroids. Best Pract Res Clin Obstet Gynaecol 22: 643-654.
25. Sevin BU, Nadji, M, Averette HE (1992) Microinvasive carcinoma of the cervix. Cancer 70: 2121-2128.
26. Kyrgiou M, Mitra A, Arbyn M (2014) Fertility and early pregnancy outcomes after treatment for cervical intraepithelial neoplasia: systematic review and meta-analysis. BMJ 28: 349-6192.
27. Bevis KS, Biggio JR (2011) Cervical conization and the risk of preterm delivery. Am J Obstet Gynecol 205: 19-27.
28. Ramondetta L (2013) What is the appropriate approach to treating women with incurable cervical cancer? J Natl Compr Canc Netw 11: 348-355.
29. Bosch FX, de Sanjosé S (2003) Chapter 1: Human papillomavirus and cervical cancer-burden and assessment of causality. J Natl Cancer Inst Monogr31: 313.
30. Cuzick J, Mayrand MH, Ronco G (2006) Chapter 10: New dimensions in cervical cancer screening. Vaccine 24: 90-97.
31. IARC GLOBOCAN (2012) Estimated Cacer Incidence, Mortality and Prevalence Worldwide in 2012.
32. Ministry of Health, Labor and Welfare (2014) Demographics statistics. Ministry of Health, Labor and Welfare, Department of Statistics and Information edition.
33. Matsuda A, Matsuda T, Shibata A, Katanoda K, Sobue T, et al. (2013) Cancer incidence and incidence rates in Japan in 2007: a study of 21 population-based cancer registries for the monitoring of cancer incidence in Japan (MCIJ) project. Jpn J Clin Oncol 43: 328-336
34. Sussman AL, Helitzer D, Sanders M, Urquieta B, Salvador M, et al. (2007) HPV and cervical cancer prevention counseling with younger adolescents: implications for primary care. Ann Fam Med. 5: 298-304.
35. Kitamura K (2013) Japan sex survey 2013. Japan association of family plan.
36. Kinsey A, Pomeroy W, Martin C (1953) Sexual Behavior in the Human Female. Saunders, Philadelphia, USA.
37. Okawa S (2009) Teenage delivery is regulated by family: Comparison of social construction for teenage mothers in the U.S., the U.K., and Japan. Sociology 45: 207-228.
38. WHO (2008) Preparing for the introduction of HPV vaccines: policy and program guidance for countries. WHO Genova, Switzerland.
39. Paavonen J, Jenkins D, Bosch FX, Naud P, Salmerón J, et al. (2007) Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. Lancet. 369: 2161-2170.

40. Joura EA, Leodolter S, Hernandez-Avila M, Wheeler CM, Perez G, et al. (2007) Efficacy of a quadrivalent prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like-particle vaccine against high-grade vulval and vaginal lesions: a combined analysis of three randomised clinical trials. Lancet 369: 1693-702.

41. FUTURE II Study Group (2007) Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 356: 1915-1927.

42. Olsson SE, Villa LL, Costa RL, Petta CA, Andrade RP, et al. (2007) Induction of immune memory following administration of a prophylactic quadrivalent HPV types 6/11/16/18 l1 virus-like particle (VLP) vaccine. Vaccine. 25: 4931-4939.

43. Schwarz TF, Leo O (2008) Immune response to human papillomavirus after prophylactic vaccination with AS04-adjuvanted HPV-16/18 vaccine: improving upon nature. Gynecol oncol. 110: S1-10.

44. Marra F, Cloutier K, Oteng B, Carlo Marra, Gina Ogilvie (2009) Effectiveness and cost effectiveness of human papilllomavirusu vaccine : a systemic review. Pharmacoeconomics, 27: 91-93.

45. Goldie SJ, Kohli M, Grima D, Weinstein MC, Wright TC, et al. (2004) Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. J Natl Cancer Inst 96: 604-615.

46. Kim JJ, Brisson M, Edmunds WJ, Goldie SJ (2008) Modeling cervical cancer prevention in developed countries. Vaccine 26: 76-86.

47. Garnett GP, Kim JJ, French K, Goldie SJ (2006) Chapter 21: Modelling the impact of HPV vaccines on cervical cancer and screening programmes. Vaccine 24: S178-86.

48. Ministry of Health, Labor and Welfare (2013) Human Papillomavirus infection, vaccination to prevent cervical cancer.

49. Slade BA, Leidel L, Vellozzi C, Woo EJ, Hua W, et al. (2009) Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. JAMA 302: 750-757.

50. Tomljenovic L, Shaw CA (2013) Human papillomavirus (HPV) vaccine policy and evidence-based medicine: are they at odds? Ann Med 45: 182-93.

51. Vaccine Adverse Event Reporting System (VAERS) (2015) HPV vaccine VERSE reports up to Jan 2015.

52. Judicial Watch (2013) JW Investigates HPV Injury Compensation Program

53. OECD (2013) Cancer Care: Assuring Quality to Improve Survival, OECD Publishing.

54. Hamashima C, Aoki D, Miyagi, E, Eiko Saito, Tomio Nakayama, et al. (2010) Japanese guideline for cervical cancer screening. Jpn J Clin Oncol 40: 485-502.

55. OECH health data (2010) Paris: Organization for Economic Co-operation and Development (OECD), OECD Publications.

56. Konno R, Sagae S, Yoshikawa H, Basu PS, Hanley SJ, et al. (2010) Cervical cancer working group report. Jpn J Clin Oncol 40: i44-i50.

57. OECD Health Statistics (2014) Definitions, Sources and Methods Cervical cancer screening, survey data and programme data.

58. Shefer A, Markowitz L, Deeks S, Tam T, Irwin K, et al. (2008) Early experience with HPV vaccine introduction in the United States, Canada and Australia. Vaccine 26: 65-75.

59. Sanjose SD, Almirall R, Lloveras B, Font R, Diaz M, et al. (2003) Cervical human papillomavirus infection in the female population in Barcelona, Spain. Sex Transm Dis. 30: 788-793.

60. Lam JU, Rebolj M, Dugué PA, Bonde J, von Euler-Chelpin M, et al. (2014) Condom use in prevention of Human Papillomavirus infections and cervical neoplasia: systematic review of longitudinal studies. J Med Screen 21: 38-50.

61. Bosch FX, Manos MM, Muñoz N, Sherman M, Jansen AM (1995) A prevalaence of human papillomavirus in cervical cancer: worldwide perspective. J Natle Cancer Inst 87: 796-802.

62. Coupé VM, van Ginkel J, de Melker HE, Snijders PJ, Meijer CJ, et al. (2009) HPV 16/18 vaccination to prevent cervical cancer in The Netherlands: model-based cost effectiveness. Int J Cancer 124: 970-978.

63. Fukuhara M (2010) Reports on Cervical cancer international conference. What to do in Japan in order to increase the visit rate of cervical cancer screening. Nikkei Business Publications, Japan.

64. Quinn M, Babb, P, Jones J, Allen E (1999) Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. BMJ 318: 904-908.

65. Mayrand MH, Duarte-Franco E, Rodrigues I, Walter SD, Hanley J, et al. (2007) Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. N Engl J Med 357:. 1579-1588.

66. Safaeian M, Solomon D, Wacholder S, Schiffman M, Castle P (2007) Risk of precancer and follow-up management strategies for women with human papillomavirus-negative atypical squamous cells of undetermined significance. Obstet Gynecol 109: 1325-1331.