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Cervical Cancer Working Group Report

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Disease burden of cervical cancer in Asia was summarized. Human papillomavirus 16 is the most oncogenic human papillomavirus type. Korea's national cervical cancer screening program targets women aged 30 or over, with coverage of almost 80%. Japan has a long history (50 years) of cervical cancer screening, and cytological screening programs have reduced the incidence/mortality of cervical cancer by 70%. But, recent cervical cancer screening coverage is ~24%. Modeling suggested that vaccination of all 12-year-old girls would reduce cervical cancer cases by 73% in Japan. India has no cervical cancer screening program, as well as a serious lack of awareness in the general population, medical professionals and policy-makers. A realistic, affordable approach would be a low-volume, once-in-a-lifetime human papillomavirus-based screening program. In Australia, the national cervical cancer program has been very successful in reducing the incidence and mortality of cervical cancer. Australia was the first country to implement free, national human papillomavirus immunization (April 2007), expected to reduce human papillomavirus 16 infections by 56% in 2010 and 92% in 2050. A comparison of the UK and Japan was demonstrated that in the UK, cervical cancer screening and human papillomavirus vaccination uptakes are high because the government provides adequate education/funding. The Japanese government needs to put more emphasis on women's health and preventative medicine. Our conclusion and recommendations are that heightened public awareness of cervical cancer prevention, focusing on screening and vaccination will lead to improved survival and a better quality of life.

Key words: cervical cancer – human papillomavirus – screening – vaccination – prevention

INTRODUCTION

The Cervical Cancer Working Group report was divided into seven topics: epidemiology of human papillomavirus (HPV) and cervical cancer; cervical cancer in Korea; status of cervical cancer screening and HPV vaccination in Japan; cervical cancer control: Indian perspective; cervical cancer in Australia; public health education for cervical cancer: a comparison of the UK and Japan; and conclusion and recommendations.

EPIDEMIOLOGY OF HPV AND CERVICAL CANCER

Early infection after sexual initiation, continuous new infections into adulthood, related to the sexual behavior patterns of the population etc. are the causes of cervical cancer. A multicentre HPV prevalence survey from 1995 through 2008 found that in Asia, Mongolia has the highest prevalence of cervical HPV DNA in sexually active women, and it is the second highest worldwide. China also shows a

slightly higher prevalence than the other Asian countries. Korea has a prevalence of almost 10%. Hanoi, Vietnam, has a very low prevalence. The prevalence rates of HPV-16 and -18 differ among the continents. In Asia, the prevalence rates were 1.7% for HPV-16, 3.7% for other HPV types and 4.2% for low-risk HPV. China, Japan and Mongolia show different profiles for the most common types of HPV (1). In February 2009, HPV-16, -18, -31 and a number of other types were reclassified as a group of human carcinogens. HPV-16 is the most potent carcinogen, causing cancer at several sites besides the cervix. HPV-18 and ten other types show sufficient evidence of causation of cervical cancer (2).

Cervical cancer epidemiological data from 1988 to 2002 show that the highest incidence of cervical cancer was in South America, followed by Africa and Asia. The lowest incidence was in Western Europe. In Eastern Asia, Thailand had the highest incidence of cervical cancer, followed by Taiwan. Japan showed a low incidence. In Western Asia, the incidence of cervical cancer was low, except in India. As a function of age, the incidence rose from ∼25 years old in all East Asia countries, and in Korea, the incidence increased until age 70 and then decreased (3). The global burden of cervical cancer was estimated to be 500 000 cases in 2002. More recent preliminary estimates show the same geographical variation as in 2002, but a lower range of incidence rates compared with 2002. The total number of cases, now estimated to be 487 000, has decreased. With regard to the burden of cervical cancer within Asia, the GLOBOCAN 2008 pooled estimates for China and Japan are based on data from the regional cancer registries and cannot be compared directly. But national estimates were employed for a number of other countries, and the data showed that the incidence has decreased since 2002 in various nations, including Korea, Taiwan, Singapore, Australia and New Zealand. When the cervical cancer burden in Asia was stratified for the Eastern, Southeastern, South-central and Western regions, the 2008 preliminary data showed that the greatest number was in South-central Asia, including India and Pakistan. Eleven percent of all female cancers were cervical cancer, and 9% of deaths were due to this malignancy (4) (caution: it will be available in the mid of May 2010). For the prevention of cervical cancer, the most important factor is public health awareness, through healthy and safe sexual behavior, followed by early detection and screening (Fig. 1).

CERVICAL CANCER IN KOREA

In Korea, cervical cancer is the sixth most common female cancer, after breast, thyroid, stomach, colorectal and lung cancers. The standardized incidence rate is 12.8. The National Cancer Registry data revealed that invasive cervical cancer is decreasing, whereas carcinoma *in situ* is increasing, perhaps due to screening and early detection. The mortality rate due to cervical cancer is also showing a decreasing trend. The age-specific incidence of cervical cancer has decreased for women in the 60–64-year-old group, but increased in elderly women, whereas the incidence of carcinoma *in situ* has increased in middle-aged Korean women (5). Pooled analysis of published data for HPV involvement in cervical cancer shows that less than 70% of cases have HPV-16 or -18 DNA.

Korea has a national cervical cancer screening program based on Pap smears for women aged 30 or more, but the Korean Society of Obstetrics and Gynecology recommends screening of all women after first intercourse or 20 years of age. Cervical screening by Pap smear was started in 1989 for health insurance beneficiaries and in 1999 for Medicaid women. The percentage of women who have been screened has increased rapidly and is now slightly a bit below 80% (Fig. 2).

With regard to HPV vaccination, the Korean Food and Drug Administration approved Gardasil™ in 2007 and Cervariax™ in 2008, but there are no guidelines for HPV vaccination at the national level. A subcommittee of the National Advisory Committee on Immunization Practices began developing HPV immunization guidelines in 2006, but they are not yet finalized. Two surveys of HPV awareness and acceptability of vaccination were conducted in 2002 and 2007 and found that awareness was very low. However, in the 2002 survey, the acceptability of vaccination was ∼55% even before the introduction of vaccination, and in the 2007 survey, ∼58% of females found vaccination acceptable (6,7). A National Cancer Incidence Data Base, Site-specific Cancer Registry and a Cervical Cancer Registry have been established in Korea, but a vaccination registry remains under consideration.

In summary, in Korea, the cervical cancer burden has gradually decreased in recent years in terms of the incidence and mortality due to early detection (CIS represented 40% of cervical malignancies and is increasing). The burden due to HPV-related diseases is still high and rising. The HPV vaccination program will depend on the cost-effectiveness of the HPV vaccine in Korea.

STATUS OF CERVICAL CANCER SCREENING AND HPV VACCINATION IN JAPAN

Cervical cancer screening was started in Japan in the late 1950s, and a national screening program was enacted in 1982 (8). Cytological screening programs have been shown to reduce the incidence and mortality of cervical cancer by 70%. Prior to the national screening program, the pattern for the age-specific rate of cervical cancer in Japan was that of a developing country. After the screening was introduced, the age-specific rate pattern has become that of a developed country, with the rate decreasing after 35 years of age (8). OECD data show high rates of cervical cancer screening coverage in the USA and Europe, while increasing coverage in Korea and very low (23.4%) coverage in Japan (9).

Figure 1. Cervical cancer incidence in Asia.

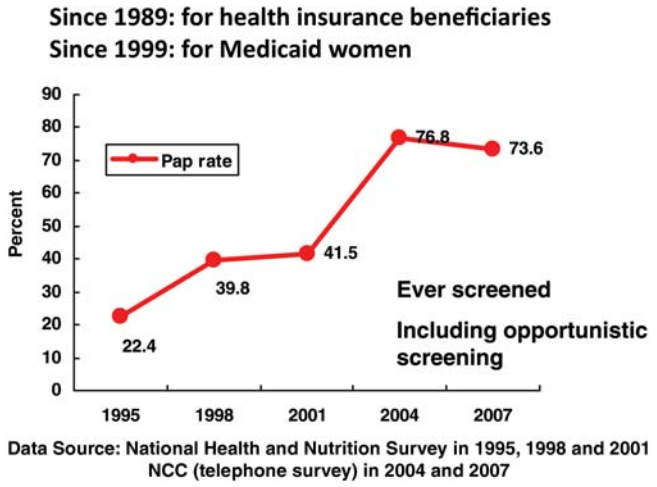

Figure 2. Cervical cancer screening in Korea.

The age-standardized mortality of cervical cancer in Japanese women has been less stable in the last 15 years. Mortality rates fell in all birth cohorts, up to those born around 1940–1945, but thereafter there has been a progressive rise in mortality in each successive generation due to the recent low coverage of cervical screening. With regard to cervical cancer prevention in Japan, in 1983, the government passed a Health and Medical Service Law for the Aged, but that law was later changed in 1998, leaving screening up to the regional governments (8).

Recently, University of Tsukuba data show that the prevalence of HPV-16/18 in cervical cancer in Japan is 67% (10). As in other countries, the percentage of adenocarcinoma or adenosquamous carcinoma in cervical cancer has been increasing in Japan. Modeling of the effect of introduction of HPV vaccination indicated that the number of cervical cancer cases could be reduced by 73% if all 12-year-old girls in Japan were vaccinated. In addition, simulation of the cost-effectiveness when vaccinating single cohorts from 10 to 45 years of age found that vaccination up to 29-year olds would generate savings to the Japanese society. Vaccination of 30-year olds would generate costs while still preventing cervical cancer cases and generating QALY over a screening program only (11) (Fig. 3). An HPV vaccine was licensed in 2009. Japan has a long history of cervical cancer screening

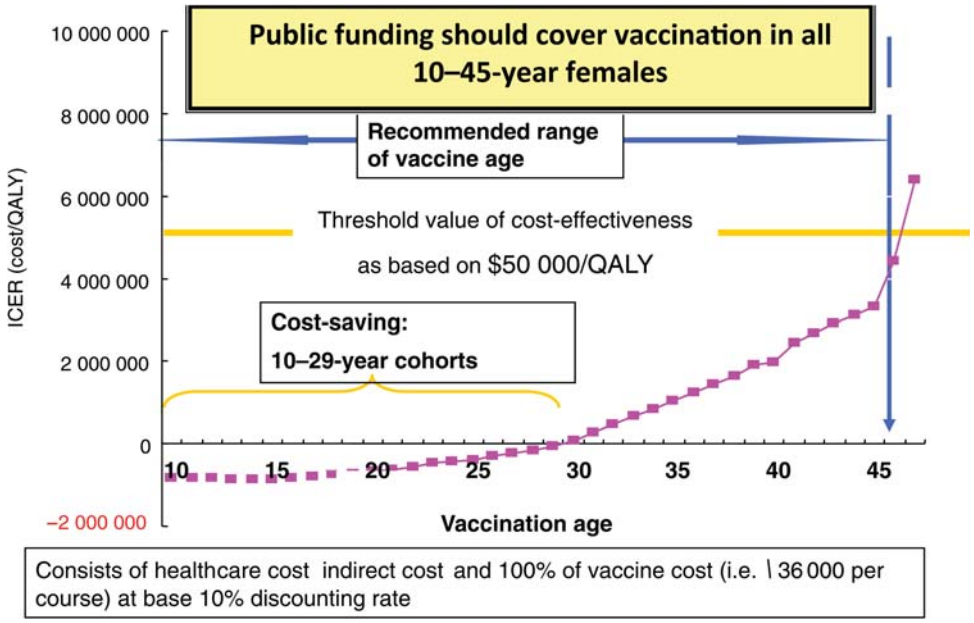

Figure 3. Public funding should cover vaccination in all 10–45-year females. Simulation of the cost-effectiveness of cervix cancer vaccination when vaccinating single cohorts from 10- to 45-year old was performed. Vaccination up to 29-year olds generates savings to the Japan society. However, vaccinating as of 30-year old will generate costs while still preventing cervical cancer cases and generating QALY over screening program only. In addition, the ICERs (incremental cost per incremental effectiveness) for 30–45-year-old single cohorts were well below the generally accepted threshold value of $50 000/QALY gained in the USA.

but a lack of long-term vision with acceptance of logical scientific evidence (12).

CERVICAL CANCER CONTROL: INDIAN PERSPECTIVE

Asia-Pacific countries are very heterogeneous in terms of their cervical cancer control activities. At one end of the spectrum is Korea, which has a good, well-organized cervical cancer screening program and vaccination program, and Japan, which has a screening program that is effective in reducing mortality. At the other end of the spectrum is India, which has no cervical cancer screening program, as a result of which no asymptomatic women are advised to undergo a Pap smear. Availability of Pap testing is very limited, and there is hardly any infrastructure for performance of colposcopy or management of cervical precancerous lesions. Thus, in the case of an abnormal Pap smear, doctors either put the patient on antibiotics or antioxidants while following her up or go straight to hysterectomy.

There is a serious lack of awareness not only in the general population but also in the medical fraternity and policy–makers in India. Women's perceptions regarding cervical cancer screening are also a problem. A small demonstration program offering free cervical cancer screening in the community attracted only 60% of the target population for testing. Interview of the 40% no-shows revealed that the main reason given was that a test was not needed because the women had no symptoms. That was followed by the burden of housework and the absence of permission from the husband or in-laws.

India thus needs a national program, but the approach must be realistic. What can be afforded at present is probably a low-volume screening program, a once-in-a-lifetime test. An HPV-based test would probably be best because of its sensitivity. Two HPV vaccines have been approved, but their high cost restricts their use to wealthier citizens. Their inclusion in a national program within the next 5 years cannot be expected, and a huge number of women in need will go unscreened and untreated. A questionnaire survey of the attitudes of the wealthy urban and educated class in the Calcutta area revealed that even in that population nearly 70% of the men and women had never heard of cervical cancer. After reading a fact sheet, nearly 75% of both sexes agreed to having their daughters vaccinated. Nearly half of parents who refused the vaccine for their daughters said the reason was that the vaccine was new and its safety unknown (Table 1).

Table 1. Assessment of cervical screening services in India

Dabash et al., Reproductive Health 2005
Screening of asymptomatic women almost absent
Pap smear available in tertiary centers only
Limited opportunities for provider training
Gap in provider knowledge and practices

CERVICAL CANCER IN AUSTRALIA

The National Cervical Screening Program (NCSP) was started in Australia in 1991 (13). It recommends screening every 2 years by Pap smear, starting at age 18 and continuing to 70 years. The program is responsible for the recruitment of women for Pap smear, educating the smear takers (such as nurses), ensuring quality assurance for laboratory reading Pap smears and for smear takers and maintenance of registries for Pap smear results. Two-year participation in 2006–07 was 61.5% for women aged 20–69 and the 3-year participation rate was 74.0%. The number of new cases of cervical cancer in Australia has continued to decline and the age-standardized incidence rate of all cervical cancer is 6.9 per 100 000 women (14). The risk of cervical cancer increases with age and 20% of new cervical cancer cases occur at an age above 70 years (15). The age-standardized mortality rate from cervical cancer has more than halved since the start of the program, from 4.0 deaths per 100 000 women in 1991 to 1.9 deaths per 100 000 women in 2006. However, this program has not reduced the incidence of adenocarcinoma. The NCSP costs around $90 million annually. Australia was the first country in the world to introduce HPV vaccination to a national immunization program, starting in April 2007 (16). It is a free, school-based program for girls in the first year of high school (aged 12–13 years old) using quadrivalent vaccine. There was also a 2-year catch-up program from July 2007 for women aged 14–26 years which ended in 2009 (Table 2). An interim report (17) indicated coverage of 70% or more among almost all school cohorts vaccinated in the program. Both quadrivalent and bivalent vaccines are also available for females up to 45 years on a self-funded basis, as well as quadrivalent for males aged 9–15 years. The next most important aspect of the program is the HPV Register, which is supported by the Australian government. All girls vaccinated in the school-based program and the catch-up program are reported to the Registry. In order to keep the Registry as complete and accurate as possible, family physicians are paid to report the vaccinations. The HPV Register will facilitate cross-referencing of the vaccination data with Pap smear results and cervical cancer registries, allowing an evaluation of the impact of vaccination (18). It is estimated that in 2010, HPV vaccination will reduce HPV-16 infections by 56% and by 92% in 2050 (19).

Table 2. HPV vaccination in Australia

Government Funded	
Since April 2007	School-based HPV vaccination program for 12-13yo girls. (Gardasil®) [Catch up program for females 14-26yo. Started in July 2007 and ceased in December 2009.]
Self-Funded	
Since June 2006	Gardasil® for males 9-15yo.
Since March 2007	Cervarix® for women and girls aged 10 to 45 years.
Since August 2009	Gardasil® for women and girls aged 14 to 45 years.

PUBLIC HEALTH EDUCATION FOR CERVICAL CANCER: A COMPARISON OF THE UK AND JAPAN

Mass screening for cervical cancer began in the UK in 1988, liquid-based cytology (LBC) was introduced in 2003, the HPV vaccine was licensed in 2006 and a school-based, free HPV vaccination program was started in 2008. Since all screening is now done by LBC, HPV DNA testing was introduced in 2009 on a triage basis (20). All of these programs are free to the patient.

Japan also had a nationally funded cervical cancer screening program until 1998, when responsibility was transferred to the regional governments. The screening age was lowered from 30 to 20 years in 2004, and the interval was increased from 1 to 2 years. Since 2009, free screening coupons have been offered to women aged 20–40 every 5 years. The bivalent HPV vaccine was approved in October 2009 and available for use in December of the same year. Regional governments subsidize 70–90% of Pap smears, but HPV DNA testing and HPV vaccination are not covered by insurance. Unfortunately, less than 25% of the target population undergoes regular Pap smears and this figure is even lower in younger women (21).

The UK's mass screening program has been successful in reducing the incidence and mortality rates of cervical cancer by 60–70%, and Scotland's HPV vaccination rates are perhaps the world's highest: the uptake rate for the first year of the school-based program which included girls aged 12–13 years and those aged 16–18 years was 94.2, 93.1 and 89.8% for the first, second and third dose, respectively (22).

To understand the differences in attitudes to cervical cancer prevention in both the UK and Japan, we must first consider what makes public health measures effective? With regard to cervical cancer prevention programs, education, environment and enforcement are very important.

Concerning education, in the UK, schools, female family members, doctors, newspapers/magazines and TV inform girls about HPV, screening and vaccination (Fig. 4). In Japan, the 'educators'—mothers, teachers and nurses—themselves have not been educated and thus do not know about or have Pap smears. Some information is spread via health magazines, but little in teen magazines.

Regarding the environment, in the UK, Pap smears are performed at the GP surgery and girls have the right to request a female doctor or nurse. The majority of smear takers are nurses, who take the smear in a private room, after a detailed explanation has been given. In this case, the patient feels she is in control. In Japan, screening takes place in an OBGYN clinic or hospital department,

Figure 4. Examples from the UK: HPV vaccine.

where women only usually go if they are pregnant. All smear takers are OBGYN doctors, most of whom are men. Explanation is limited, a curtain separates the patient from the doctor, and the patient has no control and often no privacy.

With regard to the enforcement of cervical cancer prevention measures, in the UK, the government funds research to make programs successful and produces educational campaigns/materials, and all medical care is free. HPV vaccination is promoted using posters etc., and stickers are given to girls to make the vaccination fun and fashionable. Mobile phones give reminders about the next vaccination. A homepage also provides information for girls and mothers, and even celebrities give their views on why the HPV vaccine is important (23). In Japan, volunteer groups, NPOs and drug companies do the promoting, preventative medicine is not covered by health insurance, and women's health is not a high priority. The low-dose contraceptive pill has only been licensed for 10 years, and national health insurance coverage for the treatment of conditions such as endometriosis using the Pill only started in 2009.

In summary, in the UK, there are high cervical cancer screening rates and high HPV vaccination rates, because the government provides adequate education and funding. Japan also has a good infrastructure for screening and vaccination and the necessary financial means. If the government put more emphasis on women's health and preventative medicine, then the cervical cancer prevention program could be like that of the UK.

CONCLUSION AND RECOMMENDATIONS

The WHO position paper on HPV vaccines states that these vaccines should be introduced as part of a coordinated prevention strategy for cervical cancer and other HPV-related diseases, and the strategy should include education on risk-reducing behaviors as well as diagnosis and treatment of precancerous lesions and cancer (24).

For instance, the HPV vaccine is primarily recommended for girls aged 11–14 years in Japan, since it is most effective in women who have not been exposed to HPV. Public funding is critical to achieve high coverage of HPV vaccination in this age group. HPV vaccination in older women (15–45 years), the second target (or catch-up), is also recommended, since it is highly cost-effective and it should also be publicly funded (11). Since boys do not get cervical cancer and herd immunity can be achieved if 70% of girls are vaccinated, vaccinating boys is not thought to be cost-effective. Pregnant women should avoid HPV vaccination because of limited data. HPV vaccination of HIV-infected female patients may be highly beneficial due to their compromised immune system, making it more difficult for these women to get rid of the virus naturally.

Special programs are needed to educate schoolteachers, opinion leaders, healthcare professionals and policy-makers about cervical cancer and HPV at the regional level in order to strengthen the acceptability of vaccination (12). It is increasingly clear that HPV vaccination is essential for cervical cancer prevention. Persistent infection with one of the 15 high-risk HPV types is considered a basic cause of cervical

cancer. Worldwide, meta-analyses have estimated that HPV-16 and -18 account for 70% of all cervical cancers. Any cross-protection of HPV-16/18 vaccines against disease related to other HPV types would be a bonus (25). Cervical cancer screening should continue in the future with effective modification (26).

Heightened public awareness regarding healthy and safe sexual behavior together with early detection by screening are essential for the prevention of cervical cancer, whereas advanced treatments will lead to improved survival and a better quality of life.

Conflict of interest statement

Ryo Konno has received research support, conference sponsorship, honoraria and consultant fees from GlaxoSmithKline Biologicals (GSK), Merck and Qiagen. Sharon Hanley received honoraria from both GSK and Banyu pharmaceuticals for giving educational lectures. Hiroyuki Yoshikawa has served on advisory boards for GlaxoSmithKline K.K. and Banyu pharmaceutical Co. Ltd. Jeffrey H.J. Tan received travel support to attend the 20th Asia Pacific Cancer Conference from the organizer. Local expenses support was provided by GlaxoSmithKline (GSK) he had also received travel support to conferences and honorarium for lectures from GSK.

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