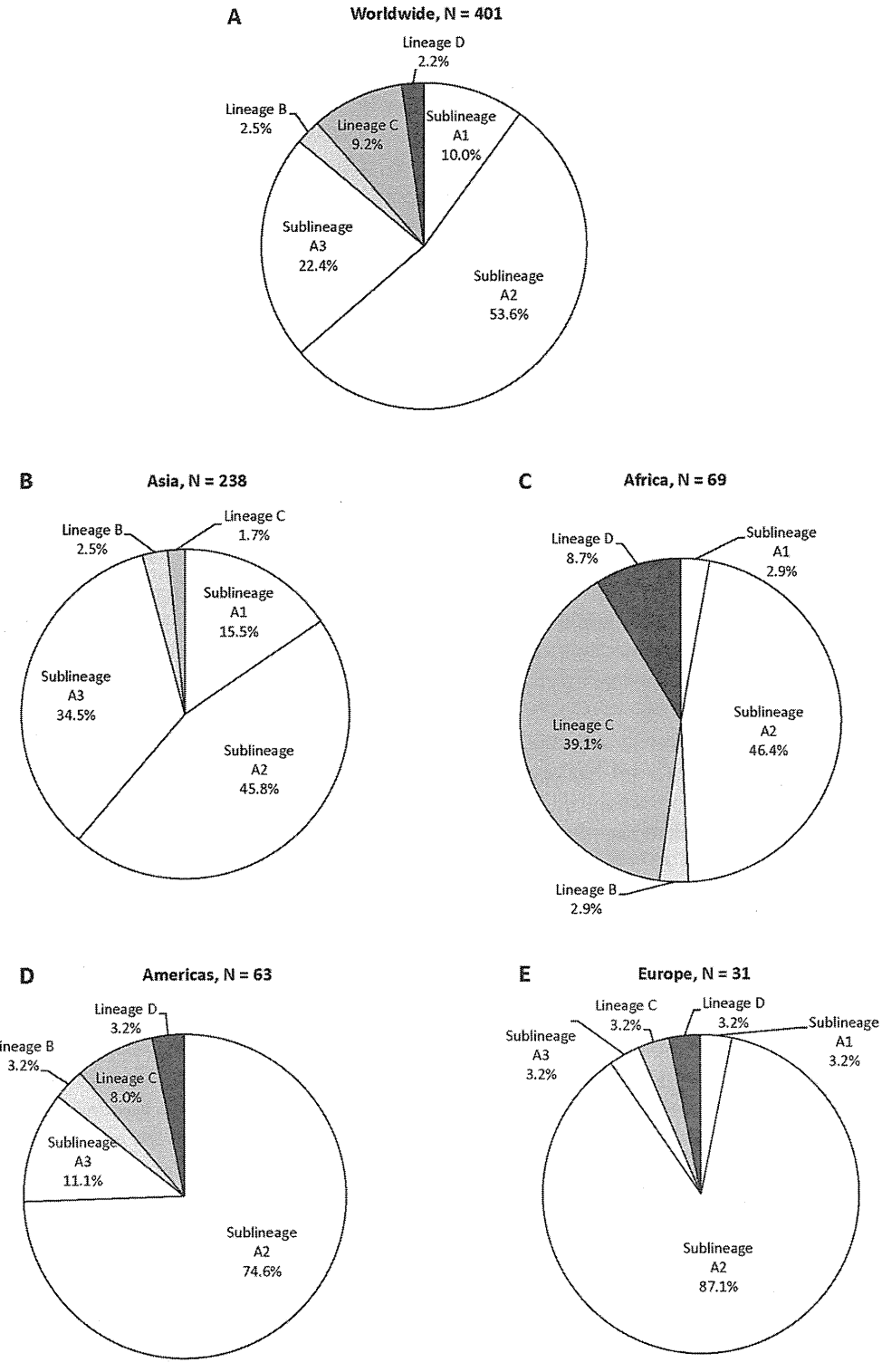

Figure 4. Geographical distribution of human papillomavirus type 58 (HPV-58) lineages. *A*, Worldwide ($N = 401$); *B*, Asia ($N = 238$); *C*, Africa ($N = 69$); *D*, the Americas ($N = 63$); *E*, Europe ($N = 31$).

understanding of the evolution and taxonomy of the virus [18, 19]. The currently available data are mainly derived from the 2 HPV types, HPV-16 and HPV-18, most commonly found in cervical cancers. Data on sequence variation of HPV-58 isolates collected worldwide are scarcely available [20, 21]. In this study, ~57% of the whole viral genome was sequenced. The selected

regions included L1, which is the most important region for defining HPV type and variant; LCR, which is the most variable region; E6, which contains informative signatures for HPV-16 variant lineage classification; E7, which has been reported to be more variable than E6 for HPV-58 [14]; and E2 and E5, which are important in oncogenesis. To our knowledge, the number of HPV-58 isolates examined in this study represents the largest reported collection sampled from multiple countries around the world. Nevertheless, one should be aware of the fact that the number of samples available from Africa and Europe for this study was relatively small, and thus the distribution of variants in these regions might not be fully elucidated.

Our analysis on the E6-E7-E2-E5-L1-LCR concatenated sequences of HPV-58 variants showed 4 phylogenetically distinct clusters, suggesting that HPV-58 variants had evolved into 4 lineages. We then attempted to identify genomic regions that could best reproduce the 4 clusters. Among the 7 genomic regions examined, 5 of them (E6, E7, E2, E4, and E5) were relatively conserved, as expected for these proteins. The tree topologies generated from these 5 regions were quite different from that of the concatenated sequences. On the other hand, the LCR and L1 regions displayed a tree topology that most closely resembled that of the concatenated sequences and were therefore regarded as the most informative surrogate regions for HPV-58 variant lineage classification. A similar topology was also observed by Calleja-Macias et al [20], who used a 461-bp fragment of LCR of 21 HPV-58 variants for tree construction.

The error frequency estimated for a standard Taq polymerase-based PCR ranges from 2×10^{-4} to 30×10^{-4} [21]. To minimize the chance of recording artificial sequence variations, we performed sequencing from both directions in independent PCRs. In addition, sequence variations observed only once were repeated. It is unlikely that the sequence variations presented are due to errors produced during the amplification process. The observed maximum nucleotide sequence divergence of the L1 ORF within each lineage ranged from .4% to 1.7%, and was 2.2% for all variants together. This limited sequence divergence indicates the absence of subtypes or intermediary genomes within the HPV-58 variants. This observation concurs with previous studies on other HPV types [20, 22]. HPV-58, as with other HPV types, probably has gone through genetic drifts that became amplified by founder effects and bottlenecks of evolution.

A clear association between phylogenetic clustering and the ethnogeographic origin of HPV-16 variants has been observed previously, and thus HPV-16 lineages were named as follows: E (European), As (Asian), AA (Asian American), and Af-1 and Af-2 (African 1 and 2) [23, 24]. The largest available series of analyses on HPV-58 variants was reported by Calleja-Macias et al [20], which included 101 samples from different parts of the world. Their analysis on a 461-bp fragment of LCR revealed 21 variants, showing a limited amount of diversification in unique geographical locations and no clear geographical association with any variants was observed. The present study allowed a more in-depth analysis based on a larger sample size. Although the ethnogeographic correlation for HPV-58 lineages was not as prominent as that for HPV-16, a predilection in distribution of HPV-58 lineages was observed in this study. Lineage A predominated in all regions except in Africa, where lineages A and C existed in comparable proportions. Although Asia comprised the largest number of samples in this study, none of them belonged to lineage D. The distribution of sublineages A1, A2, and A3 also displayed geographical variation. Although sublineage A2 predominated in Africa, the Americas and, Europe, a relatively higher frequency of sublineages A1 and A3 was found in Asia.

We hypothesize that lineage A (probably sublineage A2) was the oldest lineage, which disseminated with early human evolution and migration and had seeded into different parts of the world before other lineages emerged [24–25]. Host or environmental factors might have favored the emergence and spread of lineage C in Africa, whereas lineage D was difficult to establish in Asia.

We assigned A1 to the sublineage that contained the prototype, which was cloned from a patient with cervical cancer in Japan. In this study, sublineage A1 was rarely detected except in Asia. It is worthwhile to further investigate whether the reported higher contribution of HPV-58 to invasive cancers in East Asia is associated with a higher level of oncogenicity of sublineage A1 [7–12].

Since all the anal samples from men available for this study were collected from a single center in the United States, we compared their lineage distribution with samples from women collected from the rest of the Americas. The results showed that there were no significant differences between samples from men and those from women, and therefore pooling these samples together for the analysis of the geographical distribution of lineages was justified.

A potential limitation of the present study is the lack of sufficient samples to allow further analyses of the geographical distribution of variant lineages stratified according to cervical pathology status. Nevertheless, at least for Asia and the Americas, the proportion of samples with normal cytology or LGSIL was similar to that of samples with ASCUS, HGSIL, or carcinoma (48.7% and 48.0% of samples from Asia and the Americas, respectively, were normal/LGSIL), although Europe had a higher proportion of normal/LGSIL samples (86.2%), and information on cervical status for the samples from Africa was not known. We attempted to analyze the association between oncogenic risk and variant lineage on the basis of samples collected from Asia, Hong Kong, and South Korea, where a substantial number of samples in this study were collected, but no significant association was observed. However, such a result should not be regarded as final. Further studies are required to examine the oncogenic association of these variant lineages.

This study provides a detailed analysis on HPV-58 variant lineages and indicates that the distribution may be linked

ethnogeographically. Whether this reflects the survival fitness of these variants under different host genetic and environmental pressures or that some of these lineages are still slowly evolving and extending their ecological territories remains to be established. Further study on the evolution of HPV-58 and close monitoring of the possibility of type replacement by this virus following the widespread administration of HPV vaccines are warranted. It is worthwhile to further study the biological and pathological implications of this lineage classification system.

Supplementary Data

Supplementary tables are available online at http://jid.oxfordjournals.org.

Funding

This study was supported by the International Centre for Genetic Engineering and Biotechnology (project no. CRP/CHN08-03) and the Chinese University of Hong Kong Focused Investment Scheme Funding to Centre for Microbial Genomics and Proteomics. Specimens from Canada were obtained with the support of the Cancer Society of Canada. F. D. M. is partly supported by the Italian Ministry of Foreign Affairs, DGPC Uff V, and by the Italian Ministry of Health. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgments

We are grateful for the contributions of Sergio Andres Tonon and Cláudia Renata F. Martins, who unfortunately have passed away before the completion of this study. We thank Robert D. Burk for his advice on lineage classification and naming.

References

1. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. Lancet **2007**; 370:890–907.
2. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med **2007**; 356:1915–27.
3. Paavonen J, Naud P, Salmerón J, et al. 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, randomised study in young women. Lancet **2009**; 374:301–14.
4. Smith JS, Lindsay L, Hoots B, et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. Int J Cancer **2007**; 121:621–32.
5. Muñoz N, Bosch FX, de Sanjosé S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med **2003**; 348:518–27.
6. Muñoz N, Bosch FX, Castellsagué X, et al. Against which human papillomavirus types shall we vaccinate and screen? The international perspective. Int J Cancer **2004**; 111:278–85.
7. Huang S, Afonina I, Miller BA, Beckmann AM. Human papillomavirus types 52 and 58 are prevalent in cervical cancers from Chinese women. Int J Cancer **1997**; 70:408–11.
8. Hwang T. Detection and typing of human papillomavirus DNA by PCR using consensus primers in various cervical lesions of Korean women. J Korean Med Sci **1999**; 14:593–9.
9. Chan PK, Ho WC, Yu MY, et al. Distribution of human papillomavirus types in cervical cancers in Hong Kong: current situation and changes over the last decades. Int J Cancer **2009**; 125:1671–7.
10. Ding DC, Hsu HC, Huang RL, et al. Type-specific distribution of HPV along the full spectrum of cervical carcinogenesis in Taiwan: an indication of viral oncogenic potential. Eur J Obstet Gynecol Reprod Biol **2008**; 140:245–51.
11. Asato T, Maehama T, Nagai Y, Kanazawa K, Uezato H, Kariya K. A large case-control study of cervical cancer risk associated with human papillomavirus infection in Japan, by nucleotide sequencing-based genotyping. J Infect Dis **2004**; 189:1829–32.
12. Bao YP, Li N, Smith JS, Qiao YL; ACCPAB members. Human papillomavirus type distribution in women from Asia: a meta-analysis. Int J Gynecol Cancer **2008**; 18:71–9.
13. Chan DP, Cheung TH, Tam AO, et al. Risk association of HLA-A allele and high-risk HPV infection for cervical neoplasia in Chinese women. J Infect Dis **2005**; 192:1749–56.
14. Chan PK, Lam CW, Cheung TH, et al. Association of human papillomavirus type 58 variant with the risk of cervical cancer. J Natl Cancer Inst **2002**; 94:1249–53.
15. Swofford DL. PAUP: phylogenetic analysis using parsimony (*and other methods), version 4.0 b10. Sunderland, Massachusetts: Sinauer, 2002.
16. Posada D, Crandall KA. Modeltest: testing the model of DNA substitution. Bioinformatics **1998**; 14:817–8.
17. Huelsenbeck JP, Ronquist F. MRBAYES: Bayesian inference of phylogeny. Bioinformatics **2001**; 17:754–5.
18. Bernard HU, Calleja-Macias IE, Dunn ST. Genome variation of human papillomavirus types: phylogenetic and medical implications. Int J Cancer **2006**; 118:1071–6.
19. Sichero L, Villa LL. Epidemiological and functional implications of molecular variants of human papillomavirus. Braz J Med Biol Res **2006**; 39:707–17.
20. Calleja-Macias IE, Villa LL, Prado JC, et al. Worldwide genomic diversity of the high-risk human papillomavirus types 31, 35, 52, and 58, four close relatives of human papillomavirus type 16. J Virol **2005**; 79:13630–40.
21. Eckert KA, Kunkel TA. DNA polymerase fidelity and the polymerase chain reaction. PCR Methods Applic **1991**; 1:17–24.
22. Stewart AC, Eriksson AM, Manos MM, et al. Intratype variation in 12 human papillomavirus types: a worldwide perspective. J Virol **1996**; 70:3127–36.
23. Chan SY, Ho L, Ong CK, et al. Molecular variants of human papillomavirus type 16 from four continents suggest ancient pandemic spread of the virus and its coevolution with humankind. J Virol **1992**; 66:2057–66.
24. Ho L, Chan SY, Burk RD, et al. The genetic drift of human papillomavirus type 16 is a means of reconstructing prehistoric viral spread and the movement of ancient human populations. J Virol **1993**; 67:6413–23.
25. Li Y, Li Z, He Y, et al. Phylogeographic analysis of human papillomavirus 58. Sci China Ser C-Life Sci **2009**; 52:1164–72.

Cancer Science
The official journal of the Japanese Cancer Association JCA

Prevalence and type distribution of human papillomavirus in healthy Japanese women aged 20 to 25 years old enrolled in a clinical study

Ryo Konno,[1,5] Shinobu Tamura,[2] Kurt Dobbelaere[3] and Hiroyuki Yoshikawa[4]

[1]Department of Obstetrics and Gynecology, Jichi Medical University, Saitama Medical Center, Saitama, Japan; [2]Vaccine Clinical Development, GlaxoSmithKline K.K, Shibuya-ku, Tokyo, Japan; [3]Global Clinical Research and Development Department, GlaxoSmithKline Biologicals, Wavre, Belgium; [4]Department of Obstetrics and Gynecology, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Ibaraki, Japan

(Received December 14, 2010/Revised January 7, 2011/Accepted January 11, 2011/Accepted manuscript online January 19, 2011)

Efficacy, immunogenicity and tolerability of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine were evaluated in Japanese women aged 20–25 years, for which results have been reported previously. We analyzed the baseline data from that study and report the prevalence rates of HPV infection in young healthy Japanese women. One thousand and the forty Japanese women aged 20–25 years were enrolled in a phase II, double-blind, controlled, randomized, multicenter study. At study entry, cervical specimens were collected from the women and tested by line probe assay for 25 HPV-types and by HPV-16/18-specific polymerase chain reaction. The most frequently detected HPV-type in baseline cervical specimens was HPV-52 (8.1%), followed by HPV-16 (6.5%), HPV-51 (4.5%), HPV-18 (4.0%) and HPV-31 (3.8%). The proportion of HPV DNA-positive women increased with severity of cytological abnormalities: 26.1% (237/908) in normal cytology, 93.3% (70/75) in low-grade squamous intraepithelial lesion and 100% (7/7) in high-grade squamous intraepithelial lesion. The relative contribution of HPV-16 and HPV-18 was 4.1 and 3.0% for normal cytology cases, and 20.0 and 16.0% in low-grade squamous intraepithelial lesion, respectively. HPV-16 was found in four of seven high-grade squamous intraepithelial lesion cases (57.1%) and five of the six cervical intraepithelial neoplasia 2+ cases (83.3%). Multiple and single HPV infections were observed in 13.5% (140/1039) and 20.7% (215/1039) of all women, respectively. The HPV prevalence rates in Japanese women aged 20–25 years underline the importance of HPV vaccination at a young age and this report should be useful for monitoring changes in HPV prevalence after widespread HPV vaccination in Japanese women. (*Cancer Sci*, doi: 10.1111/j.1349-7006.2011.01878.x, 2011)

Persistent infection with HPV is the necessary cause for developing cervical cancer,[1] the second most common cancer in women worldwide.[2] HPV is a common sexually transmitted infection. Population-based studies suggest that up to as much as 80% of sexually active women are exposed to at least one genital HPV type in their lifetime.[3] While HPV infection occurrence is highest in young sexually active women, a relatively high HPV prevalence has also been detected in postmenopausal women. Infection at this later stage may be due to reactivation of earlier acquired infections or infection from new sexual partners later in life.[4] At least 14 oncogenic HPV types (high-risk HPV) have been causally linked to cervical cancer.[5] HPV-16 and HPV-18 are the most prevalent and account for more than 70% of all invasive cervical cancers worldwide; HPV-31 and HPV-45 are responsible for an additional 10% of cases[6,7] followed by HPV-33, HPV-35, HPV-52 and HPV-58.[6,7] HPV vaccines are now licensed in more than 100 countries, coinciding with large-scale national and regional immunization programs aimed at young adolescent girls.[8] Since infection with HPV may occur throughout the lifetime of a sexually active woman, it is important that vaccination induces a strong, sustained antibody response to ensure long-term protection.[9]

Currently, there are two HPV vaccines available in the world: a bivalent (Cervarix®, GlaxoSmithKline Biologicals) and a quadrivalent (Gardasil®, Merck). The bivalent vaccine is an AS04-adjuvanted vaccine specifically targeting HPV-16 and -18 types, while the quadrivalent vaccine is an aluminium-adjuvanted vaccine specifically targeting HPV-6, -11, -16 and -18 types. Both vaccines are immunogenic, generally well-tolerated, with clinically acceptable safety profiles.[10–13] Prevention by both vaccines of CIN2+ lesions caused by HPV-16 and -18 was >90% in women aged 15–25 years old and negative for these HPV-types at study entry.[11,14,15] Furthermore, excisional therapies for CIN2+ are reduced by approximately 70% for the bivalent vaccine[16] and 40% for the quadrivalent.[17] Sustained efficacy of both vaccines has been documented for 5 years or more.[11,15,16,18,19] However, it may take 5–10 years after the start of a vaccination program before significant reductions in the incidence of cervical cancer will be apparent.[20]

In Japan, cervical cancer ranks approximately 7th in women overall (incidence rate of 13.6 per 100 000) and 2nd in women aged 15–44 years (incidence rate of 12.0 per 100 000).[21,22] It is estimated that 15 000 women are diagnosed with cervical cancer yearly, leading to approximately 3500 deaths.[21–23] These figures include approximately 2000 new cases and 200 deaths that are estimated to occur every year in Japanese women in their twenties and thirties.[23,24] HPV is currently one of the least known sexually transmitted infections in Japan, resulting in a lower level of public knowledge of the risks of HPV and cervical cancer.[25] HPV-16 and HPV-18 are the most frequently identified HPV-types in invasive cervical cancers in Japan (67.1%), and HPV-52 and HPV-58 appear to be the next most common types accounting for 11.5% of cervical cancers.[26] Prevalence of HPV infection in the Japanese population has been mainly reported based on evaluations of women who have been referred to hospitals and clinics to receive cervical cancer screening. Furthermore, the women examined in previous studies have come from a wide range of ages and, thus, information on the rates of HPV infection in young women, particularly those in their twenties, is lacking. For instance, Inoue *et al.*[27] reported on a large scale study evaluating HPV testing in over 8000 women in the Ishikawa Prefecture. The median age of these women was 36 years but the age span of the participants extended from 14 to 83 years of age. A further concern is that

[5]To whom correspondence should be addressed.
E-mail: kryo772007@yahoo.co.jp
Clinical trial registry: Clinicaltrials.gov.
Name: Human papillomavirus vaccine (Cervarix) efficacy, immunogenicity and safety trial in adult Japanese women with GSK Biologicals HPV-16/18 vaccine.
Number: NCT00316693.

doi: 10.1111/j.1349-7006.2011.01878.x

these studies were usually conducted in small geographic areas relating to a particular hospital, clinic or prefecture. Very little information regarding nationwide HPV prevalence is available.

We have recently reported the results of a clinical study to evaluate the bivalent HPV-16/18 AS04-adjuvanted vaccine (Cervarix®, GlaxoSmithKline Biologicals) in healthy Japanese women aged 20–25 years.[28–30] While the results of this study showed that the HPV-16/18 AS04-adjuvanted vaccine was effective and immunogenic, with a clinically acceptable safety profile in the population studied, an accurate knowledge of the actual HPV infection rates in young healthy Japanese women could further confirm the importance of vaccination against HPV types 16 and 18. We therefore determined the HPV infection status of each woman at study entry as an indicator of the national infection rates. In particular, we analyzed DNA of 25 HPV types (14 oncogenic: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68; 11 non-oncogenic types: 6, 11, 34, 40, 42, 43, 44, 53, 54, 70 and 74) using PCR and report here the baseline prevalence of both the oncogenic and non-oncogenic HPV types in the cervical cytology samples of young healthy Japanese women.

Materials and Methods

Healthy Japanese women aged 20–25 years were recruited in this phase II double-blind (observer-blind) controlled, randomized, multicenter study (104798, NCT00316693) between April and October 2006. The 13 centers were located in Aomori, Tokyo, Fukui, Osaka, Hiroshima, Miyazaki and Kagoshima in Japan. Study participants were not screened before enrolment with respect to baseline serological, cytological or HPV DNA status. Inclusion and exclusion criteria were as previously described.[30] The study was conducted following the Declaration of Helsinki (version 1996) and all participants provided written informed consent. All recruitment materials, informed consent, protocol, and amendments were approved by independent institutional review boards.

Subjects were randomized in a 1:1 fashion to receive either the HPV-16/18 AS04-adjuvanted vaccine (containing 20 μg of HPV-16 L1 virus-like particle (VLP) and 20 μg of HPV-18 L1 VLP adjuvanted with 50 μg 3-*O*-desacyl-4′-monophosphoryl lipid A and 0.5 mg aluminium hydroxide) or a hepatitis A vaccine licensed in Japan (Aimmugen®, Chem-Sero-Therapeutic Research Institute, Kumamoto, Japan; containing 0.5 μg of inactivated hepatitis A antigen) as the control vaccine. Both vaccines were administered intramuscularly according to a 0-, 1-, and 6-month schedule. Investigators obtained cervical specimens with a cervical brush for cytology and HPV DNA as previously described.[18,28–31]

HPV DNA isolated from the cytology specimen was amplified from an aliquot of purified total DNA with the SPF_{10} broad-spectrum primers. These primers amplify a 65 bp region of the L1 gene and the generic amplification products were detected by hybridization on a microtiter plate (DEIA). HPV-positive specimens were typed by reverse hybridization LiPA. The broad-spectrum PCR SPF_{10} HPV $LiPA_{25}$ version 1 and SPF_{10} HPV DEIA (manufactured by Labo Biomedical Products, Rijswijk, the Netherlands based on licensed INNOGENETICS SPF_{10} technology) detected 25 HPV types: 14 oncogenic (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) and 11 non-oncogenic HPV types (6, 11, 34, 40, 42, 43, 44, 53, 54, 70 and 74). If a sample was negative for HPV-16 or HPV-18 by the SPF_{10}-$LiPA_{25}$ system, type-specific PCR was performed to confirm the absence of these types using HPV-16 primers that amplified a 92 bp segment of the E6/E7 gene and HPV-18 primers that amplified a 126 bp segment of the L1 gene.[18,28–31]

Cytology was assessed by liquid-based cytology (ThinPrep, Cytyc Corporation, Marlborough, MA, USA) using a central laboratory (Quest Diagnostics, Teterboro, NJ, USA). Cytology results were reported using the 2001 Bethesda system and cytological abnormalities included: (i) ASC-US; (ii) LSIL; (iii) ASC-H; (iv) HSIL; and (v) AGC. Protocol guidelines recommended colposcopy after one report of HSIL or ASC-H. Biopsy was required for any suspected lesions on colposcopy. The central laboratory (Quest Diagnostics) processed and interpreted results from histology samples. All CIN endpoints were confirmed by an expert histopathology review panel that was blinded to vaccine status, HPV DNA status before biopsy, and cytology reports.

The enrolment target of 1000 unscreened women was estimated to provide 800 women who were DNA negative for HPV-16 or HPV-18 at month 0 and 6, and who would be evaluable for assessment of the primary endpoint in the according to protocol group for efficacy analysis. All analyses were based on the TVC; however, some values were absent due to missing or non-evaluable samples. Data is presented as percentage of subjects per group along with the actual number of subjects. Statistical analysis is descriptive in nature.

Results

One thousand and forty healthy Japanese women aged 20–25 years old (mean age: 22.5) were enrolled in 13 study sites in Japan. All women were vaccinated and included in the TVC: 519 women in the HPV group (HPV-16/18 AS04-adjuvanted vaccine) and 521 women in the control group (HAV group, hepatitis A vaccine licensed in Japan). The study sites were located in seven areas with the following recruitment numbers: Tokyo 457 (44.0%), Aomori 160 (15.4%), Osaka 136 (13.1%), Fukui 128 (12.3%), Kagoshima 91 (8.8%), Hiroshima 39 (3.8%) and Miyazaki 29 (2.8%).

The distributions of the tested HPV types in the TVC (irrespective of cytology) and for each cytological status are shown in Table 1. Data was not available for one participant due to a missing sample. Three hundred and fifty-five women (34.2%) of the TVC (irrespective of cytology) tested positive for HPV DNA at study entry. In particular, oncogenic and non-oncogenic HPV types were detected in 304 (29.3%) and 112 (10.8%) women. HPV-52 (8.1%, 84/1039) was the most frequently detected HPV type, followed by HPV-16 (6.5%, 68/1039), HPV-51 (4.5%, 47/1039), HPV-18 (4.0%, 42/1039) and HPV-31 (3.8%, 39/1039).

The majority of women (87.4%, 908/1039 women) had no cytological abnormalities; 12.6% (131/1039) had cytological abnormalities including ASC-US (4.5%, 47/1039), LSIL (7.2%, 75/1039), HSIL (0.7%, 7/1039) and ASC-H (0.2%, 2/1039). Overall, 26.1% of women with normal cytology (237/908) were positive for HPV DNA (Table 1). In contrast, of the 131 women who had abnormal cytology, 90.1% (118/131) were positive for HPV DNA. The HPV positivity rate was also high for women diagnosed with ASC-US (83.0%, 39/47), LSIL (93.3%, 70/75) and 100% (9/9) for women diagnosed to have HSIL or ASC-H. HPV-16 (23.7%, 31/131) was the most frequently detected HPV type, followed by HPV-52 (19.8%, 26/131), HPV-31 and HPV-56 equally detected in 13.0% (17/131) and HPV-51 (12.2%, 16/131). Fifty-five percent (5/9) of the women diagnosed as HSIL or ASC-H had HPV-16 detected in their cytological specimens. The nine women with HSIL or ASC-H had a colposcopy after the cytology testing. CIN3 was diagnosed in five women, CIN2 in one woman, CIN1 in one woman and two women had no lesions. Four of the five women who were diagnosed with CIN3 and the woman diagnosed with CIN2 were positive for HPV-16. The positivity rate of HPV-16 in the women diagnosed as CIN2 or CIN3 reached 83.3% (5/6).

The number of multiple HPV infections is illustrated by Table 2. Multiple infections were observed in 140 women (13.5%, 140/1039) of the TVC (irrespective of cytology),

doi: 10.1111/j.1349-7006.2011.01878.x

Table 1. HPV DNA genotype status distribution in cervical samples, and cytological and histological status at study entry (total vaccinated cohort)

HPV types	Total (n = 1039)†		Cytological status												Histological status‡	
			Normal (n = 908, 87.4%)		Abnormal (n = 131, 12.6%)		ASC-US (n = 47, 4.5%)		LSIL (n = 75, 7.2%)		HSIL (n = 7, 0.7%)		ASC-H (n = 2, 0.2%)		CIN2+ (n = 6, 0.6%)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Oncogenic HPV																
16	68	6.5	37	4.1	31	23.7	11	23.4	15	20.0	4	57.1	1	50.0	5	83.3
18	42	4.0	27	3.0	15	11.5	3	6.4	12	16.0	0	0	0	0	0	0
31	39	3.8	22	2.4	17	13.0	4	8.5	11	14.7	2	28.6	0	0	1	16.7
33	1	0.1	0	0	1	0.8	1	2.1	0	0	0	0	0	0	0	0
35	8	0.8	6	0.7	2	1.5	0	0	1	1.3	1	14.3	0	0	1	16.7
39	37	3.6	24	2.6	13	9.9	4	8.5	9	12.0	0	0	0	0	0	0
45	4	0.4	1	0.1	3	2.3	1	2.1	2	2.7	0	0	0	0	0	0
51	47	4.5	31	3.4	16	12.2	5	10.6	10	13.3	0	0	1	50.0	0	0
52	84	8.1	58	6.4	26	19.8	11	23.4	12	16.0	3	42.9	0	0	0	0
56	37	3.6	20	2.2	17	13.0	6	12.8	11	14.7	0	0	0	0	0	0
58	31	3.0	17	1.9	14	10.7	4	8.5	9	12.0	1	14.3	0	0	1	16.7
59	7	0.7	3	0.3	4	3.1	1	2.1	3	4.0	0	0	0	0	0	0
66	35	3.4	23	2.5	12	9.2	1	2.1	11	14.7	0	0	0	0	0	0
68	17	1.6	12	1.3	5	3.8	2	4.3	2	2.7	1	14.3	0	0	0	0
Total	304	29.3	197	21.7	107	81.7	36	76.6	62	82.7	7	100	2	100	6	100
Non-oncogenic HPV																
6	25	2.4	17	1.9	8	6.1	2	4.3	6	8.0	0	0	0	0	0	0
11	6	0.6	5	0.6	1	0.8	0	0	1	1.3	0	0	0	0	0	0
34	12	1.2	6	0.7	6	4.6	4	8.5	2	2.7	0	0	0	0	0	0
40	9	0.9	6	0.7	3	2.3	1	2.1	2	2.7	0	0	0	0	0	0
42	4	0.4	3	0.3	1	0.8	0	0	1	1.3	0	0	0	0	0	0
43	12	1.2	7	0.8	5	3.8	2	4.3	3	4.0	0	0	0	0	0	0
44	3	0.3	3	0.3	0	0	0	0	0	0	0	0	0	0	0	0
53	38	3.7	29	3.2	9	6.9	2	4.3	7	9.3	0	0	0	0	0	0
54	14	1.3	14	1.5	0	0	0	0	0	0	0	0	0	0	0	0
70	2	0.2	2	0.2	0	0	0	0	0	0	0	0	0	0	0	0
74	3	0.3	2	0.2	1	0.8	1	2.1	0	0	0	0	0	0	0	0
Total	112	10.8	82	9.0	30	22.9	9	19.1	21	28.0	0	0	0	0	0	0
Overall total	355	34.2	237	26.1	118	90.1	39	83.0	70	93.3	7	100	2	100	6	100

†Data was not available for one participant due to missing sample. ‡Nine subjects who were diagnosed HSIL or ASC-H at study entry had a colposcopy after the cytology testing. ASC-H, atypical squamous cells, cannot exclude HSIL; ASC-US, atypical squamous cell of undetermined significance; CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; HPV, human papillomavirus; LSIL, low-grade squamous intraepithelial lesion.

Table 2. Number of human papillomavirus (HPV) infections at study entry in the total vaccinated cohort (TVC) and in HPV positive women (HPV+)

Number of infections	n	TVC	HPV+
		% (n = 1039)†	% (n = 355)
6 types	1	0.1	0.3
5 types	6	0.6	1.7
4 types	14	1.3	3.9
3 types	40	3.8	11.3
2 types	79	7.6	22.2
1 type	215	20.7	60.6

†Data was not available for one participant due to missing sample.

including one woman (0.1%) testing positive for six HPV types (45/51/52/53/56/58) and six women (0.6%) positive for five HPV types. Fourteen women (1.3%) were positive for four HPV-types, 40 women (3.8%) positive for three types and 79 of the women (7.6%) had two HPV types. When only the HPV positive women (n = 355) are examined, these percentages increase to 0.3% testing positive for six HPV types, 1.7% for five types, 3.9% for four types, 11.3% for three types and 22.2% of the HPV-positive women had two HPV types (Table 2).

Discussion

This study is the first to evaluate the HPV prevalence for healthy young Japanese women nationwide, based in seven different regions of Japan. Study sites were well-distributed with the most northern site (Aomori) located in the farthest north prefecture of the main island and the most southern site (Kagoshima) located in the farthest south prefecture of the third island of Japan. Healthy Japanese women aged 20–25 years of age were recruited for a clinical study to assess the efficacy, immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine against HPV. We assessed the baseline HPV status using a sensitive PCR and cytology of the women enrolled in this clinical study and these are the data we present.

Although the overall HPV prevalence was slightly higher in the present study, type-specific prevalence data in Japanese women with normal cervical cytology was comparable to two large scale meta-analyses of Japanese data.[32,33] HPV-52 was also the most prevalent HPV type with HPV-16 second in these findings. While HPV-51 was the third most prevalent HPV type based on the results of the current study and of Miura *et al.*,[33] HPV-51 was fourth in the study of Konno *et al.*[32] with HPV-58 third. Previous findings from other Japanese studies were strongly supported by the large dataset used for the meta-analysis, in particular for age groupings.[32,33] HPV prevalence in women in the Asia Pacific region who were in their twenties with normal cytology was highest in Australia (30.1%), followed by Japan (23.1%), India (13.2%), Korea (12.7%) and Taiwan (9.9%).[34] Our data for women aged 20–25 years with normal cytology is relatively high (26.1%) compared to other women from the Asia Pacific region, with the exception of Australian women, but similar to that previously reported for Japanese women.[34] Interestingly, the four HPV genotypes with the highest prevalence in this study matched four of the five most common high-risk HPV genotypes in Asian women with normal cytology from China, Singapore, Taiwan and Indonesia.[34]

While HPV-52 is the most prevalent in the Japanese general population, HPV-16 is more closely associated with high-grade precursor lesions and invasive cancer.[32,33] The meta-analysis of Japanese data indicated that in normal cytological samples the prevalence of HPV-16 was 0.84% and of HPV-18 was <0.50%.[32] However, these data were compiled based on screenings taken of women of all ages. While HPV prevalence in the USA was common among women between the ages of 14 and 59 years old, prevalence was highest in women between the ages of 20 and 24 years old.[35] This current nationwide study specifically examined young women aged 20–25 years and shows a higher prevalence of the HPV-16 and HPV-18 types, particularly HPV-18 in normal cytology. Furthermore, HPV prevalence in Japanese women with normal/negative cytology appears to decrease with aging; for example from 26.1% at 22.5 years (average age) in the present study to 22.5% at 35.0 years[26] and 10.2% at 52.4 years.[36] Although these studies were not based in the same geographic locations and used different primer systems for their PCR analysis, it has been previously observed that HPV-16 and HPV-18 DNA positivity appears to be very high in Japanese women aged 20–29 years with CIN2-3 or invasive cervical cancer.[26] Therefore, it is possible that, due to high prevalence of HPV-16 and HPV-18 in Japanese women with normal cytology, cervical cancer caused by these HPV types will increase in the future.

As described above, HPV type distribution in invasive cervical cancers is very similar among countries of eastern Asia (including Japan, China/Hong Kong/Taiwan and Korea). HPV-16 and -18 are the most common types accounting for approximately 70% with the next three most common types being HPV-58, HPV-52 and HPV-33 accounting for an additional 10%.[26,37] Overall HPV and oncogenic HPV prevalence were 34.1% and 29.2% in all study participants. In the pivotal clinical study (PATRICIA) to evaluate the HPV-16/18 AS04-adjuvanted vaccine with approximately 18 000 women aged 15–25 years conducted in Asia Pacific, Europe, and North and South America, oncogenic HPV types were detected in 20.1% of all study participants.[14] Particularly, the prevalence of HPV-16 and HPV-18 was 5.4% and 2.3% in the participants of the clinical study. The broader age range of the women in that study precludes direct comparison of the Japanese data presented here; however, the prevalence of oncogenic HPV types, especially HPV-16 (6.5%) and HPV-18 (4.0%), in Japanese women is higher than that in other populations.

Cervical cancer is preventable if precancerous lesions are detected early enough. Cytological analysis to detect abnormalities such as LSIL and HSIL is used in combination with histology to define the early stages (low-grade cervical lesions) and advanced stages (high-grade cervical lesions) of the disease.[38] The strong association between oncogenic HPV prevalence, particularly of HPV-16, and cytological abnormalities such as LSIL and HSIL observed in this study follows the high incidences of HPV in invasive cervical cancer, HSIL and LSIL throughout Asia.[37] Indeed, an increasing prevalence of oncogenic HPV with increasing cervical lesion severity has been previously reported in Japanese women,[26,32,33] particularly of the HPV-18 genotype.[26] In agreement with this observation, there was also a good correlation between the prevalence of oncogenic HPV types and HSIL across the different parts of Europe.[39]

While the majority of HPV-positive women in this study were infected with a single HPV-type (60.6%), multiple HPV infections were observed in the remaining 39.4%. This is much higher than the 12.0% previously reported for Japanese women with normal cytology and HPV positive that were also positive for multiple HPV infection types.[26] The higher rate observed in our study is most likely due to the differences in the ages of the groups examined as we specifically examined women aged 20–25 years of age. Women aged 20–24 years of age had the highest prevalence of HPV infection compared to younger (14–24 years) and older (25–29, 30–39, 40–49, or 50–59 years) women, especially when restricting the analysis to sexually active females, in a US study.[35] Furthermore, the rate of multiple infection has been demonstrated to be higher in younger than older women in a Danish study and was also linked to sexual behavior.[40] Therefore, HPV vaccines that provide protection against multiple HPV types may be more effective in preventing cervical cancer.

The introduction of systematic cytological screening has resulted in a fall of the death rate from cervical cancer in many countries.[41] Vaccination against HPV-16 and HPV-18 would theoretically decrease by approximately 40% the number of oncogenic HPV-positive findings in screening programs.[39] As HPV type distribution in invasive cervical cancers is very similar among countries of eastern Asia (including Japan, China/Hong Kong/Taiwan and Korea), approximately 70% of invasive cervical cancer cases could be potentially prevented by an HPV-16/18 prophylactic vaccine.[18] Moreover, this could increase to approximately 80% if the vaccine targeted additional HPV types, such as HPV-31 and HPV-45, as well as HPV-16 and HPV-18.[37] Both HPV-16 and HPV-18 are phylogenetically related to other HPV subtypes (HPV-16: HPV-31, -33, -35, -52, -58, -67; HPV-18: HPV-39, -45, -59, -68, -70),[42] suggesting that vaccines targeting HPV-16/18 could cross-react with these subtypes. Cross-protection data have been reported for both the bivalent and the quadrivalent vaccines.[11,16,43,44] The bivalent vaccine demonstrated cross-protection against persistent infection with HPV-31, -33 and -45 of 78.7%, 45.7% and 75.7%[16] while the quadrivalent showed cross protection of approximately 46% against persistent infection with HPV-31.[44] Vaccination against HPV may, thus, provide extra protection against cervical cancer caused by non-vaccine HPV types, especially those vulnerable to infection by multiple HPV types.

Indeed, the increasing prevalence of HPV-16 and HPV-18 observed in young healthy Japanese women in this study may indicate that the incidence of cervical cancer in Japan caused by HPV-16/18 will increase in the future. Therefore, a greater emphasis needs to be placed on providing information on HPV and screening for oncogenic types of HPV, in particular HPV-16 and HPV-18. Safe and effective vaccination against HPV-16 and HPV-18 will help prevent the increase of HPV infection and subsequent development of cervical cancer. Furthermore, the

doi: 10.1111/j.1349-7006.2011.01878.x

HPV prevalence data reported here in healthy young Japanese women would be very useful for monitoring the changes in HPV prevalence after widespread HPV vaccination in Japanese women in the future.

Acknowledgments

The authors acknowledge all of the investigators, staff and women enrolled in the study. This study (104798, NCT00316693) was funded and coordinated by GlaxoSmithKline Biologicals, Rixensart, Belgium and GlaxoSmithKline K.K., Tokyo, Japan. We thank Fabian Tibaldi (GlaxoSmithKline Biologicals, Global Clinical Research and Development Department, Rixensart, Belgium) for the statistical analyses, Nobuhiro Noro, Atsushi Maruyama and Marie Okutani (all from GlaxoSmithKline K.K, Vaccine Clinical Development, Tokyo Japan) contributed to data interpretation and critical reading, Claire Marie Seymour for writing assistance and Dirk Saerens and Denis Sohy for editorial assistance and manuscript coordination on behalf of GlaxoSmithKline Biologicals. Cervarix is a registered trademark of the GlaxoSmithKline group of companies. Gardasil is a registered trademark of Merck & Co. Aimmugen is a registered trademark of The Chem-Sero-Therapeutic Research Institute.

Disclosure Statement

Ryo Konno and Hiroyuki Yoshikawa have served on advisory boards for GlaxoSmithKline K.K., and received lecture fees from GlaxoSmithKline K.K.. Shinobu Tamura is employee of GlaxoSmithKline K.K.. Kurt Dobbelaere is employee of GlaxoSmithKline Biologicals and has stock ownership of GlaxoSmithKline.

Abbreviations

AGC	atypical glandular cells
ASC-H	atypical squamous cells, cannot exclude HSIL
ASC-US	atypical squamous cell of undetermined significance
CIN	cervical intraepithelial neoplasia
DEIA	DNA enzyme immunoassay
HPV	human papillomavirus
HSIL	high-grade squamous intraepithelial lesion
LiPA	line probe assay
LSIL	low-grade squamous intraepithelial lesion
PCR	polymerase chain reaction
TVC	total vaccinated cohort
VLP	virus-like particle

References

1 Walboomers JM, Jacobs MV, Manos MM *et al.* Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999; **189**: 12–9.
2 Parkin DM, Bray F, Ferlay J *et al.* Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74–108.
3 Garland SM, Smith JS. Human papillomavirus vaccines: current status and future prospects. *Drugs* 2010; **70**: 1079–98.
4 Trottier H, Franco EL. The epidemiology of genital human papillomavirus infection. *Vaccine* 2006; **24**(Suppl 1): S1–15.
5 Munoz N, Bosch FX, de Sanjosé S *et al.* Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 2003; **348**: 518–27.
6 Smith JS, Lindsay L, Hoots B *et al.* Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. *Int J Cancer* 2007; **121**: 621–32.
7 Castellsagué X, De Sanjosé S, Aguado T *et al.* HPV and Cervical Cancer in the World: 2007 report (Section I Continents and Regions). *Vaccine* 2007; **25**: C1–26.
8 Wright TC Jr, Huh WK, Monk BJ *et al.* Age considerations when vaccinating against HPV. *Gynecol Oncol* 2008; **109**: S40–7.
9 Schwarz TF, Leo O. Immune response to human papillomavirus after prophylactic vaccination with AS04-adjuvanted HPV-16/18 vaccine: improving upon nature. *Gynecol Oncol* 2008; **110**: S1–10.
10 Descamps D, Hardt K, Spiessens B *et al.* Safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine for cervical cancer prevention: a pooled analysis of 11 clinical trials. *Hum Vaccin* 2009; **5**: 332–40.
11 The GlaxoSmithKline Vaccine HPV-007 Study Group, Romanowski B, de Borba PC *et al.* Sustained efficacy and immunogenicity of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine: analysis of a randomised placebo-controlled trial up to 6.4 years. *Lancet* 2009; **374**: 1975–85.
12 Villa LL, Costa RL, Petta CA *et al.* Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol* 2005; **6**: 271–8.
13 Villa LL, Ault KA, Giuliano AR *et al.* Immunologic responses following administration of a vaccine targeting human papillomavirus types 6, 11, 16, and 18. *Vaccine* 2006; **24**: 5571–83.
14 Paavonen J, Jenkins D, Bosch FX *et al.* 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* 2007; **369**: 2161–70.
15 Ault KA, The Future II Study Group. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. *Lancet* 2007; **369**: 1861–8.
16 Paavonen J, Naud P, Salmeron J *et al.* 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, randomised study in young women. *Lancet* 2009; **374**: 301–14.
17 Olsson S-O, Paavonen J. Impact of HPV 6/11/16/18 vaccine on abnormal Pap tests and procedures. Abstract O-01.08. *25th International Papillomavirus Conference*. 2010, May 8–12, 2009, Malmo Sweden.
18 Harper DM, Franco EL, Wheeler CM *et al.* Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. *Lancet* 2006; **367**: 1247–55.
19 Harper DM. Current prophylactic HPV vaccines and gynecologic premalignancies. *Curr Opin Obstet Gynecol* 2009; **21**: 457–64.
20 Cuzick J. Long-term cervical cancer prevention strategies across the globe. *Gynecol Oncol* 2010; **117**: S11–4.
21 Castellsagué X, De Sanjosé S, Aguado T *et al.* HPV and Cervical Cancer in the World: 2007 Report (Section II Countries). *Vaccine* 2007; **25**: C27–219.
22 WHO/ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre). Human Papillomavirus and Related Cancers in Japan. Summary Report 2010. 22 June 2010. [Cited 27 Apr 2010.] Available from URL: http://www.who.int/hpvcentre/en/.
23 Japanese Ministry of Health, Labour & Welfare. Vital Statistics Japan. 21 Oct 2009. [Cited 16 Nov 2010.] Available from URL: http://ganjoho.ncc.go.jp/professional/statistics/statistics.html.
24 Marugame T, Matsuda T, Kamo K *et al.* Cancer incidence and incidence rates in Japan in 2001 based on the data from 10 population-based cancer registries. *Jpn J Clin Oncol* 2007; **37**: 884–91.
25 Garland S, Park SN, Ngan HY *et al.* The need for public education on HPV and cervical cancer prevention in Asia. Opinions of experts at the AOGIN conference. *Vaccine* 2008; **26**: 5435–40.
26 Onuki M, Matsumoto K, Satoh T *et al.* Human papillomavirus infections among Japanese women: age-related prevalence and type-specific risk for cervical cancer. *Cancer Sci* 2009; **100**: 1312–6.
27 Inoue M, Sakaguchi J, Sasagawa T *et al.* The evaluation of human papillomavirus DNA testing in primary screening for cervical lesions in a large Japanese population. *Int J Gynecol Cancer* 2006; **16**: 1007–13.
28 Konno R, Dobbelaere KO, Godeaux OO *et al.* Immunogenicity, reactogenicity, and safety of human papillomavirus 16/18 AS04-adjuvanted vaccine in Japanese women: interim analysis of a phase II, double-blind, randomized controlled trial at month 7. *Int J Gynecol Cancer* 2009; **19**: 905–11.
29 Konno R, Tamura S, Dobbelaere K *et al.* Efficacy of human papillomavirus 16/18 AS04-adjuvanted vaccine in Japanese women aged 20 to 25 years: interim analysis of a phase 2 double-blind, randomized, controlled trial. *Int J Gynecol Cancer* 2010; **20**: 404–10.
30 Konno R, Tamura S, Dobbelaere K *et al.* Efficacy of human papillomavirus type 16/18 AS04-adjuvanted vaccine in Japanese women aged 20 to 25 years: final analysis of a phase 2 double-blind, randomized controlled trial. *Int J Gynecol Cancer* 2010; **20**: 847–55.
31 Harper DM, Franco EL, Wheeler C *et al.* Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet* 2004; **364**: 1757–65.

32 Konno R, Shin HR, Kim YT *et al.* Human papillomavirus infection and cervical cancer prevention in Japan and Korea. *Vaccine* 2008; **26**(Suppl 12): M30–42.
33 Miura S, Matsumoto K, Oki A *et al.* Do we need a different strategy for HPV screening and vaccination in East Asia? *Int J Cancer* 2006; **119**: 2713–5.
34 Garland SM, Cuzick J, Domingo EJ *et al.* Recommendations for cervical cancer prevention in Asia Pacific. *Vaccine* 2008; **26**(Suppl 12): M89–98.
35 Dunne EF, Unger ER, Sternberg M *et al.* Prevalence of HPV infection among females in the United States. *JAMA* 2007; **297**: 813–9.
36 Asato T, Maehama T, Nagai Y *et al.* A large case–control study of cervical cancer risk associated with human papillomavirus infection in Japan, by nucleotide sequencing-based genotyping. *J Infect Dis* 2004; **189**: 1829–32.
37 Bao YP, Li N, Smith JS *et al.* Human papillomavirus type-distribution in women from Asia: a meta-analysis. *Int J Gynecol Cancer* 2008; **18**: 71–9.
38 Chang Y, Brewer NT, Rinas AC *et al.* Evaluating the impact of human papillomavirus vaccines. *Vaccine* 2009; **27**: 4355–62.
39 De Vuyst H, Clifford G, Li N *et al.* HPV infection in Europe. *Eur J Cancer* 2009; **45**: 2632–9.
40 Nielsen A, Kjaer SK, Munk C *et al.* Type-specific HPV infection and multiple HPV types: prevalence and risk factor profile in nearly 12,000 younger and older Danish women. *Sex Transm Dis* 2008; **35**: 276–82.
41 Levi F, Lucchini F, Negri E *et al.* Cervical cancer mortality in young women in Europe: patterns and trends. *Eur J Cancer* 2000; **36**: 2266–71.
42 de Villiers EM, Fauquet C, Broker TR *et al.* Classification of papillomaviruses. *Virology* 2004; **324**: 17–27.
43 Wheeler CM, Kjaer SK, Sigurdsson K *et al.* The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in sexually active women aged 16–26 years. *J Infect Dis* 2009; **199**: 936–44.
44 Brown DR, Kjaer SK, Sigurdsson K *et al.* The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in generally HPV-naive women aged 16–26 years. *J Infect Dis* 2009; **199**: 926–35.

doi: 10.1111/j.1349-7006.2011.01878.x

総論

諸外国における子宮頸がん検診

今野　良[1)]／林　由梨[2)]／根津幸穂[3)]／満下淳地[3)]

SUMMARY　子宮頸がん検診の効率的なプログラムをデザインするには，その国の検診精度や経済状況，資源の問題などを考慮する必要がある．海外での子宮頸がん検診の実状や臨床試験を紹介し，わが国における検診プログラムを検討する一助としたい．特に，政府が包括的に子宮頸癌予防に取り組んでいるオーストラリアの状況は素晴らしく，有用な情報となる．

〔臨床検査　55：1391-1398，2011〕

KEYWORDS　子宮頸がん検診，細胞診，HPV検査

検診方法について

プログラム化された検診システムのある先進国での従来からの検査項目は細胞診とコルポスコピー検査である一方，途上国では社会的資源の不足からVIA(visual inspection with application of acetic acid)またはVILI(visual inspection with application of Lugol's iodine)という方法がとられているが，特異度が低く[1]，ことに前癌状態を評価することは難しい(表1)．

細胞診による子宮頸部がん検診は，死亡率減少効果に対する十分な根拠があるとされており精度の高い検診手法である．しかし細胞診の特徴として特異度は高いが感度が低い(表1)[1]という問題点があり，細胞診のみに頼ると，どうしても取りこぼしがでてしまう．

がん検診プログラム

がん検診の実施体制は，organized screening(行政検診)と人間ドック型のopportunistic screening(機会検診)に大別される．organized screeningは，集団全体の死亡率減少を目的とするのに対し，opportunistic screeningでは個人の死亡リスクの減少を目的とする．子宮頸がん検診は精度管理や追跡調査が整備されておりorganized screeningの対象である．

先進諸外国での検診対象年齢および検診間隔を表2に示した．対象年齢の平均が22～65歳，検診間隔の平均は3.2年である．ドイツを除いて2～5年に1回の検診間隔であるが，年齢調整死亡率は2人弱と良好である．一方，アジア・ラテンアメリカの検診状況を表3に示した．日本と同じアジア諸国であるシンガポール，香港，台湾，韓国ではこの5年間で受診率が向上している．逆にラテンンアメリカは検診受診率はよいものの，検診精度やフォローアップ機構に問題があり死亡率が非常に高い．

子宮頸癌の自然史ではHPV感染の9割が1～2年で自然消失するが，1割が持続感染して前癌病変を経て数年かけて子宮頸癌へと進行すると言われている[2]．このことから考えると初回の性交渉より2～3年経過した時点から検診を開始する意義があり，アメリカなどでは検診開始年齢を

1）自治医科大学附属さいたま医療センター産科婦人科・教授
2）同・医員
3）同・講師

表1　検診方法別のCIN2以上を検出する感度，特異度

検査方法		感度	特異度	特徴
細胞診		44～78%	91～96%	適切な検査施設が必要かつ精度管理が大切.
HPV検査		66～100%	61～96%	検査施設が必要．客観的で再現性がありかつ確実だが高価である.
視診	VIA	67～79%	49～86%	道具が要らず，低コスト．すぐに治療を開始することができる.
	VILI	78～98%	73～93%	
コルポスコピー		44～77%	65～72%	高価であり，資源のないところには不向き.

VIA：Visual inspection with application of acetic acid，VILI：Visual inspection with application of Lugol's iodine.
細胞診は高い特異度を示すが感度が悪く，HPV検査は逆に感度に優れている．また途上国で広く用いられているVIAなどの視診は感度，特異度ともに低い.
〔文献1〕より作成〕

表2　先進国の検診概要

		受診率	年齢調節死亡率/10万人	対象年齢	検診間隔
ヨーロッパ	イギリス	78%	2人	25～64歳	3～5年
	ベルギー	61～63%	2.7人	25～64歳	3年
	デンマーク	61～69%	2.5人	23～59歳	3年
	フランス	54～74%	1.8人	25～65歳	3年
	ドイツ	55%	2.3人	20歳以上	1年
	イタリア	45～57%	1.5人	25～65歳	3年
	オランダ	59～61%	1.5人	30～60歳	5年
	スウェーデン	57～60%	1.8人	25～59歳	3年
オセアニア	ニュージーランド	63.5%	1.6人	20～69歳	3年
	オーストラリア	60%	1.4人	18～69歳	2年
北アメリカ	カナダ	72～79%	1.9人	18～69歳	1～2年
	アメリカ合衆国	84%	1.7人	21～70歳	3年

〔WHO/ICO Information Center on HPV and Cervical Cancer
http://apps.who.int/hpvcentre/statistics/dynamic/ico/SummaryReportsSelect.cfm より作成〕

21歳または初交後3年と定めている．つまり若年女性の多くはHPVに感染してもほとんどが自然消失するため，あまりに若い女性に検診を行うことは不必要な検査と不安を与えることになりかねないからである.

検診終了年齢に関しては60～69歳と設定している国が多い．高齢者の検診目的は予防ではなく早期発見に重点が置かれる．過去の定期検診で異常を指摘されなかった場合，69歳以降で子宮頸部浸潤癌になる可能性は極めて低い.

検診プログラムをデザインする際に重要になってくるのが検診間隔である．検診間隔を狭めれば癌死亡を下げられるが，コストがかかることも事実である．効率的な検診とは最小限の検診回数で，最大限の発見率を得ることである．ヨーロッパ諸国の検診開始/終了年齢，並びに検診間隔を比較すると生涯に受ける検診の回数は7～53回とかなり幅があるが，その一方で検診効果はあまり差がない(表4)[3,4]．つまり検診間隔を狭くすることより受診率を上げることが，集団に対する検診効果，すなわちがん死亡を減らすために最も重要であることをよく理解すべきである．検診回数に見合った効果が得られる検診間隔を設定しなければならない.

表3　アジア・ラテンアメリカの検診概要

		受診率	年齢調節死亡率/10万人	対象年齢	検診間隔
アジア	日本	23%	2.6人	20歳以上	2年
	韓国	70%	2.7人	30歳以上	2年
	シンガポール	70%	3.5人	20～65歳	3年
	香港	63%	—	25～65歳	3年
	台湾	61%	—	30歳以上	1年
ラテンアメリカ	メキシコ	53%	9.7人	25歳以上	3年
	ブラジル	64～82%	10.9人	25～60歳	3年
	ペルー	42%	16.3人	25～59歳	2年

〔WHO/ICO Information Center on HPV and Cervical Cancer http://apps.who.int/hpvcentre/statistics/dynamic/ico/SummaryReportsSelect.cfm より作成〕

検診間隔は長ければ長いほど経済効果が上がり，受診者および行政の負担も軽減されるが，安直に検診間隔を延ばすことは検診の取りこぼしを助長し，早期発見を遅らせることに繋がりかねない．欧米諸国では，3回連続して異常を認めなかった場合には検診頻度を3年に1度とするなど，受診間隔を延長している例が多い．受診率の高い英米では子宮頸がん検診の受診間隔を延長しても有効性が十分保たれるという報告[5,6]があり，2～3年に1度の受診頻度で有効性が示されている．

イギリスでは1988年よりコンピュータ管理されたCall/Recallセンターというものが置かれ，対象者全員に受診奨励通知が送付されるようになった．通知を受け取った対象者は家庭医で検診の予約をし，細胞診採取は家庭医が行う．検査結果は再びCall/Recallセンターより本人に通知が来るというシステムであり，専門の施設で精度管理も行っている．また検診費用はNational Health Serviceで賄われ，自己負担はない．このシステムが稼働してから受診率が飛躍的に上昇し，5年間の受診率は85.3%となり[7]，死亡率は毎年7%ずつ減少している．受診率上昇の直接的な要因としては自己負担がないことや，対象者全員に検診への招待状が来ることなどが考えられる．

表4　受診間隔と受診率のがん死亡(life-years lost)への影響

		フィンランド，オランダ	ベルギー，フランス，ギリシャ，イタリア，スペイン	ドイツ
開始年齢(歳)		30	25	20
検診間隔(年)		5	3	1
終了年齢(歳)		60	64*	72
生涯検診回数(回)		7	14	53
		%Reduction in life-years lost		
受診率(%)	25	21%	24%	25%
	50	42%	47%	50%
	75	63%	71%	75%
	100	84%	94%	99.9%

*：フランスの終了年齢は65歳．

〔文献3，4）より作成〕

オーストラリアにおける子宮頸がん検診

オーストラリアは世界で最も子宮頸癌死亡率の低い国である(表2)．オーストラリアにおける子宮頸がん検診の状況を概説する．

1．The National Cervical Screening Program

1960年代から子宮頸がん検診は始まり，1991年まではopportunistic screeningであった．80年代後半，opportunistic screening体制では50%の子宮頸癌しか予防できないと評価された．

表5　オーストラリアと日本における子宮頸癌関連の指標の違い

	オーストラリア	日本
15歳以上の女性人口	827万人	5,677万人
子宮頸癌発生(例/年)	835	7,772
子宮頸癌死亡(例/年)	249	3,573
検診受診率(%)	61.8	24.0

表7　コミュニケーションにおける重要ポイント

- 細胞診異常はそのほとんどがHPV感染が原因である
- 性交歴のあるものは誰でもHPVを持っている可能性がある
- 80%の人は生涯で一度は感染する
- 多くの場合，1〜2年のうちにひとりでに消える
- 子宮頸癌を引き起こす大部分のHPV感染を予防するワクチンがある

1988年，いくつかのパイロット検診プログラムがorganized screeningをするか否かのアセスメントを行った．その結果，1991年にはNCSP(The National Cervical Screening Program)が始まった．

NCSPの目的は，費用対効果のよいorganized approachの方法で子宮頸癌の発生と死亡を抑制することである．国の政策は，①細胞診を2年間隔で行う，②性的活動のある女性では18〜20歳の間に，あるいは，初交後1〜2年の間に検診を開始すべきである，③最後の5年間で2回の検診結果が正常であれば70歳で細胞診をやめることができる，とした．

NHMRC(National Health and Medical Research Council)ガイドラインに検診の管理方法が定められており，これによって検診および精密検査などが管理されている．プログラムの費用は，オーストラリア政府と州が分担している．2008〜2009年のプログラム費用はおよそ$1億2,520万であった．

ガバナンス(政策の実施)は，基本的に政府によって行われている．オーストラリア厚生大臣会議—オーストラリア厚生省諮問委員会—オーストラリア人口健康開発政策委員会—検診小委員会，という厚生大臣直轄の行政である．検診プログラムを遂行する役割と責任の所在は州にある．女性をプログラムにリクルートするほか，医療保健担当者の教育，州における検診レジストリの管理などを行う．レジストリでは，検診受診者，女性を

表6　オーストラリアにおける子宮頸癌の状況

- オーストラリア女性における癌の中で子宮頸癌は第13位．
- 2007および2008年では，20〜69歳の約360万人の女性が子宮頸がん検診を受診．
- 検診受診率は，2年間では61.2%，3年間では73%，5年間では86.3%を占める．
- 子宮頸癌の発生は，1,092例(1991年)だったものが715(2006年)に減少．
- 子宮頸癌死亡は，322例(1990年)だったものが208(2007年)に減少．

確実に受診させるためのリコールとフォローアップ，検診受診歴と臨床的管理の援助，クオリティーコントロールの援助を行う．一方，オーストラリア政府は，厚生省を通じて以下のような責任を持つ．国の方針の設定と指導，国によるコーデイネートと連絡(liaison)，検診小委員会の支援，国のプログラム遂行のモニタリング，国によるコミュニケーションの戦略である．

AIHW(The Australian Institute of Health and Welfare)はアニュアルモニタリングレポートを発行する．そのレポートには，すべての州における以下のperformance indicator(業務指数)を含む．①検診受診率，②早期の再受診，③軽度病変の発見数，④高度病変の発見数，⑤子宮頸癌発生数，⑥子宮頸癌死亡数．

オーストラリアと日本の鍵となる統計を表5に示す．その他の指標は表6に示す．

検診の遂行のためにはコミュニケーションが非常に重要だと考えられている．州は検診プログラムと女性および医療保健担当者のコミュニケーションをプロモーションする責任を負う．国のキャンペーンは，1993年から新しいプログラムの支援を，また，1998〜1999年には，受診率を向上させるための勧奨とバリアの排除を行った．国レベルでのHPVと子宮頸癌についてのコミュニケーションをNCSPが行うことが重要であり，表7の項目に焦点を当てた．

オーストラリア政府は子宮頸がん検診の現状認識および将来展望として，以下のような点を挙げている．NCSPは高度な成功を収めたプログラムであり，今後，さらに多くの子宮頸癌の自然史がわかるであろう．したがって，NHMRCは検診の年齢と間隔をレビューするよう勧告した．そ

表8　細胞診の結果による管理方法

Pap smear report	Management
Negative smear within normal limits	Repeat Pap smear in 2 years
Negative smear within normal limits and to endocervical cells present	Repeat Pap smear in 2 years
Negative with inflammation	Repeat Pap smear in 2 years
Unsatisfactory	Repeat Pap smear in 6–12 weeks, after appropriate treatment where indicated
Possible low grade squamous intraepithelial lesion Low grade squamous intraepithelial lesion (LSIL)	Repeat Pap smear at 12 months. If the woman is 30 + years, and has no negative cytology in previous 2–3 years, repeat Pap smear in 6 months or immediate colposcopy. See management pathway flow chart.
Possible high grade squamous intraepithelial lesion. High grade squamous intraepithelial lesion (HSIL)	Refer for colposcopy
Glandular abnormalities including adenocarcinoma in situ	Refer for colposcopy which should be performed by a gynaecologist with expertise in suspected malignancies or by a gynaecological oncologist
Invasive squamous cell carcinoma (SCC) or adenocarcinoma	Refer to a gynaecological oncologist

Note : Investigate any symptoms that are not readily explained, such as post-coital or intermenstrual bleeding. A negative Pap smear must not be taken as reassurance in these circumstances. Further investigation may involve referral to a gynaecologist.

〔AIHW：www.aihw.gov.au より転載〕

表9　高度子宮頸部病変の治療後の管理

4〜6 months after treatment-*Pap smear and colposcopy*
12 months after treatment-*Pap smear and HPV test*
24 months after treatment-*Pap smear and HPV test*

〔AIHW：www.aihw.gov.au より転載〕

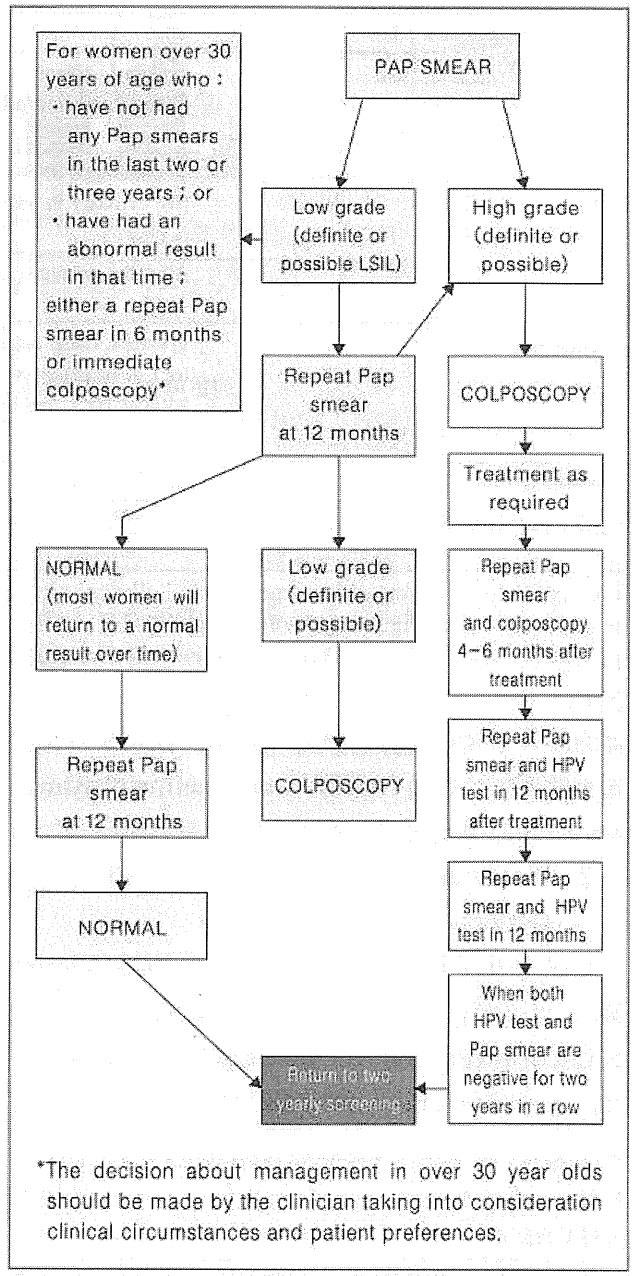

図1　細胞診異常の管理過程

〔AIHW：www.aihw.gov.au より転載〕

して，細胞異常を検出するための新しい技術が開発されているので，これを評価する．またHPVワクチンはNCSPの将来の費用対効果にインパクトを与えるだろう．これらの点を踏まえて，政府はNCSPをリニューアルすることを提案し，新たな検討に入っている．リニューアルの目的は，ワクチンを接種する，しないにかかわらず，すべてのオーストラリア人女性が，受容しやすく，効率的で，有効であるという，エビデンスに基づく子宮頸がん検診に確実にアクセスすることにある．リニューアルは，将来のオーストラリアにおいて，包括的な子宮頸癌予防の鍵となるという政策の指針である．

現在のNCSPが定めるガイドラインあるいは

表10 Victorian Cervical Cytology Registry Reminder and Follow-up

Cytology Report	Subsequent Biopsy or Colposcopy	Other Circumstances	Time	Action by Registry
High-grade squamous abnormality or any glandular abnormality	Yes		12 mths	Reminder to woman
	No		4 mths	Questionnaire to practitioner
			5.5 mths	Telephone call to practitioner
			6 mths	Letter to woman
			12 mths	Reminder to woman
Low-grade squamous abnormality	Yes		15 mths	Reminder to woman
	No	Previous smear also abnormal or fluctuating low-grade abnormality	4 mths	Questionnaire to practitioner
			6 mths	Letter to woman
			12mths	Reminder to woman
		Woman aged 30 + years and no negative cytology in preceding 36 mths	7 mths	Questionnaire to practitioner
			8.5 mths	Letter to woman
			15 mths	Reminder to woman
		All other women	12 mths	Reminder to practitioner
			15 mths	Reminder to woman
Negative		Previous smear abnormal or past history of biopsy proven CIN 2 or CIN 3 without HPV 'test of cure'	15 mths	Reminder to woman
		All other women	27 mths	Reminder to woman
Unsatisfactory	Yes		12 mths	Reminder to woman
	No		6 mths	Reminder to practitioner
			9 mths	Reminder to woman

This protocol is adjusted in some unusual clinical circumstances (eg post-hysterectomy, after a diagnosis of cervical or endometrial malignancy, women aged 70 + years).

〔Victorian Cervical Cytology Registry：http://www.vccr.org/practitioners.html より転載〕

細胞診異常後の管理方法について，表8,9および図1で紹介する(AIHW：www.aihw.gov.au, www.cancerscreening.gov.au)．

2．Victorian Cytology Service と Victorian Cervical Cytology Registry

ビクトリア州メルボルンにある VCS(Victorian Cytology Service)は1965年，ビクトリア州政府と Cancer Council Victoria によって設立され，子宮頸がん検診の検査機関およびレジストリ業務を行ってきた．現在ではビクトリア州の NSCP レジストリおよびオーストラリア連邦の NHVPR のレジストリ業務を行っている．

中心となる検査業務は年間300,000例の従来法の細胞診報告を行っており，これはビクトリア州の半数に及ぶ．オーストラリア最大の検査室である．オーストラリア連邦と州の財源によりすべての女性は無料で細胞診を受けることができる．VCS は VCCR(Victorian Cervical Cytology Registry)のレジストリ業務を，VCS および他の検査機関と連携して行っている．VCCR は子宮頸がん検診プログラムの鍵となるコンポーネントであり，ビクトリア州で行われているほぼすべての細胞診結果を記録している．VCCR は，ビクトリア州で登録されているすべての女性の子宮頸がん検診に関する包括的 Reminder and Follow-up プログラムを導入している(表10，Victorian Cervical Cytology Registry：http://www.vccr.org/practitioners.html)．

HPV 検査の導入について

近年，HPVDNA 検査がスクリーニングに用いられるようになってきた．一般に中等度異形成以上の病変に対する細胞診のみの感度は70%程度だが，HPV 検査を併用することでほぼ100%の感度が得られる[8]．アメリカの産婦人科学会勧告では細胞診と HPV 検査が両方陰性だった場合，異形成あるいは癌が見逃される危険性は1/1,000程度であると報告された[9]．さらに HPV 検査のもう一つのメリットは検診間隔を延長できるということである．HPV 感染の自然史や臨床研究を総合的に判断すると細胞診と HPV 検査が

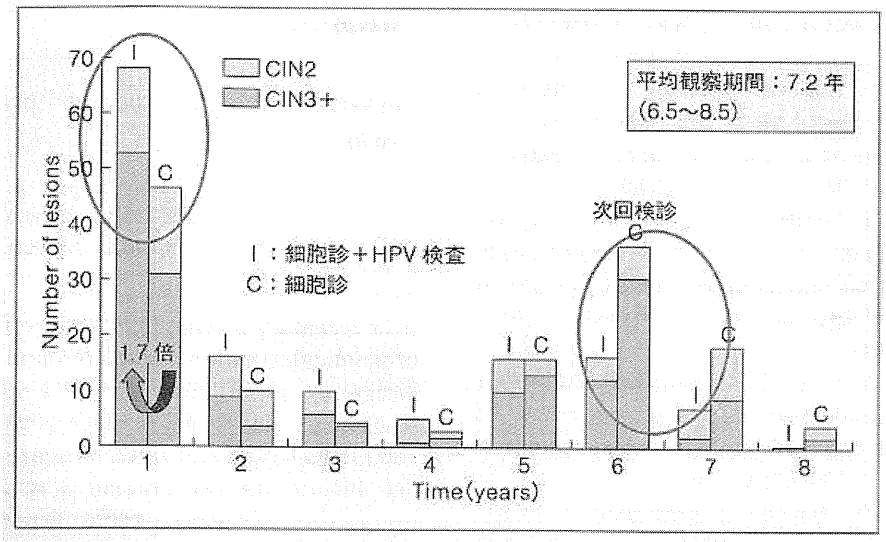

図2　地域住民を対象としたアムステルダムでのスクリーニング試験；POBASCAM(2007年)
HPV検査併用の方がより早期にCINを検出することができる．
⇒HPV併用検診では検診間隔を5年以上に延長することが可能．
〔文献10)より作成〕

両方陰性だった場合，もし新しいパートナーを得たとしても3年以内の再検査は必要ないというエビデンスも同勧告により打ち出された．

一次スクリーニングとしてHPV検査を単独で行い，異常者を細胞診でトリアージするという大規模試験が多く報告されている(図2)．オランダでの大規模試験では検診間隔が5年以上延長できるということを証明された[10]．初回検診でのCIN3以上の検出率は介入群ではコントロール群の1.7倍だったが，その後のラウンドの発見率は0.55倍で有意に減少した．またコントロール群では6年後に2度目のピークが来るのに対し，介入群では6.5年以上のフォローアップ期間全体でCIN2，3とも発見率に有意差がない．つまりHPV併用検診では検診間隔を5年以上に延長できるとしている．この結果をもとに，2011年9月から，オランダではHPVテストを中心とする子宮頸がん検診が導入される可能性が高くなっている．HPV検査の導入に関しては，誌面の関係で他著を参考されたい[11]．

おわりに

受診率を向上させるための要素としては①検診費用の自己負担をなくすこと，②国民が検診の必要性を理解すること，③啓発活動を行うこと，④検診の契機作りをすること，などが挙げられる．最も重要なことは一貫した国家レベルのがん対策プログラムを確立することである．国家をあげて検診受診率の向上と効率的な検診プログラムを確立することが必須課題と言えよう．ワクチン時代に入った今，一次予防であるHPVワクチンと二次予防である検診をモニタリングし，再評価を重ねてわが国に最適なプログラムを構築してくことが必要である．

文　献

1) Denny L, Quinn M, Sankaranarayanan R : Chapter 8 : Screening for cervical cancer in developing countries. Vaccine 24(Suppl 3) : 71-77, 2006
2) Wright TC Jr, Schiffman M : Adding a test for human papillomavirus DNA to cervical-cancer screening. N Engl J Med 348 : 489-490, 2003
3) Cervix Cancer Screening-IARC Handbooks of Cancer Prevention Vol.10, IARC Press, Lyon, pp 122-211, 2005
4) van Ballegooijen M, van den Akker-van Marle E, Patnick J, et al : Overview of important cervical cancer screening process values in European Union (EU) countries, and tentative predictions of the corresponding effectiveness and cost-effectiveness. Eur J Cancer 36 : 2177-2188, 2000
5) Sasieni P, Adams J, Cuzick J, et al : Benefit of cervical screening at different ages : evidence from the UK audit of screening histories. Br J Cancer 89 : 88-93, 2003

6) Sawaya GF, McConnell KJ, Kulasingam SL, et al : Risk of cervical cancer associated with extending the interval between cervical-caner screenings. N Engl J Med 349 : 1501-1509, 2003
7) Patnick J : Cervical cancer screening in England. Eur J Cancer 36 : 2205-2208, 2000
8) Wright TC Jr, Schiffman M, Solomon D, et al : Interim guidance for the use of human papillomavirus DNA testing as an adjunct to cervical cytology for screening. Obstet Gynecol 103 : 304-309, 2004
9) Wright TC Jr, Cox JT, Massad LS, et al : 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities. JAMA 287 : 2120-2129, 2002
10) Bulkmans NW, Berkhof J, Rozendaal L, et al : Human papillomavirus DNA testing for the detection of cervical intraepithelial neoplasia grade3 and cancer : 5-year follow-up of a randomised controlled implementation trial. Lancet 370 : 1764-1772, 2007
11) 今野良，岩成治：HPV DNA検査．化療の領域 27 : 323-334, 2011

Summary

Cervical cancer screening programs in the world

Ryo Konno[1)], Yuri Hayashi[2)], Sachiko Netsu[3)], Junji Mitsushita[3)]

It is necessary to consider the screening accuracy, the economical situation and the resource of the country for designing an efficient program of cervical cancer screening. The systems of cervical cancer screening and clinical studies in foreign countries are informative and helpful for encouraging a renewal of screening programs in our own country. Especially, the situation in Australia where the government is actively working on cervical cancer prevention is a good role model supplying useful information for Japan.

〔Rinsho Kensa 55 : 1391-1398, 2011〕

1～3) Department of Obstetrics and Gynecology, Jichi Medical University Saitama Medical Center, 1-847 Amanuma-cho, Omiya-ku, Saitama-shi, Saitama 330-8503, Japan

子宮頸がんワクチン

1　子宮頸がん予防のためのHPVワクチン

今野　良*

子宮頸部におけるほとんどのハイリスク型HPV感染は症状を伴わず一過性であるが，持続感染すると子宮頸がんが発生することがある。また，外陰がん，膣がん，陰茎がん，肛門がんなど）や性器疣贅，再発性呼吸器乳頭腫の発生の原因になる。HPV感染は粘膜の上皮内層に限定されており，活発な免疫応答を誘発しない。HPVに感染した女性の約半数で検出可能な血清抗体が生じるが，必ずしも同じHPV型によるその後の感染に対する防御とならない。ハイリスク型HPV持続感染は，CINまたはAISをきたし，進行すると扁平上皮がんおよび腺がんとなる。最初にHPVに感染してから子宮頸がんが発生するまでの期間は最低5～10年以上である。

はじめに

子宮頸がんの一次予防としてのhuman papillomavirus（HPV）ワクチンが，2006年に初めて米国で承認されることに遅れて3年，2009年10月に日本での使用が承認された。2010年の終わりには補正予算で公費による思春期女子への接種が決定された。本稿が掲載される頃には，国と自治体の補助により全国での接種が始まっている。

HPVワクチンは，「がんを予防できる」という話題性が高いことから各方面で取り上げられることが多いが，いまだに正しい理解が徹底されているとは言い難い。医師あるいは産婦人科医においても，不十分な理解や誤解がみられるようである。

現在，子宮頸がん領域における基礎および疫学・臨床医学の発展と広がりは格段に速くなっている。このシリーズにおいては，トランスレーショナルリサーチによる一次予防が子宮頸がんの診療形態に大きな変化をもたらしていることを，HPVワクチンを通して解説したい。

1．子宮頸がんの原因としてのHPV

多くのHPV感染は症状を伴わず一過性であるが，子宮頸部に持続感染すると子宮頸がんが発生することがある。また，男女を問わずその他の種類の肛門性器がん（外陰がん，膣がん，陰茎がん，肛門がんなど）や性器疣贅，再発性呼吸器乳頭腫の発生の原因になることがある。これまでに約100種類のHPV型が特定されており，このうち40種以上が性器などの粘膜に感染する[1]。発生学的な系統樹を図1に示す。一方，HPVは子宮頸がんとの疫学的関連に基づいてリスク分類されている。ローリスク型HPV（6型や11型など）の感染では，良性または軽度の子宮頸部細胞変化，性器疣贅，再発性呼吸器乳頭腫などが生じることがある。一方，ハイリスク型HPVは子宮頸がんやその他の肛門性器がんの発がん因子になる[2][3]。ハイリス

＊　Ryo Konno　自治医科大学附属さいたま医療センター産婦人科

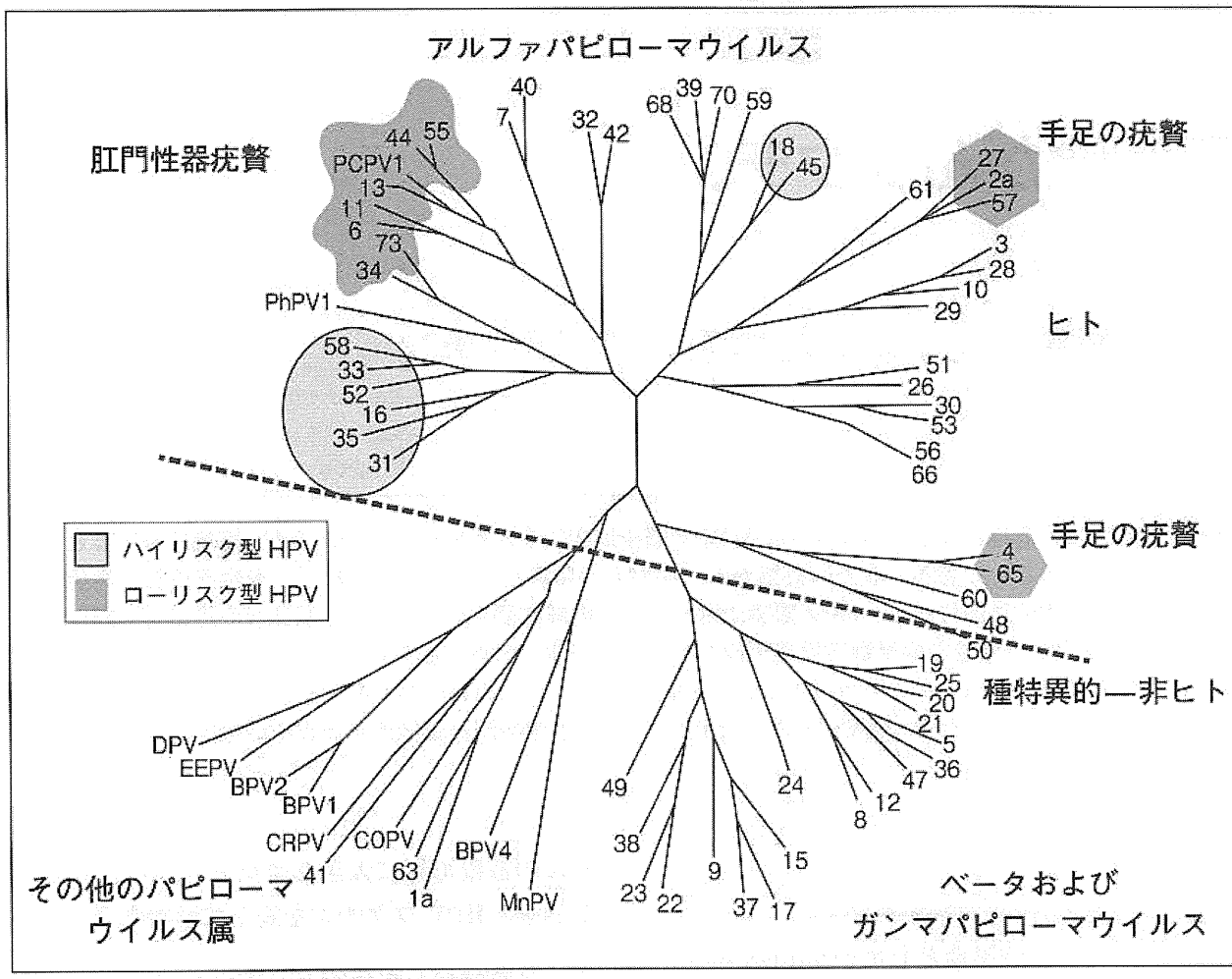

図1 パピローマウイルスの系統樹

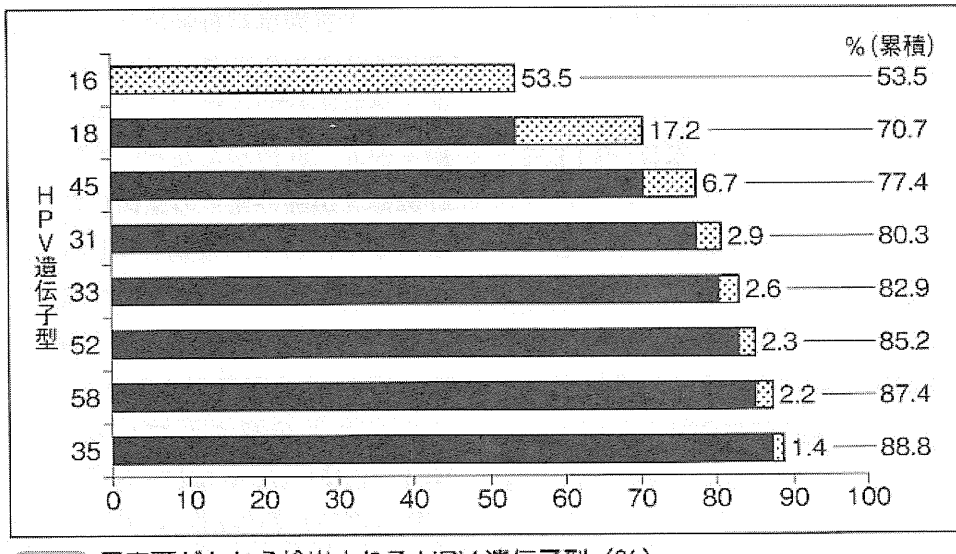

図2 子宮頸がんから検出されるHPV遺伝子型（%）

ク型に分類されるのは16，18，31，33，35，39，45，51，52，56，58，59，68，69，73および82型で，軽度および高度の子宮頸部ならびに肛門性器がん前駆病変を引き起こし，その一部ががんに至る[4]。子宮頸がんの99%にハイリスク型HPVが検出されており[5]，世界中の子宮頸

表1 HPV関連がんの症例数とハイリスク型HPVが原因となっている割合
—2003年度米国データ

がん種	症例数*	発がん性HPVが原因となっている割合†
子宮頸がん§	11,820	100
肛門がん¶	4,187	90
外陰がん¶	3,507	40
膣がん¶	1,070	40
陰茎がん¶	1,059	40
口腔・咽頭がん¶	29,627	≤12

*：U.S. Cancer Statistics Working Group. United States cancer statistics：2003. Incidence and motality. Atlanta, GA：US Department of Health and Human Services, CDC, and the National Cancer Institute；2006. Available at http://www.cdc.gov/uscs.
†：Parkin M. The global health burden of infection-associated cancers in the year 2002. Int J Cancer 2006；118：3030-44.
§：計70%がHPV 16型または18型に起因する。
¶：これらのがんの大多数がHPV 16型に起因する。

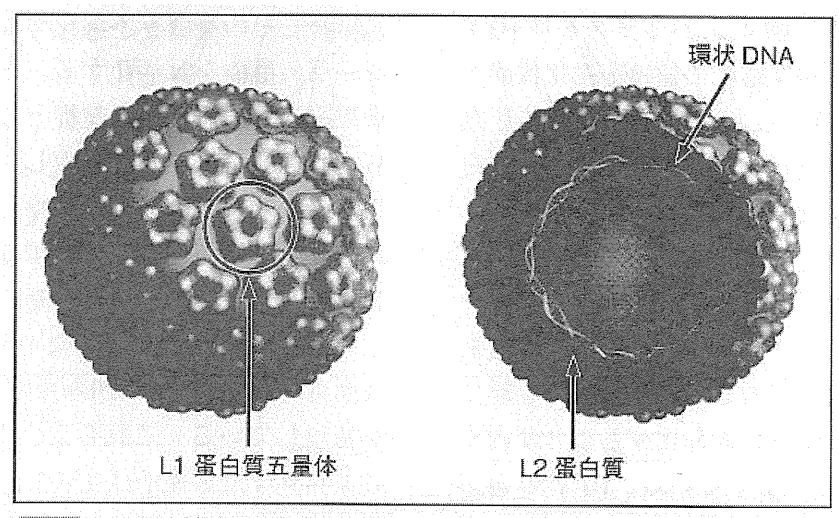

図3 ヒトパピローマウイルスの構造
HPVは，球形の殻（カプシド）内に二本鎖DNAを持つ。カプシドは2種類の構造蛋白質（L1およびL2蛋白質）で構成されている。

がんの約70%が16型および18型によるものである（図2）[6]。子宮頸がん以外に肛門性器がんや口腔がん，頭頸部がんにも関連しているが，いずれも子宮頸がんほど多くない（表1）[7)~13)]。

2．HPVの生物学

HPVは，エンベロープを持たない二本鎖DNAウイルスで，パピローマウイルス科に属する。HPV分離株は「型」として分類され，発見された順に番号が割り当てられている[14]。型はゲノムの特定領域のヌクレオチド配列に基づいて割り当てられる。いずれの型のHPVも，主要カプシド蛋白L1と微量カプシド蛋白L2からなるカプシド殻の内部に8 kbの環状ゲノムを持つ。精製されたL1蛋白は自己会合し，ウイルス様粒子（virus-like particle；VLP）と呼ばれるウイルスに似た中空の殻を形成する（図3）。これらの構造遺伝子（L1およびL2）以外にも，ゲノムは，ウイルスの転写・複製を可能にして宿主ゲノムと相互に作用するいくつかの