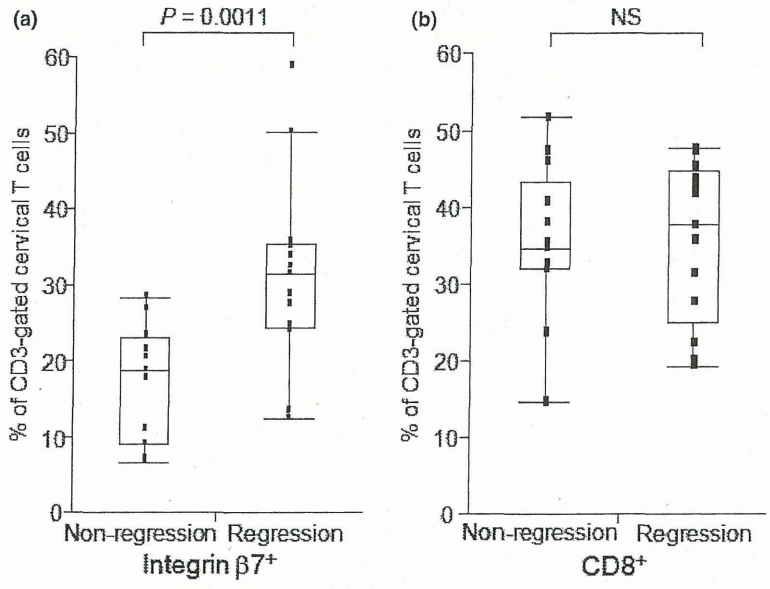


Fig. 4 Association between gut-derived cervical intraepithelial lymphocyte and cervical intraepithelial neoplasia (CIN) regression. Populations of integrin $\beta7^+$ (a) and $CD8^+$ (b) cells among $CD3^+$ cervical T cells were compared between CIN regression (n = 13) and non-regression (n = 13) groups, paired according to follow-up duration. A P-value ≤0.05 was considered significant using Wilcoxon rank test comparisons.

$CD8^+$ memory T cells are essential for adaptive cytotoxic immune responses to CIN.[21,22] Among our patients with CIN, the proportion of integrin $\beta7^+$ cervical T cells that expressed CD8 [median 53% (IQR: 28–69)] was greater than that for total cervical T cells (Fig. 3d). Approximately half [median 43% (IQR: 31–57)] of integrin $\beta7^+$ T cells were CD45RO memory T cells, while the other half were CD45RA effector T cells (Fig. 3e).

Association of Gut-derived Cervical IEL with CIN Course

Integrin β7 is a more ubiquitous homing receptor in mucosal lymphocytes rather than integrin αE or α4. To determine whether there was an association between the presence of gut-derived cervical IEL and spontaneous regression of CIN, comparisons were made between populations of integrin $\beta7^+$ $CD3^+$ and $CD8^+$ $CD3^+$ cervical T cells in CIN regressors (n = 13) and non-regressors (n = 13), paired according to their duration of follow-up. No significant differences were seen in the detection rates of high-risk HPV (69 versus 77%, P = 0.50), the squamous intraepithelial lesion (SIL) grade (high-grade SIL: 54 versus 54%, P = 0.65), and the median ages (34 years old versus 35) of patients in the regression and non-regression groups. The percentage of integrin $\beta7^+$ cervical T cells varied from 6 to 57% among the 26 study subjects. Among regressors, integrin $\beta7^+$ cervical T cells comprised a median of 31.6% (IQR: 24.5–35.5) of $CD3^+$ cervical T cells; the rate among non-regressors was 18.8% (IQR: 9.2–23.3), P = 0.0011 (Fig. 4a). In contrast, there was no difference in populations of $CD8^+$ $CD3^+$ cervical T cells between CIN regressors and non-regressors (Fig. 4b). The proportion of $CCR9^+$ and $CD45RA^+$ $CD3^+$ cervical T cells was likewise similar in the two groups (data not shown).

Discussion

Human papillomavirus preferentially infects, and CIN develops in the human cervical epithelium. It is clear that HPV antigens are recognized by the systemic cell-mediated immune system, but remains unclear whether systemic cellular immune responses predict the regression of CIN.[16,17] Local mucosal immune responses in the cervix are likely to be important in immunological clearance of CIN lesions. Integrin $\alpha4\beta7$ is essential for recruiting activated mucosal lymphocytes from the circulation into local LP in a manner entirely dependent on interaction between lymphocyte integrin $\alpha4\beta7$ and the MAdCAM-1 that is constitutively expressed on LP post-capillary venules.[23] In contrast, integrin αE (CD103) β7 is expressed by only 2% of circulating blood lymphocytes, but more than 90% of IEL and a minority of lamina propria lymphocyte (LPL); its ligand is E-cadherin expressed on the epithelial cells.[24] Activated integrin $\alpha4\beta7^+$ T cells differentiate within the

LP into integrin αEβ7$^+$ T cells upon exposure to TGF-β locally secreted by epithelial cells.[5] Binding of integrin αEβ7 to E-cadherin provokes retention of the activated IEL within the epithelium. Recognition of target epithelial cells by IELs is important in the initiation of cytolytic effector function by activated IELs and modulation of adaptive immune responses to control potentially destructive epithelial immunity. Adhesion of integrin αEβ7$^+$ IEL to epithelial E-cadherin is promoted by CCL25–CCR9 interactions.[4] This suggests that, when compared to integrin α4β7$^+$ LPL, integrin αEβ7$^+$ IELs may be more directly linked to essential adaptive immune responses to target epithelial cells at local effector sites.

Several studies have reported that integrin α4β7 is expressed on gut-derived mucosal lymphocytes within the cervix.[9,11] However, our data indicate that more than 90% of integrin β7$^+$ T cells were positive for integrin αE and few express α4. Pudney et al.[10] have shown using immunohistochemistry that integrin αEβ7$^+$ lymphocytes are primarily located in the epithelium of the ectocervix and often occur as focal accumulations in the LP of the transformation zone. Our brushing methodology enables us to preferentially collect cervical mucosal lymphocytes from the epithelium and occasionally from the LP. Others who have recently reported that nearly all cervical tissue T cells are integrin α4β7^{+9} used cervical tissue specimens and equally valuable methodologies that would be expected to isolate cells from deeper within the cervical tissue, possibly favoring isolation of LPL over cells tightly adhered to the epithelium.

Our cervical samples were contaminated by numerous granulocytes, a finding supported by several previous studies using cervical mucosa unlike peripheral blood samples.[10,11] Granulocyte contamination variability was likely the result of differing levels of cervical inflammation among patients. Although the number of lymphocytes among CD45$^+$ cervical leukocytes varied from 10 to 30%, the absolute number of cervical lymphocytes present in a sample appeared to be relatively constant and independent of patient source. The efficient homing of lymphocytes to the gut is dependent on the homing receptors integrin β7 and CCR9. We showed that integrin β7 and CCR9 did not always co-express. This agrees with reports showing that expression of the mucosal homing receptors, integrin β7 and CCR9, is not always linked, but instead depends on lymphocyte differentiation and the location of the effector sites infiltrated by these cells.[25,26]

Expression of MAdCAM-1 is essential for trafficking of integrin α4β7$^+$ lymphocytes into the LP, while the expression of E-cadherin on the epithelium is essential for the retention of integrin αEβ7$^+$ lymphocytes. Inflammation of the mucosa enhances MAdCAM-1 expression on the endothelial cells of post-capillary venules in the genital tract,[8] and inflammatory changes are often observed in CIN when compared with normal cervical mucosa.[27,28] Trimble et al.[9] reported that MAdCAM-1 expression correlates with non-specific CD8$^+$ LPL infiltration of the LP and CIN regression. In our sampled IELs, there was no association between CD8$^+$ cells and CIN regression. Studies have also demonstrated that oncoproteins from high-risk HPV subtypes downregulate E-cadherin expression in CIN lesions and that this downregulation is closely associated with disease progression.[29–31] E-cadherin plays an important role in the maintenance of normal adhesion in epithelial sites and its loss is associated with poor prognosis for many tumors other than CIN.[32] The downregulation of E-cadherin may interfere with the retention of integrin αEβ7$^+$ T cells in CIN lesions, and our results suggest that IEL retention varies among patients with CIN. We have shown that populations of integrin αEβ7$^+$ IEL in CIN lesions vary markedly among patients and that higher IEL numbers are associated with spontaneous regression of CIN. Although HPV-specific cytotoxic T lymphocyte activity was not investigated here, the accumulation of integrin αEβ7$^+$ IEL in CIN lesions and their association with CIN regression suggests these cells, rather than non-specific CD8$^+$ T cells, may have important local effector functions in the cervical epithelium. In the present study, the adaptive immune system was focused, but the innate immune responses play equally important roles in controlling HPV infection. Daud et al.[33] has recently reported the mechanism of interference with innate immune system by HPV16, dampened toll-like receptor expression, which results in the viral persistence. The interaction of innate with adaptive immunity at the local mucosa should be investigated.

In summary, our report is the first to specifically phenotype cervical IEL in CIN lesions. Our results indicate that the presence of elevated numbers of gut-derived integrin αEβ7$^+$ IELs in specimens gathered from patients with CIN using a cervical cytobrush may represent a possible biomarker for CIN regression. Sampling of cervical IEL using this methodology is relatively non-invasive and techni-

cally easier than the isolation of cervical LPL from tissue biopsies. Future investigations using our sampling methods will focus on HPV-specific cell-mediated immune responses by cervical IELs isolated from patients with CIN. These and related investigations should improve our understanding of cervical mucosal immunity and hasten the development of a therapeutic HPV vaccine.

Acknowledgements

This work was supported by a grant-in-aid from the Ministry of Health, Labour and Welfare of Japan for the Third-Term Comprehensive 10-Year Strategy for Cancer Control, by a cancer research grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and by a grant from the Okinawa New Industry Creation Project.

References

1 Gorfu G, Nieves JR, Ley K: Role of beta7 integrins in intestinal lymphocyte homing and retention. *Curr Mol Med* 2009; 9:836–850.
2 Iwata M, Hirakiyama A, Eshima Y, Kagechika H, Kato C, Song SY: Retinoic acid imprints gut-homing specificity on T cells. *Immunity* 2004; 21:527–538.
3 Edelee F, Molenaar R, Gutle D, Dudda JC, Jakob T, Homey B, Mebius R, Hornef M, Martin SF: Cutting edge: instructive role of peripheral tissue cells in the imprinting of T cell homing receptor patterns. *J Immunnol* 2008; 181:2745–2749.
4 Ericsson A, Svensson M, Arya A, Agace WW: CCL25/CCR9 promotes the induction and function of CD103 on intestinal intraepithelial lymphocytes. *Eur J Immunol* 2004; 34:2720–2729.
5 El-Asady R, Yuan R, Liu K, Wang D, Gress RE, Lucas PJ, Drachenberg CB, Hadley GA: TGF-b-dependent CD103 expression by $CD8^+$ T cells promotes selective destruction of the host intestinal epithelium during graft-versus-host disease. *J Exp Med* 2005; 201:1647–1657.
6 Kawana K, Matsumoto J, Miura S, Kawana Y, Nagamatsu T, Yasugi T, Fujii T, Yang H, Quayle AJ, Taketani Y, Schust DJ: Expression of CD1d and ligand-induced cytokine production are tissue-specific in mucosal epithelia of the human lower reproductive tract. *Infect Immun* 2008; 76:3011–3018.
7 Hawkins RA, Rank RG, Kelly KA: Expression of mucosal homing receptor $\alpha4\beta7$ is associated with enhanced migration to the Chlamydia-infected murine genital mucosa in vivo. *Infect Immun* 2000; 68:5587–5594.
8 Kelly KA, Rank RG: Identification of homing receptors that mediate the recruitment of CD4 T cells to the genital tract following intravaginal infection with *Chlamydia trachomatis*. *Infect Immun* 1997; 65:5198–5208.
9 Trimble CL, Clark RA, Thoburn C, Hanson NC, Tassello J, Frosina D, Kos F, Teague J, Jiang Y, Barat NC, Jungbluth AA: Human papillomavirus 16-associated cervical intraepithelial neoplasia in humans excludes CD8 T cells from dysplastic epithelium. *J Immunol* 2010; 185:7107–7114.
10 Pudney J, Quayle AJ, Anderson DJ: Immunological microenvironments in the human vagina and cervix: mediators of cellular immunity are concentrated in the cervical transformation zone. *Biol Reprod* 2005; 73:1253–1263.
11 Kelly KA, Wiley D, Wiesmeier E, Briskin M, Butch A, Darville T: The combination of the gastrointestinal integrin ($\alpha4\beta7$) and selectin ligand enhances T-cell migration to the reproductive tract during infection with *Chlamydia trachomatis*. *Am J Reprod Immunol* 2009; 61:446–452.
12 Holowaty P, Miller AB, Rohan T, To T: Natural history of dysplasia of the uterine cervix. *J Natl Cancer Inst* 1999; 91:252–258.
13 Moscicki AB, Schiffman M, Kjaer S, Villa LL: Chapter 5: updating the natural history of HPV and anogenital cancer. *Vaccine* 2006; 24:42–51.
14 Ellerbrock TV, Chiasson MA, Bush TJ, Sun XW, Sawo D, Brudney K, Wright TC Jr.: Incidence of cervical squamous intraepithelial lesions in HIV-infected women. *JAMA* 2000; 283:1031–1037.
15 Ognenovski VM, Marder W, Somers EC, Johnston CM, Farrehi JG, Selvaggi SM, McCune WJ: Increased incidence of cervical intraepithelial neoplasia in women with systemic lupus erythematosus treated with intravenous cyclophosphamide. *J Rheumatol* 2004; 31:1763–1767.
16 Trimble CL, Peng S, Thoburn C, Kos F, Wu TC: Naturally occurring systemic immune responses to HPV antigens do not predict regression of CIN2/3. *Cancer Immunol Immunother* 2010; 59:799–803.
17 Nakagawa M, Gupta SK, Coleman HN, Sellers MA, Banken JA, Greenfield WW: A favorable clinical trend is associated with CD8 T-cell immune responses to the human papillomavirus type 16 E6 antigens in women being studied for abnormal pap smear results. *J Low Genit Tract Dis* 2010; 14:124–129.
18 Gravitt PE, Peyton CL, Alessi TQ, Wheeler CM, Coutlee F, Hildesheim A, Schiffman MH, Scott DR, Apple RJ: Improved amplification of genital human papillomaviruses. *J Clin Microbiol* 2000; 38:357–361.
19 Bosch FX, Sanjose S: Human papillomavirus and cervical cancer – burden and assessment of causality. *J Natl Cancer Inst Monogr* 2003; 31:3–13.
20 Prakash M, Patterson S, Kapembwa MS: Evaluation of the cervical cytobrush sampling technique for the preparation of $CD45^+$ mononuclear cells from the human cervix. *J Immunol Methods* 2001; 258:37–46.
21 Passmore JA, Milner M, Denny L, Sampson C, Marais DJ, Allan B, Gumbi PP, Hitzeroth II, Rybicki EP, Williamson AL: Comparison of cervical and blood T-cell responses to human papillomavirus-16 in women with human papillomavirus-associated cervical intraepithelial neoplasia. *Immunology* 2006; 119:507–514.
22 Monnier-Benoit S, Mauny F, Riethmuller D, Guerrini JS, Capilna M, Felix S, Seilles E, Mougin C, Pretet JL: Immunohistochemical analysis of $CD4^+$ and $CD8^+$ T-cell subsets in high risk human papillomavirus-associated pre-malignant lesions of the uterine cervix. *Gynecol Oncol* 2006; 102:22–31.
23 Hamann A, Andrew DP, Jablonski-Westrich D, Holzmann B, Bucher EC: Role of alpha 4-integrins lymphocyte homing to mucosal tissues in vivo. *J Immunol* 1994; 152:3282–3293.
24 Cepek KL, Parker CM, Madara JL, Brenner MB: Integrin alpha E beta 7 mediates adhesion of T lymphocytes to epithelial cells. *J Immunol* 1993; 150:3459–3470.
25 Mora JR, Andrian UHV: T-cell homing specificity and plasticity: new concepts and future challenges. *Trends Immunol* 2006; 27:235–243.

26 Carramolino L, Zaballos A, Kremer L, Villares R, Martin P, Ardavin C, Martinez AC, Marquez G: Expression of CCR9 beta-chemokine receptor is modulated in thymocyte differentiation and is selectively maintained in $CD8^+$ T cells from secondary lymphoid organs. *Blood* 2001; 97:851–857.
27 Kobayashi A, Greenblatt RM, Anastos K, Minkoff H, Massad LS, Young M, Levine AM, Darragh TM, Weinberg V, Smith-McCune KK: Functional attributes of mucosal immunity in cervical intraepithelial neoplasia and effects of HIV infection. *Cancer Res* 2004; 64:6766–6774.
28 Kobayashi A, Weinberg V, Darragh T, Smith-McCune K: Evolving immunosuppressive microenvironment during human cervical carcinogenesis. *Mucosal Immunol* 2008; 1:412–420.
29 Branca M, Giorgi C, Ciotti M, Santini D, Di Bonito L, Costa S, Benedetto A, Bonifacio D, Di Bonito P, Paba P, Accardi L, Mariani L, Syrjanen S, Favalli C, Syrjanen K: Down-regulation of E-cadherin is closely associated with progression of cervical intraepithelial neoplasia (CIN), but not with high-risk human papillomavirus (HPV) or disease outcome in cervical cancer. *Eur J Gynecol Oncol* 2006; 27:215–223.
30 Matthes K, Leong CM, Baxter L, Inglis E, Yun K, Backstrom BT, Doorbar J, Hibma M: Depletion of langerhans cells in human papillomavirus type 16-infected skin is associated with E6-mediated down regulation of E-cadherin. *J Virol* 2003; 77:8378–8385.
31 Welles A, Yates C, Shepard CR: E-cadherin as an indicator of mesenchymal to epithelial reverting transitions during the metastatic seeding of disseminated carcinomas. *Clin Exp Metastasis* 2008; 25:621–628.
32 Boulenouar S, Weyn C, Noppen MV, Moussa AM, Favre M, Delvenne PO, Bex F, Noel A, Englert Y, Fontaine V: Effects of HPV-16 E5, E6 and E7 proteins on survival, adhesion, migration and invasion of trophoblastic cells. *Carcinogenesis* 2010; 31:473–480.
33 Daud II, Scott ME, Ma Y, Shiboski S, Farhat S, Moscicki AB: Association between toll-like receptor expression and human papillomavirus type 16 persistence. *Int J Cancer* 2011; 123:879–886.

DOI: 10.1111/j.1471-0528.2011.03036.x
www.bjog.org

Introducing HPV vaccine and scaling up screening procedures to prevent deaths from cervical cancer in Japan: a cost-effectiveness analysis

N Yamamoto,[a,b] R Mori,[a] P Jacklin,[c] Y Osuga,[b] K Kawana,[b] K Shibuya,[a] Y Taketani[b]

[a] Department of Global Health Policy and [b] Department of Obstetrics and Gynecology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan [c] National Collaborating Centre for Women's and Children's Health, London, UK

Correspondence: N Yamamoto, Department of Global Health Policy, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. Email nyamamoto@m.u-tokyo.ac.jp

Accepted 15 April 2011. Published Online 28 July 2011.

Objective To assess the cost-effectiveness of universal vaccination of 11-year-old girls against human papillomavirus (HPV) infection and increased screening coverage to prevent cervical cancer in Japan where the coverage of Papanicolaou smears is very low.

Design A cost–utility analysis from a societal perspective.

Setting Japan, 2010.

Population The female Japanese population aged 11 years or older.

Methods A Markov model of the natural history of cervical cancer was constructed to compare six strategies: i.e. a screening coverage rate of 20, 50 and 80% with and without routine vaccination at age 11.

Main outcome measures Cervical cancer incidence, quality-adjusted life years (QALYs), costs and incremental cost-effectiveness ratios.

Results Expanding the coverage of Papanicolaou smears from the current level of 20–50 and 80% yields a 45.5 and 63.1% reduction in cervical cancer incidence, respectively. Impact of combined strategies increases with coverage. Coverages of 20, 50 and 80% showed a 66.1, 80.9 and 86.8% reduction in disease, respectively. The costs of strategies with vaccination are four times higher than the cost of strategies without vaccination. Vaccinating all 11-year-old girls with bivalent vaccines with a Papanicolaou smear coverage rate of 50% is likely to be the most cost-effective option among the six strategies.

Conclusions The introduction of HPV vaccination in Japan is cost-effective as in other countries. It is more cost-effective to increase the coverage of the Papanicolaou smear along with the universal administration of HPV vaccine.

Keywords Cost-effectiveness analysis, economics, human papillomavirus, vaccines.

Please cite this paper as: Yamamoto N, Mori R, Jacklin P, Osuga Y, Kawana K, Shibuya K, Taketani Y. Introducing HPV vaccine and scaling up screening procedures to prevent deaths from cervical cancer in Japan: a cost-effectiveness analysis. BJOG 2011; DOI: 10.1111/j.1471-0528.2011.03036.x.

Introduction

Cervical cancer is the fifth leading cause of female cancer death in the world.[1] The overall frequency of cervical cancer in Japan, including carcinoma *in situ*, was reported as 17 000 per year.[2] In Japan, it is the third leading cause of cancer death among women <40 years of age.[2] The age-adjusted mortality rate of cervical cancer in Japan has remained at almost the same level for the past two decades, although it has declined in the USA and UK.[2–4]

Screening with cervical cytology [i.e. Papanicolaou (Pap) smear] has been the key national strategy for early detection and treatment of cervical cancer to reduce its burden.[5] However, the coverage of Pap smear screening in Japan remains between 10 and 20%,[6] much lower than in other countries such as the UK (81%), France (54%) and the USA (>82%).[7]

Persistent human papillomavirus (HPV) infection, particularly with oncogenic types 16, 18, 52 and 58, is associated with a higher risk of incident cervical cancer precursor lesions.[8] A prophylactic vaccine to prevent infection from HPV16 and 18 to reduce the burden of cervical cancer has been developed and implemented in some countries.[9] The idea of introducing HPV vaccine in the Japanese population has evoked public debate and become a huge political

issue. The bivalent vaccine was officially approved for use in Japan by the end of 2009, but there has been an ongoing debate on whether the use of HPV vaccine should be underpinned by tax-payers' money and if so, how much the government should spend.[9]

Despite its proven cost-effectiveness in other settings[10–12] a simple extrapolation of the costs and effectiveness of HPV vaccine in countries other than the Japanese setting is not appropriate because of the differences in cervical cancer epidemiology and health systems. The prevalence of HPV types differs between geographic regions. In the case of squamous cell carcinoma, HPV16 was the predominant type (46–63%) followed by HPV18 (10–14%), 45 (2–8%), 31 (2–7%) and 33 (3–5%) in all regions except Asia, where HPV types 58 (6%) and 52 (4%) were more frequently identified.[13] In Japan, HPV52 and HPV58 are most frequently found in squamous intraepithelial lesion following HPV16.[14] A relatively lower prevalence of HPV16 and HPV18 in Japan has cast doubt on the effectiveness of the current HPV vaccine when compared with other countries.[15]

Only one study has evaluated the cost-effectiveness of HPV vaccination in the Japanese setting.[16] However, the study did not compare strategies with a variable screening rate. Nor did it consider the effect of HPV type prevalence by age in Japan. Therefore, a cost-effectiveness analysis of screening coverage and vaccination, taking into account the age-specific prevalence by HPV type in the Japanese setting is urgently needed to inform and support policy decisions. Healthcare resources are limited; resources dedicated to screening and vaccination are no longer available for alternative healthcare uses and therefore the chosen strategy should represent a cost-effective use of scarce resources. The major objective of the present study is to assess the cost-effectiveness of universal vaccination against HPV in Japan from a societal perspective where the coverage of Pap smears is low and HPV oncogenic types are different from in other settings.

Methods

Natural history model of HPV infection

We developed a state-transition Markov model that simulates the natural history of HPV infection and carcinogenesis, in which transitions take place from one state to another at 1-month intervals (Figure 1). The model has 25 Markov states. The entry point into the model is girls aged 11 years with no previous exposure to HPV. We assumed that when girls/women enter the model, they start sexual activities, so acquiring a risk for HPV with the currently observed probabilities. In each cycle, they proceed to one of the four states: HPV16 and 18 DNA-positive group (HPV16 and 18), the other high-risk HPV DNA-positive group (other HR), the low-risk HPV DNA-positive group (LR), and the non-infected group (Normal) using monthly transition probabilities based on the systematic review of published literature.[17]

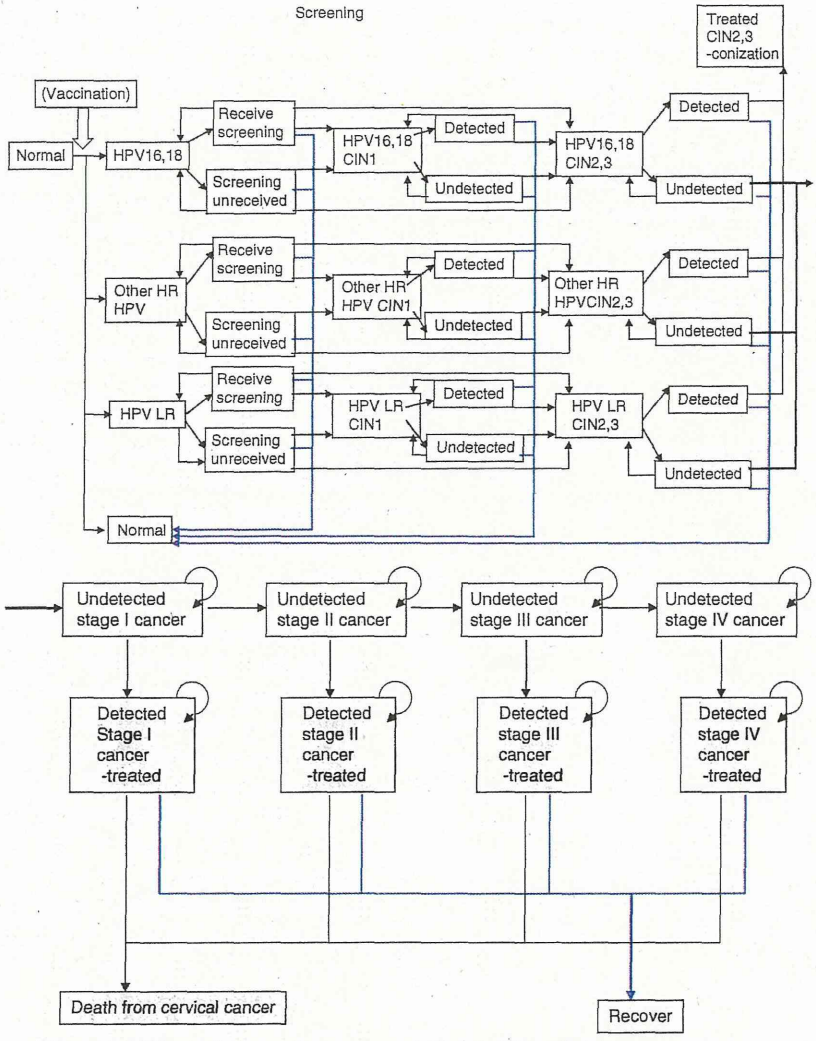
Each group follows a natural history unless they are screened. When cervical intraepithelial neoplasia (CIN) 2, 3 or invasive cancer is identified by the screening, a treatment intervention conditional on cancer stage is implemented. After the treatment for an invasive cancer, a certain proportion of patients die whereas others survive according to the survival probabilities compiled from the cancer registry data.[18,19] Age-dependent transition rates of disease progression from the susceptible to those infected with either HPV16/18, other HR (excluding HPV16 and 18) or LR were estimated from recent Japanese data.[20] All individuals are followed up for 50 years until they reach 60 years of age, which is the average retirement age in Japan, unless they die earlier.

Vaccine efficacy

The vaccine efficacy was evaluated in eight randomised controlled trials.[21,22] There was a substantial variation in follow-up periods and outcome measures among the studies. The World Health Organization adopted CIN2/3 as surrogate endpoints for cervical cancer in trials assessing vaccine efficacy.[21] In our model we used the relative risk of HPV16 and 18 persistent infection risk, as the vaccine immunises against the contraction of HPV. The hypothesis that persistent infection with one of the 15 carcinogenic HPV types is the fundamental cause of cervical cancer is clearly supported by scientific evidence.[23] We assumed relative risks of 0.12 (95% CI 0.03–0.48) for persistent HPV16 and 18 infection and 0.5 (range 0.3–0.7) for persistent HPV high-risk type excluding 16, 18.[21,22,24,25] Additionally, we assumed 100% lifetime protection against HPV16 and 18 once fully vaccinated.

Intervention strategies

The bivalent vaccine was approved for use in women and girls who are over 10 years old. The Japan Society of Obstetrics and Gynaecology recommended administering HPV vaccine among girls from 11 to 14 years of age as a priority, partly because they are old enough to understand the meaning of the vaccination and partly because the vaccination in this age group is efficient and ensures early protection against HPV with high immunogenicity. Therefore, for strategies which include vaccination, all 11-year-old girls are vaccinated at the entry point into the model. We assumed that there is no exposure to any HPV types before the entry to the model. At 20 years of age, they start receiving screening every 2 years according to the current Japanese recommendations.[5] Our reference strategy is the screening programme only with the current level of



*The probabilities to die from other causes are included at all each states.

Figure 1. HPV natural history model.

Table 1. Strategies

1. 20% coverage rate of screening with no vaccination
2. 50% coverage rate of screening with no vaccination
3. 80% coverage rate of screening with no vaccination
4. 20% coverage rate of screening with vaccination for all 11-year-old girls
5. 50% coverage rate of screening with vaccination for all 11-year-old girls
6. 80% coverage rate of screening with vaccination for all 11-year-old girls

coverage (i.e. 20%).[6,7] Table 1 summarises six strategies that were analysed in the present study. The sensitivity of the Pap smear was assumed to be 94.7% as previously reported.[26] The specificity (reported to be 98.9%) is not included in the model because screening will be repeated in false positives as determined by the cytology results.

Survival rates of women with cervical cancer

We used the data from life tables of Japanese vital registration to estimate the population-based mortality rates by age from cervical cancer and other competing risks.[27] Cumulative nationwide survival rates by cancer stages of FIGO classification were not available in Japan. We adopted the data from the US SEER programme (Surveillance Epidemiology and End Results),[18,19] which were calibrated using data from an existing Japanese regional cancer registry.[28]

Transition probabilities

Several natural history models of HPV have been developed and used in policy evaluations.[29,30] Whereas a particular

parameter has been common to several natural history models, there is a huge variation in the structure and parameters used in the previous models.[29] We used age-dependent type-specific HPV prevalence data from Japanese women[20] to derive transition probabilities from the susceptible to those infected with HPV16/18, other HR types and LR types.

Other model parameters were estimated from systematic literature reviews and then calibrated to the Japanese setting (Table 2).[17] We simulated the model by using the transition rates of CIN2, 3 to the undetected stage I cancer of HPV16/18 and other HR depending on their age groups in Japan. Then we adjusted them by using the data of age-dependent incident rates of cervical cancer. We validated the model by goodness-of-fit statistics using age-dependent mortality rates of cervical cancer.

Table 2. Transition rates

Variable	Baseline values	Range
Progression		
HPV DNA to CIN1		
Low-risk HPV	0.0264	0.0245–0.0284
High-risk 16, 18 HPV	0.0150	0.0026–0.0274
High-risk other HPV	0.0376	0.0271–0.0480
HPV DNA to CIN2, 3		
Low-risk HPV	0.00003	0.000003–0.00006
High-risk 16, 18 HPV	0.0012	0.000014–0.0024
High-risk other HPV	0.000025	0.000002–0.00005
CIN1 to CIN2, 3		
Low risk HPV	0.0003	0.00002–0.0005
High-risk 16, 18 HPV	0.0042	0.0001–0.0082
High-risk other HPV	0.0015	0.0001–0.0028
CIN2, 3 to undetected stage 1 cancer		
High-risk 16, 18 HPV	0.0049*	0.00001–0.0098
High-risk other HPV	0.0088*	0.00004–0.0176
Progression rates in unscreened women with cancer		
Stage I to stage II	0.0188	
Stage II to stage III	0.0250	
Stage III to stage IV	0.0375	
Regression		
HPV DNA to Normal		
Low-risk HPV	0.1951	
High-risk 16, 18 HPV	0.1951	
High-risk other HPV	0.1951	
CIN1 to Normal		
Low-risk HPV	0.0854	
High-risk 16, 18 HPV	0.1406	0.1316–0.1497
High-risk other HPV	0.0430	
CIN2, 3 to Normal (70% of women)		
Low-risk HPV	0.0145	0.0052–0.0238
High-risk 16, 18 HPV	0.0045	0.0010–0.0080
High-risk other HPV	0.0082	0.0029–0.0134
CIN2, 3 to HPV DNA or to CIN1 (15% of women each)		
Low-risk HPV	0.0031	0.0011–0.0051
High-risk 16, 18 HPV	0.0010	0.0002–0.0017
High-risk other HPV	0.0018	0.0006–0.0029

*Multiplied by age-dependent rate derived from calibration.

Cost estimation

A societal perspective was adopted for this cost analysis. Cost estimates are presented in Table 3 that include programme costs and time costs. We approximated the programme costs by using the current national tariff used by the national health insurance scheme.[31] These data were cross-validated by the cost of treatments and care for gynaecological patients at the University of Tokyo Hospital between August 2007 and November 2009. Both variable costs and doctor's fees are included in the programme costs according to the fee schedule set by the national tariff.[31] We estimated patients' time cost by using the national average hourly wage of part-time workers from a national survey.[32]

Cost-effectiveness analysis

We calculated quality-adjusted life-years (QALYs) from the model outputs on incidence, duration and mortality. The quality-of-life weights for different health states were based on those used in previous studies (Table 4).[33–35] All costs and benefits were discounted at 3%, a frequently used rate for cost-effective analysis done in Japanese settings.[36]

In line with a standard health economic evaluation, strategies are ranked in order of effectiveness after excluding dominated strategies.[37] Incremental cost-effectiveness ratios (ICERs) are then calculated for each strategy relative to the next best alternative. The preferred strategy is the most effective strategy with an ICER within the willingness to pay threshold of 4.5 million yen. A commonly applied threshold for acceptable cost-effectiveness in the USA is $50,000;[38] it is often used as a basis of cost-effective analysis in a Japanese setting.

Table 3. Cost data

Costs involving patient's time costs	Yen
Screening visit (Pap-test) per event	7460
CIN1 detected patient per month	4228
CIN2, 3 detection per event	28,360
Conisation cost per case	310,900
Treatment cost for stage I cancer case	664,300
Treatment cost for stage II cancer per case	2,869,900
Treatment cost for stage III cancer per case	3,066,500
Treatment cost for stage IV cancer per case	2,940,200
Average monthly wage for a Japanese case	226,100
Vaccination cost (for three doses/visits)	58,000

Table 4. Quality of life weights

Variable	Baseline values	Range
Quality of life weights for CIN		
CIN1	0.97	0.97–1.00
CIN2, 3	0.93	0.93–1.00
Quality of life weights for invasive cancer		
Stage I	0.65	0.49–0.81
Stage II	0.56	0.42–0.70
Stage III	0.56	0.42–0.70
Stage IV	0.48	0.36–0.60
Quality of life weights after treatment for invasive cancer		
Stage I	0.97	0.73–0.99
Stage II	0.9	0.68–0.98
Stage III	0.9	0.68–0.98
Stage IV	0.62	0.47–0.78

Results

Reduction in lifetime risk of cancer

Figure 2 shows the lifetime risk of cervical cancer by strategy estimated from a two-dimensional probabilistic sensitivity analysis. The range represents the minimum and maximum numbers of cervical cancer incidence per 100 000 population and its interquartile range (IQR). The bars represent the median value. Increasing the coverage of screening from the current level of 20–50 and 80% will substantially reduce the number of incident cervical cancer cases by 45.5% (IQR 42.0–48.7) and 63.1% (IQR 60.5–65.7), respectively. Combined strategies of 20, 50 and 80% screening coverage rate yields, respectively, a 66.1% (IQR 68.3–64.2), 80.9% (IQR 78.6–83.3) and 86.8% (IQR 85.4–87.9) reduction in cervical cancer incidence.

Total costs and QALYs of vaccination and screening programmes

Total QALYs gained per 100 000 population for each strategy showed slight increase as the screening coverage increases and the universal vaccination is added (Figure 3). Figure 4 shows cost per person for each strategy. The squares represent average values and the range represents average value ± 2 SD. Costs of strategies including vaccination are approximately four times higher than that of strategies without vaccination. Increasing the screening coverage rate was cheaper than introducing vaccination for all 11-year-old girls.

Incremental cost-effectiveness ratio

Table 5 shows the ICER of each strategy compared with its next best alternative strategy. Using the default model values, 50% screening coverage with a vaccination strategy was the most cost-effective when using a willingness to pay for a QALY threshold of 4,500,000 yen (≅ US$500,000) (Figure 5).

Sensitivity analysis on vaccine efficacy

We performed a sensitivity analysis on vaccine efficacy. The vaccine efficacy is determined by the combination of risk ratios to acquire HPV16/18 and other HR in our model. Table 6 shows cost and QALYs derived from the reference vaccine efficacy, minimum and maximum vaccine efficacy per 1000 people. Differences in vaccine efficacy would result in the differences in programme costs ranging from approximately 4,000,000–8,000,000 yen (≅US$480,000–960,000).

Table 7 shows the ICERs derived from the sensitivity analysis. The current strategy is dominated by strategies with a higher screening rate. A screening rate of 20% with a vaccination strategy is always ruled out because of extended dominance. The ICER for a screening rate of 50 and 80% with vaccination strategies was sensitive to the

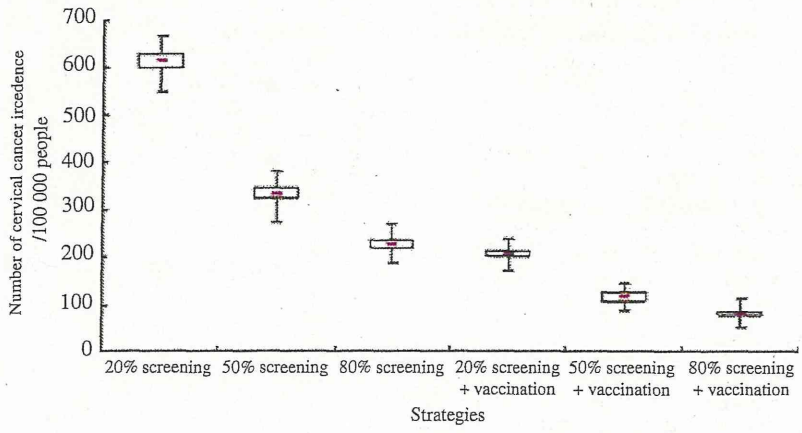


Figure 2. Lifetime risk of cancer for each strategy.

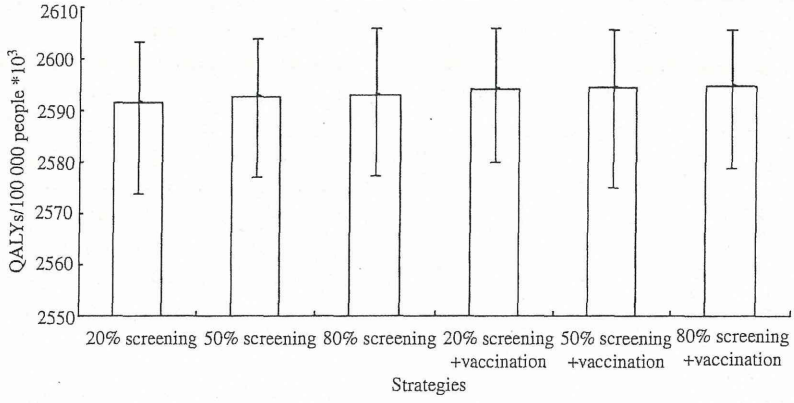


Figure 3. Total QALYs per 100,000 people for each strategy.

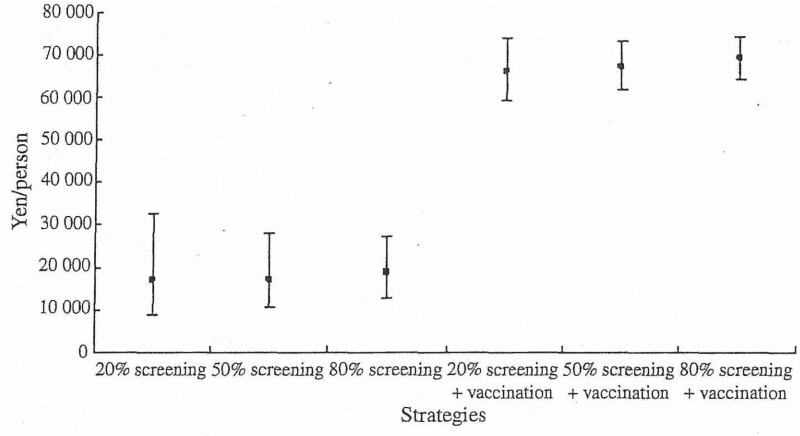


Figure 4. Cost per person for each strategy.

Table 5. Cost effectiveness of alternative screening and vaccination strategies

Strategy	Incremental cost effectiveness Ratio* (Yen/QALY)	
20% Screening	–	Dominated
50% Screening	658	
80% Screening	571 015	
20% Screening + vaccination	–	Extended Dominance
50% Screening + vaccination	2 920 636	
80% Screening + vaccination	8 568 182	not cost effective

*Ratio of additional costs and benefits of a particular strategy compared with the previous strategy.

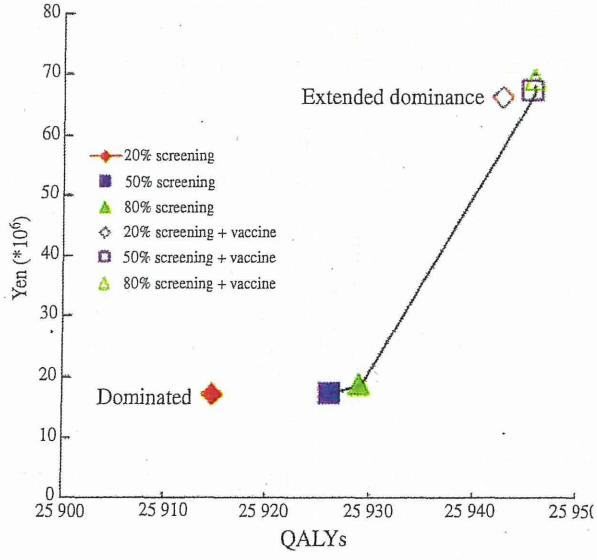


Figure 5. Cost and QALYs per 1000 people.

differences in incremental costs and effectiveness given by the result of a two-dimensional probabilistic sensitivity analysis of the model with each vaccine efficacy. With the