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Review Article

The Japanese Guideline for Cervical Cancer Screening

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Cervical cancer is the 11th leading cause of death from cancer for females in Japan. In 2005, there were 2486 deaths from cervical cancer, accounting for 1.8% of the total number of cancer deaths in Japan. Cervical cancer screening using conventional cytology has been conducted worldwide. The guideline for cervical cancer screening was developed based on the established method. The efficacies of conventional and liquid-based cytology, human papillomavirus testing alone and two combination methods were evaluated. On the basis of the balance of the benefits and harms, recommendations for population-based and opportunistic screening were formulated. Five methods of cervical cancer screening were evaluated. On the basis of the analytic framework involving key questions, 3450 articles published from January 1985 to October 2007 were selected using MEDLINE and other methods. After the systematic literature review, 66 articles were confirmed. The results of 33 studies were consistent, and the evidence was sufficient to evaluate the effect of conventional cytology screening. The accuracy of liquid-based cytology was almost equal to that of conventional cytology. Although human papillomavirus testing and combination methods showed high sensitivity, no study has evaluated the reduction in mortality from cervical cancer. Except for the possibility of overdiagnosis, no serious adverse effects of cervical cancer screening were found. Cervical cancer screening using conventional and liquid-based cytology is recommended for population-based and opportunistic screening due to sufficient evidence. Cervical cancer screening using either human papillomavirus testing alone or two combination methods is not recommended for population-based screening due to insufficient evidence.

Key words: cervical cancer – cancer screening – guideline – recommendation – conventional cytology – liquid-based cytology – HPV testing

INTRODUCTION

Cervical cancer is the 11th leading cause of death from cancer for females in Japan. In 2008, there were 2486 deaths from cervical cancer, accounting for 1.8% of the total number of cancer deaths in Japan (1). The incidence of cervical cancer among all age groups decreased gradually until 1990 and then flattened. For two decades until 2002, although the incidence among women over age 40 years

decreased, the incidence among women in the 20–39 years age group gradually increased. On the other hand, the mortality of the 40–59 years age group increased, with a peak in the 55–59 years age group in 2006.

In 2001, the Research Group for Cancer Screening Guidelines funded by the Ministry of Health and Welfare of Japan recommended the following six cancer screening programs (the Hisamichi reports) (2): gastrofluorography for gastric cancer; fecal occult blood testing for colorectal cancer; a combination of chest radiography and sputum cytology (added for current smokers only) for lung cancer; Pap smear for cervical cancer; a combination of physical examination and mammography for breast cancer and hepatitis virus markers for hepatocellular carcinoma. These guidelines did not recommend cervical cancer screening using human papillomavirus (HPV) testing because of insufficient evidence. However, liquid-based cytology was not included in that evaluation.

Since the publication of the previous guidelines, new studies dealing with HPV testing alone and in combination have been reported worldwide. Meanwhile, a new research group established a standardized method for developing the Japanese Guidelines for Cancer Screening (3). On the basis of this methodology, the effects of conventional, liquid-based cytology and HPV testing for cervical cancer screening were evaluated, and a new guideline was developed.

PATIENTS AND METHODS

The target audiences for the cervical cancer screening guideline include the public health professionals working in cancer screening programs, providers of cancer screening programs and policy makers. The members of the guideline development group for cervical cancer screening (Japanese Research Group for Development of Cervical Cancer Screening Guidelines) were selected from various specialties. The cervical cancer screening guideline was developed using the standardized method (3).

Target Methods

The efficacies of conventional and liquid-based cytology, HPV testing alone and two combination methods were evaluated. Conventional cytology is the traditional method of collecting cells from the surface of the uterine cervix and analyzing the smeared cells directly using a microscope. Liquid-based cytology is a new technique for transferring the cellular material to a microscope slide. The sampling device carrying the material is immersed in a container with a special liquid transport medium. Most clinical investigations of HPV testing have used the Hybrid Capture (HC) system. The HC system is a nucleic acid hybridization assay with signal amplification for the qualitative detection of DNA of high-risk, cancer-associated HPV types in cervical specimens.

Analytic Framework

The target population for cervical cancer screening was defined to be asymptomatic females with an average risk of cervical cancer. To select appropriate evidence, an analytic framework for cervical cancer screening was developed (Fig. 1). For each stage of the analytic framework, key

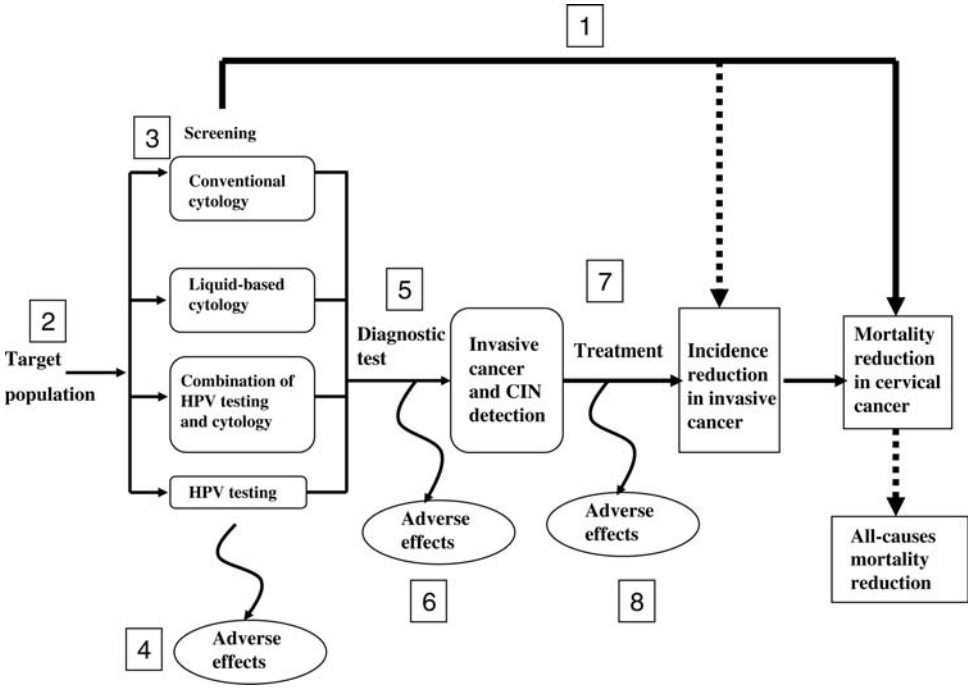

Figure 1. Analytic framework and key questions for cervical cancer screening. The numbers in the analytic framework refer to the key questions, which are listed in Appendix 2.

questions based on the PICO (population, intervention, comparison and outcome) format were prepared. Direct evidence was defined as evidence provided by a study that evaluated the effect of cancer screening for reducing cervical cancer incidence and mortality (Fig. 1, arrow 1). However, to determine the level of evidence appropriately, the primary outcomes of mortality from cervical cancer and incidence of invasive cancer were differentiated. Other studies that provided indirect evidence were selected based on key questions related to other stages of the analytic framework (Fig. 1, arrows 2–8).

Systematic Literature Review

A systematic literature review was conducted by the members of the review committees for cervical cancer screening. A search of the literature published from January 1985 to October 2007 was performed using MEDLINE, EMBASE and the Japanese Medical Research Database (Igaku-chuo-zasshi). Key journals were searched manually, including the Journal of the Japanese Association for Obstetrics and Gynecology and the Journal of the Japanese Association for Clinical Cytology. Further references were obtained through the IARC handbook (International Agency for Research on Cancer) (4), previous guidelines (2) dealing with the evaluation of cervical cancer screening were checked and relevant articles were included. Additional references recommended by the Review Committee were identified and included as needed. If the result from a branch of a large-scale randomized-control trial (RCT) was published during guideline development, the study was included. To select appropriate evidence, a systematic review of the retrieved articles was conducted using the checklist according to the study design (3).

Translation into Recommendations

Considering the balance of the benefits and harms, five grades of recommendations were determined for population-based and opportunistic screening (3). The recommendations were assessed in conjunction with the board members of the Japanese Research Group for Cancer Screening Guidelines. The body of evidence for each screening method was summarized in an evidence table based on the analytic framework's key questions. The benefit of each screening modality was determined based on the level of evidence (3). The evidence was divided into eight levels based on study design, quality and consistency. The harms, including overdiagnosis and LEEP (loop electrosurgical excision procedure) with conization as complications of diagnostic tests and treatment, were assessed.

Since they are supported by sufficient evidence, both Grade A and B recommendations could be conducted as both population-based and opportunistic screening programs. A Grade A recommendation is supported by RCTs, and a Grade B recommendation is supported by observational studies. However, a method with a Grade D recommendation should not be used for either population-based or opportunistic screening programs. A Grade C recommendation implies that the method should not be used for population-based screening. However, a Grade C recommendation implies that the method could be used in clinical settings if both adequate risk management and informed consent with respect to the harms were assured. Screening methods for which there is insufficient evidence are graded as I; they are not recommended for population-based screening or as routine screening methods in clinical settings, although the decision to undergo screening could be made at the individual level based on proper information provided by health professionals in clinical settings.

Formulating the Guideline

A draft guideline was written and released on the Promoting Evidence-based Cancer Screening website (http://canscreen.ncc.go.jp/). To improve and confirm the guideline, two types of consultation were conducted. First, the guideline was reviewed in draft form by nine independent referees from two expert groups: an expert group for cervical cancer and another specialty group. In addition, major issues identified during review of the draft were discussed at the guideline forum that everyone could attend. Taking into account the comments received from external reviewers and the guideline forum, the appropriateness of the recommendation and its language was again discussed, and the guideline was refined. After the consultations were completed, the guideline was published and posted on the Promoting Evidence-based Cancer Screening website.

FINDINGS

Systematic Literature Review

On the basis of the literature search using MEDLINE and other databases, 3450 articles published from January 1985 to October 2007 were identified. The abstracts were reviewed, and 161 articles were selected for the full text review. After the full text review, which included a new paper from a Swedish study that was published after the above literature search, 33 articles were confirmed as providing direct evidence dealing with the reduction in incidence and mortality of cervical cancer by screening, and 33 articles were confirmed as providing indirect evidence (Table 1).

Level of Evidence

Conventional Cytology (Level of Evidence: 2++)

There is no evidence to evaluate the reduction in mortality from cervical cancer based on RCTs. Three cohort studies, 11 case–control studies and 21 ecological studies dealing with conventional cytology were identified. Since the results

Table 1. Evidence for cervical cancer screening

Methods	Level of evidence	Total number of references	Direct evidence (AF1): reduction in mortality from cervical cancer or incidence of invasive cancer (numbers of references)			Indirect evidence			
			Cohort study	Case–control study	Time series and ecological studies	AF3 (test accuracy)	AF4 (overdiagnosis)	AF7 (Survival)	AF7-8 (LEEP)
Conventional cytology	2++	55	3	11	21[a]	8	1	1	10
Liquid-based cytology	2+	5	0	0	0	5[b]	–	–	–
HPV testing (alone)	2−	17	0	0	0	13[c]	4[d]	–	–
(i) Combination of HPV testing and cytology and (ii) HPV testing with cytology triage	2−	8	0	0	0	8[e]	–	–	–

AF, analytic framework (see Fig. 1); HPV, human papillomavirus; LEEP, loop electrosurgical excision procedure.
[a]Reference including duplication of one reference for cohort study and one for case–control study.
[b]Reference including duplication of three references for conventional cytology.
[c]Reference including duplication of two references for conventional cytology.
[d]Reference including duplication of four references for test accuracy studies of HPV testing alone.
[e]Reference including duplication of eight references for HPV testing alone.

of these studies were consistent, the evidence was sufficient to evaluate the effect of conventional cytology screening.

Cohort Studies. The outcome of the Danish and Japanese studies was mortality from cervical cancer and that of the Italian study was incidence of invasive cancer of the cervix (Table 2) (5–7). In the Japanese study, the cohort from 45 local municipalities, involving a total of 53 003 subjects, was followed from 1988 to 2003 (6). On the basis of the screening history within the previous year of the questionnaire survey at the time of enrollment, the subjects were divided into screened and unscreened groups. However, during the follow-up periods, participation in screening was unclear in both groups. Mortality from cervical cancer in the screened group was reduced 70% compared with that in the unscreened group (hazard ratio 0.30, 95% CI: 0.12–0.74). The rate of reduction was greater for cervical cancer mortality than for deaths other than cervical cancer deaths (hazard ratio 0.73, 95% CI: 0.68–0.78).

Case–control Studies. The outcome of the Scottish and Japanese studies was mortality from cervical cancer, whereas that of other studies was incidence of invasive cancer (8–18). The details of the studies are shown in Table 3. In the Japanese study, which had a small sample size, a 78% reduction in mortality from cervical cancer was shown, but this was not significant (odds ratio = 0.22, 95% CI: 0.33–1.95) (9). Although the outcome was different, the incidence of invasive cancer was reduced by 84% in other Japanese studies (odds ratio = 0.16, 95% CI: 0.090–0.278) (13). In a recent report from Australia, 96% of invasive cancer could be prevented in women with a regular screening history compared with women without a screening history (RR = 0.043, 95% CI: 0.033–0.057) (11).

Ecological Study. All studies reported reduced cervical cancer mortality by screening (5,8,19–37). The impact of the reduction was greater in the countries that conducted organized screening than in countries that did not. Although the target age group and screening interval differ among these countries, the incidence of invasive cancer was reduced by at least 80% (4). In the Japanese study, mortality from cervical cancer decreased by 63.5% in high-participation areas compared with a 33.3% reduction in low-participation areas (29).

The incidence of invasive cancer decreased with an accompanying mortality reduction in all studies. Although the incidence of cervical cancer has decreased in the 30 years and over age group, which is the target for the screening program in Miyagi Prefecture, that of the 20–29 years age group has gradually increased (31). Similar trends could be observed in several developed countries that conducted population-based screening.

Test Accuracy

Test accuracy studies for conventional cytology were conducted using diagnostic testing with colposcopy as the reference (Table 4) (38–41). In a Japanese study using low-grade

Table 2. Cohort studies for cervical cancer screening using conventional cytology

Authors	Research area	Reported year	Target age (years)	Control group	Numbers in target population		Follow-up	Outcome	
					Intervention group	Control group		Endpoint: mortality of invasive cancer	Endpoint: incidence of invasive cancer
Berget (5)	Denmark	1979	≥20	No participation	13 148	2109	1976–1975	Participation 3.8 (4 of 13 148); no participation 47.4 (8 of 2109)	Participation 425.9 (56 of 13 148); no participation 1232.8 (26 of 2109)
Aklimunnessa et al. (6)	Japan	2006	30–79	No participation	24 417	28 586	1988–2003	Hazard ratio 0.30, 95% CI: 0.12–0.74	–
Ronco et al. (7)	Italy	2005	25–64	No invitation; no participation	9972	9973	1992–1998	–	Invitation/no invitation RR 0.8 (95%CI: 0.59–1.09); participation/no participation RR 0.25 (95% CI: 0.13–0.50)

RR, relative risk; CI, confidence interval.

squamous intraepithelial lesion as the cut-off point, the sensitivity to detect cervical cancer was 94.7% (38). The result of the Italian study was similar results for 1-year follow-up based on the regional cancer registry. Although the finding of atypical squamous cells of undetermined significance was mostly used as a cut-off point, the target disease differed among studies. In a Canadian study, the sensitivity of conventional cytology was around 50% when CIN2 (cervical intraepithelial neoplasia) or worse was targeted (42). On the other hand, in a Swedish study, the sensitivity was maintained when either CIN2 or CIN3 was used for the threshold (43). The accuracy of conventional cytology differed among the studies because of different reference tests and different target groups (44,45). However, the sensitivity ranged from 50% to 80%, and the specificity ranged from 70% to 90%.

Survival Analysis

In the report from the Osaka cancer registry, the relative survival of patients with screening-detected cancer (30–54 years, 84.3%; and 55–64 years, 75.4%) was higher than that of symptomatic patents (30–54 years, 77.6%; and 55–64 years, 67.1%) (46).

Liquid-based Cytology (Level of Evidence: 2+)

No study using liquid-based cytology has evaluated the reduction in mortality from cervical cancer. Although there is no RCT evaluating conventional cytology, mortality reduction from cervical cancer has been evaluated by many observational studies conducted worldwide. Except for the method used to prepare the sample, liquid-based cytology is almost the same as conventional cytology. Thus, evidence for conventional cytology could be used for evaluation of liquid-based cytology. Since the sensitivity and specificity of liquid-based cytology are similar to those of conventional cytology, we concluded that the evidence for conventional cytology could be employed. Therefore, the evidence was sufficient to evaluate the effect of liquid-based cytology. However, since no study has compared the sensitivity and specificity of both methods in Japan, an evaluation study, including investigation of unsatisfactory samples of conventional cytology, is needed before introduction of population-based screening.

Test Accuracy

Five studies to investigate the accuracy of liquid-based cytology were selected (Table 4) (39,40,44,47,48). In an RCT compared with conventional cytology, the sensitivity to detect CIN2 or worse was 69.1% (95% CI: 55.2–80.9) for conventional cytology and 60.3% (95% CI: 47.4–71.9) for liquid-based cytology (39). On the other hand, the specificity was 94.5% (95% CI: 93.5–95.4) for conventional cytology and 94.1% (95% CI: 93.2–94.9) for liquid-based cytology. Neither the sensitivity nor the specificity was statistically different. In another RCT, the ratio of the detection rate for liquid-based cytology compared with that of conventional

Table 3. Case–control studies dealing with cervical cancer screening using conventional cytology

Authors	Published year	Research area	Target age	Numbers		Screening rate		Endpoint	Odd ratio (95% CI) Relative protection (95% CI)[a]
				Case	Control	Case	Control		
Macgregor et al. (8)	1994	Scotland	25–60 years	15	150	35%	73%	Cervical cancer mortality	Reference: women with a negative screening result obtained within 5 years; screening history in past 5–10 years, 1.63 (90.62–4.25)[a]; screening history in past 10 years or more, 2.20 (0.86–5.60)[a]; no screening history, 6.75 (3.43–13.41)
Sobue et al. (9)	1988	Japan	≤80 years	15	150	6.7%	53.3%	Cervical cancer mortality	0.22 (0.33–1.95)
Macgregor et al. (10)	1985	Scotland	Unclear	(i) Symptomatic cancer 35 and (ii) Stage 1 50	(i) 139 and (ii) 250	Unclear	Unclear	(i) Symptomatic cancer and (ii) Stage 1	Reference: women with a negative screening result obtained 10 or more years previously (i) 30–47 months, 3.5 (1.1–2.2)[a]; 48–71 months, 1.9 (0.8–6.5)[a]; 72–79 months, 1.0 (0.4–3.9)[a]; (ii) 30–47 months, 6.6[a]; 48–71 months, 10.5[a]; 72–119 months, 2.1[a]
Yang et al. (11)	2008	Austo	20–69 years	877	2614	33.3%	87.3%	Invasive cancer	Reference: women without Pap test One time screening history 0.152 (0.119–0.194); two times screening history 0.043 (0.033–0.057)
Hernández-Avila et al. (12)	1998	Mexico	Average case: CIS, 44.7 years; invasive cancer, 47.7 years; control, 48 years	CIS, 233; invasive cancer, 397	1005	CIS, 42.4%; invasive cancer, 42.4%	50.70%	CIS and invasive cancer	CIS, 0.68 (0.45–1.00); invasive cancer, 0.38 (0.28–0.52)
Sato et al. (13)	1997	Japan	35–79 years; average: case, 49.0 years; control, 48.8 years	109	218	55.0%	88.5%	Invasive cancer	0.16 (0.090–0.278)
Jiménez-Prez and Thomas (14)	1999	Mexico	≤70 years; average: case, 49.5 years; control, 49.1 years	143	311	54.6%	81.7%	Invasive cancer	0.3 (0.2–0.4)
Palli et al. (15)	1990	Italy	≤75 years	191	540	18.8%	47.7%	Invasive cancer	0.15 (0.09–0.25)
Herrero et al. (16)	1992	Colombia, Mexico, Costa Rica and Panama	≤70 years	759	1430	50.1%	71.0%	Invasive cancer	No screening history, 2.5 (2.1–3.3)[a]
Celentano et al. (17)	1989	USA	21–84 years	153	(i) Neighborhood 153; (ii) random selection 392	153	(i) 92.8%; (ii) 91.1%	Invasive cancer	(i) 4.30 (1.46–12.7)[a]; (ii) 3.63 (1.38–9.57)[a]
Makino et al. (18)	1995	Japan	35–79 years	198	396	48.4%	83.8%	Invasive cancer	0.14 (0.088–0.230)

[a]Relative protection (inverse of relative risk).

Table 4. Accuracy of cervical cancer screening (conventional and liquid-based cytology, HPV testing)

Authors	Published year	Target age group	Definition of true-positive cases	Method for follow-up	Follow-up years	Conventional cytology			Liquid-based cytology			HPV testing (alone)		Combination of HPV testing and liquid -based cytology	
						Cut -off point	Sensitivity	Specificity	Cut -off point	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Yoshida et al. (38)	2001	Unclear	COI	Cancer registry	1 year	LSIL	94.7	98.7	–	–	–	–	–	–	–
Strander et al. (47)	2007	23–60 years	CIN2	Regional database for prevention of cervical cancer	2 years 9 months	–	–	–	–	Relative sensitivity compared conventional cytology Follow-up 1.5 years 1.60 (1.12–2.28); follow-up 3–7 years 1.51 (1.13–2.01)	–	–	–	–	–
Taylor et al. (39)	2006	35–64 years	CIN1	Diagnostic tests (Coloposcopy)	–	ASCUS	83.6 (71.2–92.2)	94 (92–96)	ASCUS	70.6 (58.3–81.0)	84.8 (83.5–86.1)	–	–	–	–
						LSIL	69.1 (55.2–80.9)	94.5 (93.5–95.4)	LSIL	60.3 (47.7–71.9)	94.1				
Cochand-Priollet et al. (40)	2005	High-risk group average 37.8 years	CIN1	Diagnostic tests (Coloposcopy)	–	ASCUS	85 (81–89)	92 (89–94)	ASCUS	78 (73–83)	94 (93.2–94.9)	80 (74–86)	54 (49–60)	80 (74–86)	93 (90–96)
		Screening group average 33.3 years					60 (45–75)	99 (99–99)		65 (50–80)	98 (98–99)	96 (88–100)	85 (83–87)	76 (59–93)	97 (97–98)
Cecchini et al. (41)	1989	18–60 years	Invasive cancer	Cancer registry	9 years	–	Screening interval: 1 year, 0.9; 3 years, 0.78; 5 years, 0.68	–		–	–	–	–	–	–
Belinson et al. (48)	2002	35–45 years	CIN2	Cancer registry	–	–	–	–	(i) ASCUS; (ii) LSIL; (iii) HSIL	(i) 94; (ii) 87; (iii) 77	–	–	–	–	–
			CIN3						(i) ASCUS; (ii) LSIL; (iii) HSIL	–	(i) 78; (ii) 94; (iii) 98				

CIN, cervical intraepithelial neoplasia; ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.

cytology (so called relative sensitivity) was calculated. The relative sensitivity was reported to be 1.60 (95% CI: 1.12–2.28) compared with that of conventional cytology based on 1.5 years of follow-up (40). In a systematic review of 24 studies using Thin Prep, the sensitivity was 68% for conventional cytology and 76% for liquid-based cytology, and the specificity was 79% and 86%, respectively (45).

HPV Testing (Level of Evidence: 2−)

There have been no studies that evaluated the reduction in mortality from cervical cancer. Although RCTs were performed, the defined outcomes were sensitivity, specificity and positive predictive value (PPV); the reductions in cervical cancer incidence and mortality are unclear. To detect CIN2 or worse, the sensitivity of HPV testing is always higher than that of conventional cytology. When the target lesion is changed to detect CIN3 or worse, the sensitivity of HPV testing is equal to or higher than that of conventional cytology. The high CIN detection rate does not lead to an absolute reduction in the incidence of invasive cancer because there is a high possibility of no progression. Both the specificity and PPV are lower than those of conventional cytology. The high sensitivity of HPV testing suggests the possibility of reducing mortality from cervical cancer. At present, there is insufficient evidence to determine its role based on studies that reported test accuracy alone.

Test Accuracy: Randomized Controlled Trials

The RCTs that compared HPV testing and conventional cytology were conducted in three countries (Canada, Italy and Finland; Table 5) (42,43,49–52). The design of these studies differed based on each country's current system of cervical cancer screening. In the Swedish study, accuracy was calculated in the experimental arm within the RCT (43).

When the cut-off point was changed, the relative sensitivity decreased in the Finnish study (52) and the Italian study (49). The Italian study compared HPV testing to conventional cytology, and the relative sensitivity of HPV testing to detect CIN2 or worse was 1.92 (95% CI: 1.28–2.87) in the 35–60 years age group and 3.50 (95% CI: 2.11–5.82) in the 25–34 years age group (49). When the target disease was changed to CIN3 or worse, the relative sensitivity of HPV testing was higher in the younger group: 2.06 (95% CI: 1.16–3.68) in the 35–60 years age group and 2.61 (95% CI: 1.21–5.61) in the 25–34 years age group. However, the sensitivity and the specificity were similar to both cut-off points in the Swedish study.

Test Accuracy: Other Designs

In the systematic review, the sensitivity to detect CIN2 or worse was 96.1% (95% CI: 94.2–97.4) for HPV testing and 53.0% (95% CI: 48.6–57.4) for conventional cytology (45). When the target disease was changed to CIN3 or worse, the sensitivity of HPV testing was 96.1% and that of conventional cytology was 55.0%. However, the specificity for excluding CIN2 or worse was higher for conventional cytology than for HPV testing. In this study, methods of HPV testing were combined with HC 1 and 2, and polymerase chain reaction.

In split-sampling studies that compared sensitivity between HPV testing and conventional cytology, the sensitivity to detect CIN2 or worse was higher with HPV testing than with conventional cytology, but the specificity was the opposite (53–56). The most serious problem when comparing both the methods was that the test accuracy differed among countries. Cuzick et al. (57) calculated the sensitivity and the specificity limited to the 35 years and over age group based on the diagnostic test for positive results. When the target disease was changed to CIN3 or worse, the sensitivity of HPV testing was 96.0% and that of conventional cytology was 82.4%. However, the specificity of both methods was almost equal: 95.4% for HPV testing and 96.4% for conventional cytology. In this study, the results suggested that HPV testing may be a possible screening method when the target age group is limited to 35 years and over.

Combination of HPV Testing and Cytology (Level of Evidence: 2−)

HPV Testing with Cytology Triage (Level of Evidence: 2−)

Although RCTs were performed with defined outcomes of sensitivity, specificity and PPV, no studies evaluated the reduction in mortality from cervical cancer. The sensitivity of both methods was higher than that of conventional cytology, and the specificity was lower. The high sensitivity of the combination with HPV testing suggests that it may reduce mortality from cervical cancer. Increased sensitivity reflects the inclusion of regressing lesions. Although the specificity is lower than that of conventional cytology, the PPV could be improved by using HPV testing with cytology triage. There is insufficient evidence to determine the role of this approach based on the studies that reported test accuracy only.

Test Accuracy: Combination of HPV Testing and Cytology

Two RCTs were conducted in the Netherlands and in Italy (Table 6) (51,58,59). In the studies conducted in Sweden, sensitivity was calculated within the intervention arm in the RCT (42,43). The methods in these studies included several options using HPV testing compared with conventional cytology.

The Dutch study involved subjects in the 29–56 years age group who participated in regular screening programs (58). The incidence of CIN3 or worse was 70% higher at baseline with the combination method than with cytology screening (68 of 8575 vs. 40 of 8580, $P = 0.007$). In the subsequent round, the numbers of cases of CIN3 and invasive cancer reversed between the groups (24 of 8413 vs. 54 of 8456, $P = 0.007$). The total numbers of cases of CIN3 and

Table 5. Accuracy of HPV testing alone

Authors	Country/study	Published year	Target age	Numbers in target population		Cut-off point of cytology	Target disease: CIN2			Target disease: CIN3		
				Conventional cytology	HPV testing		Sensitivity/ relative sensitivity	Specificity	Positive predictive value/relative positive predictive value	Sensitivity/ relative sensitivity	Specificity	Positive predictive value/relative positive predictive value
Kotaniemi-Talonen et al. (52)	Finland	2008	30–60 years	30 585	30 564	LSIL	1.64[a] (95% CI: 1.08–2.49)	HPV testing, 92.9% (95% CI: 92.6–93.3)	HPV testing, 5.4%: (95% CI: 4.3–6.6)	1.10[a] (95% CI: 0.57–2.12)	HPV testing, 92.7% (95% CI: 92.3–93.0)	HPV testing1.5% (95%CI:0.9–2.2)
								Conventional cytology, 99.3% (95% CI: 99.1–99.4)	Conventional cytology, 27.6% (95% CI: 21.5–34.4)		Conventional cytology, 99.0% (95% CI: 99.0–99.2)	Conventional cytology, 10.1% (95% CI: 6.2–15.1)
Mayrand et al. (42)	Canada	2007	30–69 years	5059	5055	ASCUS	HPV testing, 94.6% (95% CI: 84.2–100.0)	HPV testing, 94.1% (95% CI: 93.4–94.8)	HPV testing, 6.4% (95% CI: 5.0–8.0)	–	–	–
	Canadian Cervical Cancer Screening Trial Study Group						Conventional cytology, 55.4% (95% CI: 33.6–77.2)	Conventional cytology, 96.8% (95% CI: 96.3–97.3)	Conventional cytology, 7.1% (95% CI: 4.8–10.3)	–	–	–
Ronco et al. (49)	Italy	2008	25–60 years	24 535	24 661	ASCUS	25–34 years: 3.50[a] (95% CI: 2.11–5.82)	–	25–34 years: 0.89[b] (95% CI: 0.55–1.44)	25–34 years: 2.61[a] (95% CI: 1.21–5.60)	–	25–34 years: 0.66[b] (95% CI: 0.31–1.40)
	New Technologies for Cervical Cancer Screening Working Group						35–60 years: 1.92[a] (95% CI: 1.28–2.87)		35–60 years: 0.80[b] (95% CI: 0.55–1.18)	35–60 years: 2.06[a] (95% CI: 1.16–3.68)	–	35–60 years: 0.86[b] (95% CI: 0.49–1.52)
Naucler et al. (43)	Sweden	2009	32–38 years	–	6257	ASCUS	HPV testing 95.4% (95% CI: 88.6–98.7)	HPV testing 94.2% (95% CI: 93.5–94.7)	HPV testing 19.2% (95% CI: 15.6–23.2)	HPV testing 96.0% (95% CI: 86.3–99.5)	HPV testing 93.6% (95% CI: 93.0–94.2)	HPV testing 11.1% (95% CI: 8.3–14.4)
							Conventional cytology 71.3% (95% CI: 60.6–80.5)	Conventional cytology 98.6% (95% CI: 98.3–98.5)	Conventional cytology 42.5% (95% CI: 34.6–50.9)	Conventional cytology 74.0% (95% CI: 59.7–85.4)	Conventional cytology 98.2% (95% CI: 97.9–98.5)	Conventional cytology 25.3% (95% CI: 18.5–33.2)

[a]Relative sensitivity.
[b]Relative positive predictive value.

Table 6. Accuracy of combination of HPV testing and cytology

Authors	Country/study	Published year	Target age	Cut-off point of cytology	Numbers in target population		Target disease: CIN2		Specificity	Target disease: CIN3	
					Conventional cytology	Combination of HPV testing and conventional cytology	Sensitivity/relative sensitivity	Positive predictive value/relative positive predictive value		Sensitivity/relative sensitivity	Positive predictive value/relative positive predictive value
Naucler et al. (43)	Sweden	2009	32–38 years	ASCUS	–	6257	HPV testing + cytology 100% (95% CI: 95.8–100.0)	HPV testing + cytology 38.1% (95% CI: 31.6–44.9)	–	HPV testing + cytology 100% (95% CI: 92.9–100.0)	HPV testing + cytology 22.0% (95% CI: 16.7–44.9)
							Cytology 71.3% (95% CI: 60.6–80.5)	Cytology 42.5% (95% CI: 34.3–50.9)		Cytology 74.0% (95% CI: 59.7–85.4)	Cytology 25.3% (95% CI: 18.5–33.2)
Bulkmans et al. (58)	The Netherland	2007	29–56 years	ASCUS	9196	9207	First round 1.56[a]	–	–	First round 1.70[a]	–
							Second round 0.53[a]			Second round 0.45[a]	
Ronco et al. (59)	Italy	2006	25–34 years	ASCUS	6002	5808	1.61[b] (95% CI: 1.05–2.48)	0.55[b] (95% CI: 0.37–0.82)	–	0.70[b] (95% CI: 0.37–1.34)	0.24[b] (95% CI: 0.13–0.45)
	New Technologies for Cervical Cancer Screening Working Group		35–60 years		16 658	16 706	1.47[b] (95% CI: 1.03–2.09)	0.40[b] (95% CI: 0.23–0.66)		1.25[b] (95% CI: 0.78–2.01)	0.34[b] (95% CI: 0.21–0.54)

[a]Relative sensitivity.
[b]Relative positive predictive value.

invasive cancer did not differ between the groups ($P = 0.89$). The increased incidence in the intervention group at the baseline was based on the lead time.

The Italian studies reported two age groups: 25–34 and 35–64 years. Although CIN2 or worse was detected more often with a combination of HPV testing and cytology than with cytology alone in both age groups (1.47 for 25–34 years and 1.61 for 35–64 years), the PPV was lower than with cytology alone (51,59). When the target lesion was limited to CIN3 or worse, the relative sensitivity of combined HPV testing and cytology was higher than with cytology alone in the 35–64 years age group only (1.58, 95% CI: 1.03–2.44). The PPV for CIN3 or worse was lower in both age groups. However, the results of first and subsequent rounds were consistent in both age groups.

Test Accuracy: HPV Testing with Cytology Triage

Three RCTs were conducted in Finland, Sweden and Italy (Table 7) (43,50–52,59). In the Swedish study, the detection of CIN2 or worse using HPV testing with cytology triage was increased by 51% (relative risk = 1.51, 95% CI: 1.13–2.02) compared with the control group using cytology alone for prevalence screening (50). However, in subsequent screening, the incidence was reduced by 42% (relative risk = 0.58, 95% CI: 0.36–0.96). The increased incidence of CIN2 diagnosed at the initial screening in the intervention group was not followed by a statistically significant reduction in CIN2 at later screening. Although HPV testing as an adjunct to cytology increased sensitivity, the lesions might regress spontaneously.

In the Finnish study, compared with conventional cytology, the relative sensitivity of HPV screening with cytology triage for CIN2 or worse was 1.64 (95% CI: 1.08–2.49), but that for CIN3 or worse was equal (1.10, 95% CI: 0.57–2.12) (52). The specificity for CIN2 or worse was 99.1% (95% CI: 99.0–99.2) and that for CIN3 or worse was 98.8% (95% CI: 98.7–99.0). Compared with conventional cytology, the specificity was lower when the target disease was changed.

In the Italian study, which targeted the 35–60 years age group, the relative sensitivity compared with cytology for CIN2 or worse was 1.02 (95% CI: 0.69–1.50), and it was 0.96 (95% CI: 0.58–1.59) for CIN3 or worse (51). The PPV was improved: 1.66 (95% CI: 1.16–2.36) for CIN2 or worse and 1.57 (95% CI: 0.97–2.54) for CIN3 or worse.

Harms of Cervical Cancer Screening

Cervical cancer screening is not associated with serious adverse effects. However, three major points must be considered as harms of cervical cancer screening.

Overdiagnosis

Increasing detection of CIN is likely to result in overdiagnosis, since most mild lesions regress. Within 10 years, mild and moderate dysplasia regressed by 87.7% and 82.9%, respectively (60). On the other hand, mild and moderate dysplasia progressed to severe or worse by 9.9% and 32.0%, respectively. Although the sensitivity of HPV screening is higher than that of cytology, the high detection rate of CIN could lead to overdiagnosis (49–52).

Diagnostic Examinations

Colposcopy with and without punch biopsy is used as the standard diagnostic examination. Although some bleeding may occur following biopsy, there are no serious adverse effects.

Loop Electrosurgical Excision Procedure

LEEP including conization is used to exclude CIN lesions. For maintenance of fertility, LEEP is often performed for young females. There were ambivalent reports about whether LEEP was associated with preterm delivery or not (61–66). It is difficult to make conclusions about the adverse effects of LEEP, since both increases and no effect on pregnancy loss in the early gestation period have been reported.

DISCUSSION

In the present systematic review, sufficient evidence for cervical cancer screening using conventional and liquid-based cytology was identified. Although the technique for transferring the cellular materials to a microscope slide differs between the two methods, collecting cells from the uterine cervix and the microscopic analysis was the same. The results of evaluation studies using conventional cytology have been conducted worldwide, and these results have been consistent. Although there were limitations because of the potential bias of ecological studies, the studies of conventional screening were sufficient to sustain the evidence for reduced mortality from cervical cancer. In addition, both the sensitivity and the specificity of liquid-based cytology were similar to those of conventional cytology based on many studies that included important factors that were part of the analytic framework for cervical cancer screening. Therefore, we decided that the evidence for liquid-based cytology was at a 2+ level, because the mortality reduction was as valid as that for conventional cytology. On the other hand, HPV testing is a new technology that is different in its basic concept and its procedure for measurement. To date, the effect of HPV testing on mortality reduction in cervical cancer has not been properly evaluated. The results of five RCTs concerning HPV testing have been published, but the outcomes of these studies were sensitivity, specificity and PPV for CIN2 or worse. Three methods using HPV testing were evaluated based on these studies. Although the sensitivity is increased with all methods, the specificity is not improved compared with conventional cytology alone. An

Table 7. Accuracy of HPV testing with cytology triage

Authors	Country/study	Published year	Target age	Cut-off point of cytology	Numbers in target population		Target disease: CIN2			Target disease: CIN3		
					Conventional cytology	HPV testing with cytology triage	Sensitivity/ relative sensitivity	Specificity	Positive predictive value/relative positive predictive value	Sensitivity	Specificity	Positive predictive value
Kotaniemi-Talonen et al. (52)	Finland	2008	30–60 years	LSIL	30 585	30 564	1.64[a] (95% CI: 1.08–2.49)	HPV testing with cytology triage 99.1% (95% CI: 99.0–99.2) Cytology 99.3% (95% CI: 99.1–99.4)	HPV testing with cytology triage 32.4% (95% CI: 26.6–38.6) Cytology 27.6% (95% CI: 21.5–34.4)	1.10[a] (95% CI: 0.57–2.12)	HPV testing with cytology triage 99.1% (95% CI: 99.0–99.2) Cytology 99.3% (95% CI: 99.1–99.4)	HPV testing with cytology triage 8.9% (95% CI: 5.7–13.2) Cytology 10.1% (95% CI: 6.2–15.1)
Naucler et al. (43)	Sweden	2009	32–38 years	ASCUS	6270	6257	Prevalence screening 1.51 (95% CI: 1.31–2.02) Interval screening 0.58 (95% CI: 0.36–0.96)	–	–	Prevalence screening 1.31 (95% CI: 0.92–1.87) Interval screening 0.53 (95% CI: 0.29–0.98)	–	–
Ronco et al. (51)	Italy	2006	25–34 years	ASCUS	6002	5808	HPV testing ≥1 pg/ml 1.58[a] (95% CI: 1.03–2.44)	–	HPV testing ≥1 pg/ml 0.78[b] (95% CI: 0.52–1.16)	HPV testing ≥1 pg/ml 0.66 (95% CI: 0.34–1.27)	–	HPV testing ≥1 pg/ml 0.33[b] (95% CI: 0.17–0.61)
	New Technologies for Cervical Cancer Screening Working Group						HPV testing ≥2 pg/ml 1.58[a] (95% CI: 1.03–2.44)		HPV testing ≥2 pg/ml 0.84[b] (95% CI: 0.56–1.25)	HPV testing ≥2 pg/ml 0.66 (95% CI: 0.34–1.27)		HPV testing ≥2 pg/ml 0.35[b] (95% CI: 0.19–0.66)
Ronco et al. (51)	Italy New Technologies for Cervical Cancer Screening Working Group	2006	35–60 years	ASCUS	16 658	16 706	1.02[a] (95% CI: 1.16–2.36)	–	1.66[b] (95% CI: 1.16–2.36)	0.96[a] (95% CI: 0.58–1.59)	–	1.57[b] (95% CI: 0.97–2.54)

[a]Relative sensitivity.
[b]Relative positive predictive value.

appropriate method that includes HPV testing may reduce the incidence and mortality of cervical cancer. However, at present, there is no conclusive evidence of the effect of HPV testing.

After the guideline draft was completed, the cluster RCT in India and the results of the second round of the ARTISTIC (A Randomized Trial in Screening to Improve Cytology) study were published. In the HPV testing group, mortality from cervical cancer was reduced by 48% compared with the control group that received standard care (hazard ratio = 0.52, 95% CI: 0.33–0.83) (67). No significant reductions in advanced cancer and death from cervical cancer were observed in the cytology and visual inspection groups. This is the first report to evaluate mortality reduction in cervical cancer by HPV testing. However, the Indian RCT had several limitations that need to be considered. Although cervical cancer was detected more in the cytology group than in the HPV testing group, there was no decrease in invasive cancer and death in the cytology group. Since there is little screening for cervical cancer in India, few women had previous screening histories (67,68). Although the characteristics of the four clusters were nearly equal, smoking habit and medical services use were unclear. It might be suggested that there were differences in the incidence of cervical cancer among the four clusters. On the other hand, in the ARTISTIC study, for the first and second round combined, the proportion of women with CIN3 or worse was similar for liquid-based cytology screening and for the combination of liquid-based cytology screening and HPV testing (69). The result was nearly equal to those of the Dutch and Swedish studies, which were selected as the evidence for our guideline. In addition, to detect CIN3 or worse, the sensitivity of liquid-based cytology alone was only slightly higher than that of HPV testing with cytology triage and of cytology with HPV triage. Although the effect of HPV testing was only shown by the Indian clustered RCT, changing the current recommendation is not warranted, given the limitations of the study and the different healthcare system in Japan.

Around 1960, cervical cancer screening using the Pap smear was started in Miyagi Prefecture, and this approach was adopted nationwide. In 1983, under the Health Service Law for the Aged, cervical cancer screening was introduced for all residents aged 40 years and over. Previous guidelines published in 2001 recommended cytology screening using the conventional method, not liquid-based cytology. HPV testing was not recommended because of insufficient evidence (2). There was no change in the implementation of cervical cancer screening because new technologies were not common in 2001. In 2003, the target age and screening interval were changed based on changes in the age distribution of both cancers and the limited resources available for screening programs. The target age group was expanded from 30 years and over to 20 years and over, and the screening interval was prolonged from 1 year to every 2 years (70). The purpose of this change was to increase the opportunities for testing for women who had never participated in cervical cancer screening. However, screening uptake increased slightly after the change in the screening interval in 2004. In 2006, 3.3 million women participated in population-based screening for cervical cancer; the screening uptake has been around 18% (71).

In developed countries, population-based screening for cervical cancer has been conducted since the 1960s. Nordic countries and the UK have organized screening systems to reduce mortality from cervical cancer. A well-organized screening program could achieve high coverage of the target population and demonstrate good quality at all levels. European guidelines recommended 3–5-year screening intervals depending on available resources (72). The USPSTF (US Preventive Services Task Force) recommended at least a 3-year interval, but others recommended annual screening in the USA. The target group differs among the countries, but mainly includes the 30–60 years age group (73). The IARC handbook concluded that organized programs should not include women aged less than 25 years (4). On the other hand, American guidelines, including the USPSTF, recommended that screening should begin within 3 years of starting sexual activity or at 21 years (73–78). In 2009, the American College of Obstetricians and Gynecologists revised the guideline and starting age was changed to 21 years of age regardless of sexual history to avoid unnecessary and harmful diagnostic tests and treatment (79). In a recent study in the UK, compared with the substantial reduction in mortality in older women, cervical screening in women aged 20–24 years has little or no impact on the rate of invasive cancer up to age 30 years (80). Although we could find several studies including the 20–29 years age group, the mortality reduction in this age group was uncertain. At the next revision of the guidelines, we have to reconsider the appropriate target age group based on the balance of benefits and harms.

The main method for cervical screening is the Pap smear (conventional cytology), except in Denmark and the UK, which mainly used liquid-based cytology. In the UK, based on the systematic review by NICE, liquid-based cytology was used to decrease inadequate samples (81). Cervical screening using HPV testing has not been conducted at the community level. However, a guideline published by the American Cancer Society, the American College of Obstetricians and Gynecologists and the American Society for Colposcopy and Cervical Pathology recommended the method including HPV testing (74–78). In the USA, HPV testing has been used in combination with cytology or triage in clinical settings. European Guidelines concluded that new primary screening programs should not be introduced without first performing RCTs to investigate the effect at the population level (72). If new technologies are used in clinical settings, shared decision-making based on appropriate information relating to the benefits and harms should be performed.

Genital HPV infection is common and acquired soon after onset of sexual activity. However, persistent HPV infection with a high-risk HPV type causes cervical cancer. Although

HPV types 16 and 18 are common high-risk types worldwide (82), the distribution of HPV types in Japan differs from that in Western countries. In Japan, HPV type 16 and 18 infection accounts for 69.3% of invasive cancer cases lower than in other countries (83). Two prophylactic HPV vaccines have been licensed in Europe and the USA: the quadrivalent vaccine and the bivalent vaccine. Both vaccines protect against the high-risk HPV types 16 and 18, which could reduce CIN by over 90% (84,85). HPV vaccination programs have been introduced in several countries, including Australia (86–90). At present, antibody persistence and protection against persistent infection have been shown for up to 5 years after vaccination. The main target age group of vaccination is before the start of sexual activity. However, vaccination does not eliminate the need for cervical cancer screening. Based on the introduction of HPV vaccination in Canada in 2007, Howlett et al. (91) outlined the short-, medium-, and long-term requirements of an evaluation strategy related to HPV vaccination and cervical cancer screening. The European Center for Disease Prevention and Control (ECDC) recommended that organized screening should continue, and the coverage and quality of screening programs should be improved (92). In addition, monitoring of vaccination is needed.

Although the effect of conventional cytology has already been proven, the quality assurance system for cervical cancer screening is immature in Japan. To reduce the mortality from cervical cancer, improvements in screening uptake and appropriate management are required. In addition, to achieve its aims, the preferred target age group and the screening interval must be considered. The effects of new technologies, including liquid-based cytology and HPV testing, must be evaluated at the community level in Japan. Liquid-based cytology is expected to decrease unsatisfactory samples compared with conventional cytology. Akamatsu et al. (93) reported unsatisfactory samples with both methods in Japan: 0.95% with liquid-based cytology and 11.54% with conventional cytology, recalculated based on the definition of the Bethesda system. If liquid-based cytology is introduced, its cost-effectiveness compared with conventional cytology must be considered based on original Japanese data. Furthermore, sensitivity and specificity should be examined at the community level. Although HPV testing has the possibility to decrease invasive cancer, the appropriate use of this approach has not been determined. The RCTs conducted in Finland and the UK have been continued to evaluate incidence and mortality reduction using HPV testing (94,95). As for liquid-based cytology, Japanese studies evaluating its sensitivity and specificity are needed. When HPV vaccine will be introduced in the near future, comprehensive programs to prevent cervical cancer should be considered. For planning new screening programs, original Japanese studies including evaluation of HPV vaccines should be required. We have a schedule to revise the guideline within 5 years, given that new evidence may become available.

Table 8. Recommendations for cervical cancer screening

Screening method	Recommendation grade	Recommendations for language	
		Population-based Screening	Opportunistic Screening
Conventional cytology	B	Recommend	Recommend
Liquid-based cytology	B	Recommend	Recommend
HPV testing (alone)	I	Not recommend[a]	Decision-making at individual[b]
Combination of HPV testing and cytology	I	Not recommend[a]	Decision-making at individual[b]
HPV testing with cytology triage	I	Not recommend[a]	Decision-making at individual[b]

[a]There is insufficient evidence to recommend for or against.
[b]If required, the health professional should explain that the evidence regarding mortality and incidence reduction by cancer screening is unclear. In addition, information about the harms is required. In such situations, the decision regarding cancer screening should be made on the individual level.

RECOMMENDATIONS

On the basis of the balance of benefits and harms, recommendations were formulated for population-based and opportunistic screening (Table 8). Benefits were defined as evidence that mortality from a specific cancer was reduced by a cancer screening program.

Cervical cancer screening using conventional and liquid-based cytology is recommended for population-based and opportunistic screening because of sufficient evidence (Recommendation Grade B). However, to introduce liquid-based cytology, it is necessary to identify the volume of adequate samples in conventional cytology and investigate the sensitivity compared with conventional cytology in Japan. Cervical cancer screening using either HPV testing alone or a combination of HPV testing and cytology including the triage method is not recommended for population-based screening due to insufficient evidence (Recommendation Grade I). With respect to opportunistic screening, if individuals request screening, they should be given appropriate information and decision-making is required at the individual level.

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Conflict of interest statement

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APPENDIX 1

Peer Review Committee for the Japanese Cervical Cancer Screening Guideline

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APPENDIX 2

Key Questions: The Numbers in the Analytic Framework Refer to the Key Questions as Follows

(i) Compared to no screening (or other screening strategy), is there direct evidence that following screening, the incidence and/or mortality are reduced?
  (a) Conventional cytology
  (b) Liquid-based cytology
  (c) Combination of HPV testing and cytology
  (d) HPV testing

To determinate the level of evidence appropriately, the primary outcomes of mortality from cervical cancer and incidence of invasive cancer were differentiated.

Method for combination of HPV testing and cytology included the following;

- Combination of HPV testing and cytology is used for screening
- HPV testing is used for screening and subsequently cytology is used as triage to decide necessity of coloposopy

(ii) What is the prevalence of cervical cancer in the target group? What strategy can reliably identify a high-risk group from among average- risk persons?

(iii) Can the screening test accurately detect the target cancer? The screening methods are conventional cytology, liquid-based cytology, combination of HPV testing and cytology and HPV testing alone.
  (a) What are the sensitivity and specificity of the test?
  (b) Is there significant variation between examiners in how the test is performed?
  (c) In actual screening programs, how much earlier are patients identified and treated?

(iv) Does screening result in adverse effects compared to no screening?
  (a) Is the test acceptable to patients?
  (b) What are the potential harms, and how often do they occur?

(v) Can the diagnostic test accurately detect the target cancer? The diagnostic method is LEEP (loop electrosurgical excision procedure).
  (a) What are the sensitivity and specificity of the test?
  (b) Is there significant variation between examiners in how the test is performed?
  (c) In actual screening programs, how much earlier are patients identified and treated?

(vi) Does the diagnostic test result in adverse effects compared to no test?
  (a) Is the test acceptable to patients?
  (b) What are the potential harms, and how often do they occur?

(vii) For cervical cancer patients, does any treatment reduce the incidence of an intermediate outcome compared to no treatment (or other treatment)?
  (a) Does treatment work under ideal, clinical trial conditions?
  (b) How do the efficacy and effectiveness of treatments compare in community settings?

(viii) Does any treatment result in adverse effects?