EUROPEAN JOURNAL OF CANCER 47 (2011) 1633–1646

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Cost-effectiveness of primary HPV screening for cervical cancer in Germany – a decision analysis

G. Sroczynski [a], P. Schnell-Inderst [a], N. Mühlberger [a], K. Lang [b], P. Aidelsburger [b], J. Wasem [c], T. Mittendorf [d,l], J. Engel [e], P. Hillemanns [f], K.U. Petry [g], A. Krämer [h], U. Siebert [a,i,j,k,*]

[a] Department of Public Health and Health Technology Assessment, UMIT – University for Health Sciences, Medical Informatics and Technology, Eduard Wallnoefer Center I, A-6060 Hall i.T., Austria
[b] CAREM GmbH, Mühlweg 2c, 82054 Sauerlach, Germany
[c] Institute for Health Services Research and Management, University of Duisburg-Essen, Schützenbahn 70, 45127 Essen, Germany
[d] Center for Health Economics, Leibniz University Hanover, Welfengarten 1, 30167 Hanover, Germany
[e] Munich Cancer Registry of the Munich Cancer Centre, IBE/Clinic Grosshadern, Ludwig-Maximilians-University, Marchioninistr. 15, 81377 Munich, Germany
[f] Department of Obstetrics and Gynecology, Hanover Medical School, Carl-Neuberg-Str. 1, 30625 Hanover, Germany
[g] Department of Obstetrics and Gynecology, Teaching Hospital Wolfsburg, Hanover Medical School, Sauerbruchstr. 7, 38440 Wolfsburg, Germany
[h] Department of Public Health Medicine, School of Public Health, University of Bielefeld, Universitätsstraße 25, 33615 Bielefeld, Germany
[i] Center for Health Decision Science, Department of Health Policy and Management, Harvard School of Public Health, 718 Huntington Ave., Boston, 02115 MA, USA
[j] Institute for Technology Assessment and Department of Radiology, Massachusetts General Hospital, Harvard Medical School, 101 Merrimac Street, 10th Floor, Boston, 02114-4724 MA, USA
[k] Division of Public Health Decision Modelling, Health Technology Assessment and Health Economics, ONCOTYROL Center for Personalized Cancer Medicine, Wilhelm-Greil Str. 25, A-6020 Innsbruck, Austria
[l] Herescon GmbH – Health Economic Research & Consulting, Koenigsworther Str. 2, D-30167 Hannover, Germany

ARTICLE INFO

Article history:
Received 16 December 2010
Received in revised form 3 March 2011
Accepted 4 March 2011
Available online 7 April 2011

Keywords:
Human papillomavirus
Screening
Cervical cancer
Decision analysis
Cost benefit analyses
Cost-effectiveness

ABSTRACT

Objectives: To systematically evaluate the long-term effectiveness and cost-effectiveness of HPV-based primary cervical cancer screening in the German health care context using a decision-analysis approach.

Methods: A Markov-model for HPV-infection and cervical cancer was developed for the German health care context, and applied to evaluate various screening strategies that differ by screening interval and test algorithms, including HPV-testing alone or in combination with cytology. German clinical, epidemiological, and economic data, and test accuracy data from international meta-analyses were used. Outcomes predicted included the reduction in cervical cancer cases and deaths, life expectancy and discounted incremental cost-effectiveness ratios (ICER). The analysis was performed from the perspective of the healthcare system adopting a 3% annual discount rate for costs and outcomes. Extensive sensitivity analyses were performed.

Results: HPV-based screening is more effective than cytology alone. It results in a 71–97% reduction in cervical cancer cases as compared to 53–93% for cytology alone. The ICER

* *Corresponding author:* Address: Institute of Public Health, Medical Decision Making and Health Technology Assessment, Dept. of Public Health and Health Technology Assessment, UMIT – University for Health Sciences, Medical Informatics and Technology, Eduard Wallnoefer Center I, A-6060 Hall i.T., Austria. Tel.: +43 50 8648 3930; fax: +43 50 8648 673930.
E-mail address: public-health@umit.at (U. Siebert).

0959-8049/$ - see front matter
doi:10.1016/j.ejca.2011.03.006

range from 2600 Euro/LYG (cytology, 5-year-interval) to 155,500 Euro/LYG (annual HPV-testing starting at age 30 years, cytology age 20–29 years). Annual cytology alone, the current recommended screening strategy in Germany, is dominated by HPV-strategies. Increasing the age at screening initiation from 20 to 25 years does not result in a relevant loss in effectiveness but results in lower costs.

Conclusions: Based on our analyses, HPV-based cervical cancer screening is more effective than cytology alone and could be cost-effective if performed at intervals of two years or longer. In the German context, an optimal screening strategy may be biennial HPV screening starting at age 30 years preceded by biennial cytology for women aged 25–29 years. Longer screening intervals may be considered in low-risk women with good screening adherence and in populations with low HPV-incidence.

1. Introduction

In Germany, an opportunistic cervical cancer-screening programme with annual Pap cytology for women aged 20 years and older is currently recommended.[1,2] However, despite the annual screening policy in Germany, with 5470 new cervical cancer cases and 1492 deaths a year, both reported for the year 2006, Germany is ranking in the upper third as compared to other European countries.[1,3] The development of cervical cancer is associated with persistent infection with high-risk types of human papillomavirus (HPV).[4] In a meta-analysis, HPV testing achieved higher sensitivity than Pap cytology (relative sensitivity increase: 33%; 95%-CI: 20–47%) in detecting high-grade cervical intraepithelial neoplasia (CIN) and invasive cervical cancer but lower specificity when compared to cytology (relative reduction in specificity: 6%; 95%-CI: 4–7%).[5]

Thus, the introduction of HPV testing in primary cervical cancer screening has the potential to improve both the long-term effectiveness and the efficiency of screening programmes when risk tailored screening with longer intervals is considered. In this health technology assessment (HTA) report commissioned by the German Agency for HTA/German Institute for Documentation and Information (DAHTA@DIMDI), an Institute of the German Federal Ministry of Health, we used decision-analytic modelling to systematically evaluate patient-relevant long-term clinical effectiveness and cost-effectiveness of HPV testing alone or in combination with cytology in primary screening for cervical cancer. Based on the results, recommendations were derived for optimising the cervical cancer screening programme in Germany.

2. Methods

2.1. Model design and assumptions

Based on the previously published and validated German Cervical Cancer Screening Model[6] (GCCSM), we developed a decision-analytic Markov model[7–9] for the natural history of HPV infection and cervical cancer (Fig. 1). The model compares 18 screening strategies that differ by screening interval, test combinations and follow-up algorithms. In accordance with the current German guidelines, cervical cancer screening should start at age 20 years, with no upper age limit for the end of screening. However, we varied the age at the start and end of screening in scenario analyses.

We considered the following screening strategies (1.) no screening; (2.–5.) Pap cytology alone in women aged 20 years and older in intervals of one, two, three or five years; (6.–9.)

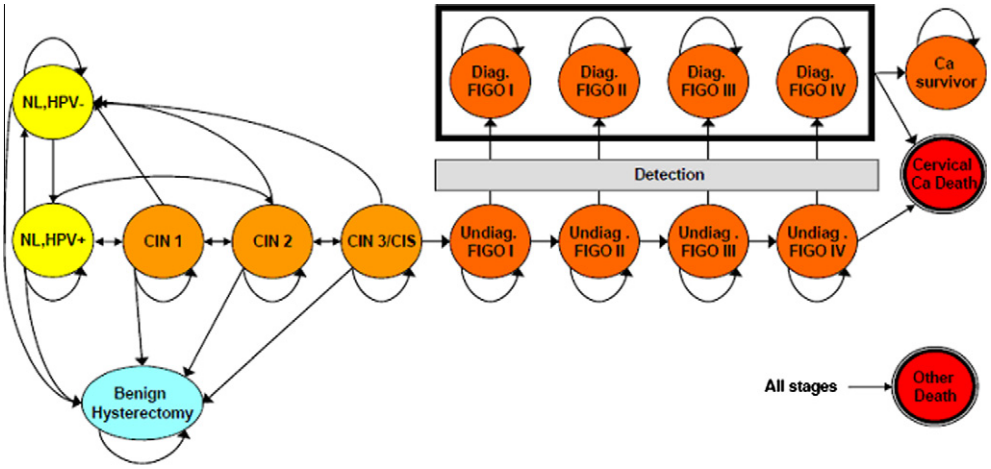

Fig. 1 – Natural history of the German Cervical Cancer Screening Model. This is a schematic diagram of the natural history model. CIN: cervical intraepithelial neoplasia, CIS: carcinoma in situ, Diag.: diagnosed cervical cancer, FIGO: cervical cancer stage classification Fédération Internationale de Gynécologie et d'Obstétrique, HPV: human papillomavirus, NL: no lesion, Undiag.: undiagnosed cervical cancer.

Table 1 – Natural history model parameters.

Transition		Age (years)	Annual probability	References
From	To			
Start prevalence HPV	–	15	0.1	15
Start prevalence CIN1	–	15	0.01	15
No Lesion, HPV-negative	No Lesion, HPV-positive	15–19	0.1000–0.1700	12–14,19[a]
		20–23	0.1000–0.2025	
		24–29	0.0550	
		30–49	0.0120–0.0140	
		50 and older	0.0045–0.0050	
No Lesion, HPV-positive	CIN1 (90%)		0.1075	12,14–15,17,19[a]
No Lesion, HPV-positive	CIN2 (10%)		0.1075	12,14–15,17,19
CIN1	CIN2	15–34	0.0176	[a]13,15,18–21
		35 and older	0.0718	
CIN2	CIN3	16–34	0.0389	
		35–44	0.0797	11
		45 and older	0.1062	
CIN3 or CIS	Cancer FIGO I	15–24	0.0011	
		25–34	0.0013	16
		35–38	0.0300	[a]
		39–49	0.0650	
		50–64	0.0820	
		65 and older	0.0831	
Cancer FIGO I	Cancer FIGO II		0.2933	
Cancer FIGO II	Cancer FIGO III		0.2793	10
Cancer FIGO III	Cancer FIGO IV		0.3461	[a]
				10
No Lesion, HPV-positive	No Lesion, HPV-negative	15–24	0.8026	[a]
		25–29	0.4621	10
		30 and older	0.1083	[a]
CIN1	No Lesion, HPV-negative (90%)	15–34	0.1750	13,15,18–21
		35 and older	0.0851	
CIN1	No Lesion, HPV-positive (10%)	15–34	0.1750	
		35 and older	0.0851	
CIN2	No Lesion, HPV-negative (50%)		0.0693	13,15,18–21
CIN2	CIN1 (50%)		0.0693	
CIN3	No Lesion, HPV-negative (50%)		0.0693	13,15,18–21
CIN3	CIN2 (50%)		0.0693	
Non-symptomatic	*Symptomatic*			13,15,18–21
Cancer FIGO I	Cancer FIGO I		0.150	13,15,18–21
Cancer FIGO II	Cancer FIGO II		0.225	13,15,18–21
Cancer FIGO III	Cancer FIGO III		0.600	13,15,18–21
Cancer FIGO IV	Cancer FIGO IV		0.900	

CIN: cervical intraepithelial neoplasia, CIS: carcinoma in situ, FIGO: invasive cancer stage classification Fédération Internationale de Gynécologie et d'Obstétrique, HPV: human papillomavirus.
[a] Callibrated model parameter.

HPV testing in women aged 30 years and older in intervals of one, two, three or five years, with annual Pap testing from age 20 to 29 years; (10.–12.) HPV testing in women aged 30 years and older in intervals of two, three or five years with biennial Pap testing from age 20 to 29 years; (13.–15.) combined HPV- and Pap testing in women aged 30 years and older in intervals of two, three or five years with biennial Pap testing from age 20 to 29 years; and (16.–18.) HPV testing in women aged 30 years and older, in intervals of two, three or five years for HPV-negative women and Pap-Triage for HPV-positive women with biennial Pap testing from age 20 to 29 years. HPV-positive women with negative Pap test result underwent a control test after 12 months.

In this model, a hypothetical cohort of women aged 15 years and older moved in annual cycles through different health states, including HPV-infection and various pre-cancer and cancer states throughout their lifetime. Transitions from one state to another were defined by annual transition probabilities derived from the literature[10–22], and calibrated to original data from German cancer registries.[6] Women were able to remain in the same health state, progress or regress to another health state, die of cervical cancer as a function of FIGO-specific survival rates, or die from other causes as a function of age and gender.

In our model, invasive cervical cancer could develop through a progression from persistent HPV-infection and the onset of different stages of cervical intraepithelial neoplasia (CIN1 to CIN3/CIS) including rapid progression to CIN2. We did not consider heterogeneity of the population with respect to infection with different HPV-types. Precancerous lesions could regress to a situation without lesions. However, the regression of invasive cervical cancer to precancerous lesions

Table 2 – Model parameters for screening.

Screening test	Threshold	Sensitivity (%)	95% CI	Specificity (%)	95% CI	References
HCII HPV	(1 pg/ml)/CIN1+	80.6	76.3–4.3	91.7	90.3–3.1	66
	(1 pg/ml)/CIN2+	98.1	96.8–99.4			5
	(1 pg/ml)/CIN3+	98.1	96.8–99.4			5
Pap cytology	(LSIL+)/CIN1+	47.1	44.8–49.4	95.0	94.5–96.4	33,34
	(LSIL+)/CIN2+	71.8	67.0–76.2			33,34
	(LSIL+)/CIN3+	71.8	67.0–76.2			33,34
HCII HPV + Pap	(1 pg/ml/LSIL+)/CIN1+	81.5	76.8–84.8	87.3	84.2–90.4	32
	(1 pg/ml/LSIL+)/CIN2+	99.2	97.4–100.0			32
	(1 pg/ml/LSIL+)/CIN3+	99.2	97.4–100.0			32

Age (years)	Average screening adherence (%)
20–29	54.6–55.9
30–39	53.9–52.1
40–49	50.3–49.5
50–59	48.8–46.9
60–69	43.8–37.6
70–79	27.5–19.3
80+	9.0

ASC-US: Atypical squamous cells of undetermined significance, CIN: cervical intraepithelial neoplasia, HCII: Hybrid Capture II, HPV: Human papillomavirus, CI: confidence interval, LSIL: low-grade squamous intraepithelial lesion, Pap: Papanicolaou test.

was not allowed. We assumed that precancerous lesions could be detected by screening only, whereas invasive cancer cases could be detected by the onset of symptoms or screening. Precancerous lesions and invasive cancer were assumed to be treated according to the German treatment guidelines.[2,23–26] Women treated for precancerous lesions were assumed not to have a continuing HPV infection or lesion, and would return to the healthy state, but were still at risk for future disease. Women treated for invasive cervical cancer were assumed to have higher mortality rates than women without cervical cancer within the first five years. After five years, mortality was the same as for women without cervical cancer. We considered benign hysterectomy, since removal of the organ at risk affects the calculation of cervical cancer incidence.

2.2. *Model parameters*

2.2.1. *Natural history data*

Natural history parameters for progression and regression of the disease were derived from the literature (Table 1).[10–22] Age-specific benign hysterectomy rates were 0.884% for age 35–39 years, 1.125% for 40–44 years, 1.074% for 45–49 years and 0.597% for age 50 years and older.[22] Stage-specific annual cervical cancer mortality rates were based on original data from the Munich Cancer Registry (MCR) for the years 1988–2006. Based on these data, five-year survival rates for FIGO I–IV were 94.2%, 73.5%, 42.0%, and 27.7%, respectively. Women could die from causes other than cervical cancer according to German age-specific all-cause mortality rates for females using German life tables from 2004–2006 from the German Federal Statistical Office.[27,28]

As described previously, the model was calibrated in a systematic and hierarchical fashion to fit specific epidemiologic data observed in an unscreened population in Germany.[6] We did not correct for hysterectomy in the calibration, since population-based registries do not make a similar correction. Epidemiologic data from the German Common Cancer Registry (CCR) from the years 1964–1966 were used to calibrate the model to fit cervical cancer incidence and FIGO-stage distribution. Age-specific HPV-incidence was calibrated such that the model predicted age-specific HPV prevalence as observed in German population.[29]

2.2.2. *Clinical data*

Clinical practice data were derived from current guidelines[26,30] for cervical cancer screening, diagnosis, and treatment and were extended using expert estimates (data can be obtained from authors upon request).

In the absence of individual data, screening adherence was modelled independently from screening history. An average, age-specific screening adherence (overall mean of 55%) was calculated using published German data on screening attendance (Table 2).[31]

Test sensitivity and specificity for the base-case were derived from international meta-analyses (Table 2).[5,32–34] In scenario analyses, we used published German screening trial data, where the relative sensitivity increase from HPV testing as compared to cytology was higher due to lower sensitivity rates for cytology.[35]

For colposcopy/biopsy, we used 96% sensitivity and 48% specificity.[36] For simplicity, the model assumes that a positive biopsy will always diagnose the true underlying health state.

We assumed that women with invasive cancer were detected through gynaecological examination. The probabilities of being detected with invasive cancer stage FIGO I–IV were 30%, 60%, 80%, and 87.5%, respectively, and were derived by expert estimates.

2.2.3. *Cost data*

Direct annual costs were calculated based on actual reimbursement costs, including frequencies of diagnostic and laboratory testing, medication and treatment procedures related

Table 3 – Aggregated costs of screening, diagnostic work-up, therapy, follow-up, and palliative procedures.

Procedure	Costs (Euro)
Screening (Pap) until 59 years[a]	36.90
Screening (Pap) 60+ years[a]	37.80
Screening (HPV) until 59 years[a]	51.63
Screening (HPV) 60+ years[a]	52.53
Control (Pap) until 59 years	22.27
Control (Pap) 60+ years	23.17
Control (HPV) until 59 years	42.93
Control (HPV) 60+ years	43.83
Colposcopy/Biopsy	19.04
HPV test[b]	22.04
Conisation until 39 years	416.58
Conisation 40 to 59 years	423.60
Conisation 60+ years	426.33
Follow-up after conisation until 59 years[a]	143.31
Follow-up after conisation 60+ years[a]	103.38
Therapy FIGO IA1 until 39 years	2943.91
Therapy FIGO IA1 40 to 59 years	2947.54
Therapy FIGO IA1 60+ years	2948.95
Therapy FIGO IA2 until 39 years	4073.31
Therapy FIGO IA2 40 to 59 years	4075.65
Therapy FIGO IA2 60+ years	4076.57
Therapy FIGO IB1 until 18 years	4136.26
Therapy FIGO IB1 19 to 39 years	3689.67
Therapy FIGO IB1 40 to 59 years	3681.00
Therapy FIGO IB1 60+ years	3682.96
Therapy FIGO IB2 until 18 years	5144.96
Therapy FIGO IB2 19+ years	4593.83
Therapy FIGO IIA until 18 years	5482.85
Therapy FIGO IIA 19+ years	4879.01
Therapy FIGO IIB until 18 years	4952.95
Therapy FIGO IIB 19+ years	3872.30
Therapy FIGO III until 18 years	5871.42
Therapy FIGO III 19+ years	4383.71
Therapy FIGO IV until 18 years	6623.20
Therapy FIGO IV 19+ years	5024.12
Follow-up after cancer therapy until 59 years, year 1 and 2 after therapy[a]	573.25
Follow-up after cancer therapy 60+ years, year 1 and 2 after therapy[a]	576.85
Follow-up after cancer therapy until 59 years, year 3, 4 and 5 after therapy[a]	286.63
Follow-up after cancer therapy 60+ years, year 3, 4 and 5 after therapy[a]	288.43
Follow-up after cancer therapy until 59 years, year 6 after therapy[a]	143.31
Follow-up after cancer therapy 60+ years, year 6 after therapy[a]	144.21
Palliative costs until 18 years	5415.32
Palliative costs 19+ years	6125.54

FIGO: cervical cancer stage classification Fédération Internationale de Gynécologie et d'Obstétrique, HPV: Human papillomavirus, Pap: Pap cytology test. Screening costs: including reimbursement for gynaecological work-up and laboratory costs for cytology.

[a] Aggregated costs per year.

[b] For HPV testing additional laboratory costs are reimbursed. Control costs: reimbursement for follow-up testing and work-up is considered.

to the specific cervical cancer stages. Health resource utilisation frequencies were derived from diagnostic and treatment guidelines and a German expert panel. Reimbursement costs were derived from healthcare databases and applicable pharmaceutical prices. We adjusted reimbursement prices for ambulatory care costs using a weighted average for East and West Germany and social and private health insurance from published data.[37]

Inpatient costs for cervical cancer treatment procedures were based on Diagnosis Related Groups (DRG). All economic data were assessed in 2007 Euros or inflated to this index year using the consumer price index (CPI).[38]

Table 3 depicts the aggregated cost packages for cervical cancer screening, diagnostic work-up and therapy, medications, follow-up and palliative procedures.

We adopted the perspective of the health care system and used a 3% annual discount rate for costs and effects.[39,40]

2.2.4. *Model analyses*

In our decision analysis, we predicted the following outcomes: the reduction in cervical cancer risk and mortality, life expectancy, lifetime costs and discounted incremental cost-effectiveness ratios (ICER) expressed as Euros per life-year gained (LYG).

In Germany, there is no explicit cost-effectiveness threshold for the adoption of a medical technology.[40] In the literature, the most commonly cited values for the cost-effectiveness threshold range between 50,000 and 100,000 USD or Euro per quality-adjusted life year (QALY). The National Institute for Health and Clinical Excellence (NICE) in the United Kingdom recommends thresholds of 20,000–30,000 GBP/QALY (30,000–44,000 Euro/QALY).[41–43]

In our base-case analysis, we selected model parameter values conservatively, that is, against the new technology of HPV testing. As such, we are likely to have underestimated the incremental effectiveness and cost-effectiveness of HPV screening strategies as compared to Pap screening alone.

We performed one-way and multi-way sensitivity analyses as well as scenario analyses to evaluate the robustness of the results and identify future research priorities. In the sensitivity analyses, we used lower and upper 95%-confidence interval limits or ranges derived from the published literature. Costs were doubled and halved. The discount rate was varied from 0% to 10% and screening adherence was varied from 0% to 100%. HPV-incidence was reduced by a maximum of 90%. Age at initiation of screening was varied between 20 and 25 years. In the scenario analyses, we used published German screening trial data for the sensitivity and specificity of HPV testing and Pap cytology.[35] In this latter study, the relative sensitivity increase for HPV testing as compared to cytology was much higher than in international meta-analyses due to the very poor performance of cytology.

2.2.5. *Model validation*

The model was internally validated using epidemiologic data from German cancer registries. Additionally, we performed an external model validation that compared the predicted model outcomes to (1) observed epidemiologic data from German cancer registries that were not used in the model development and (2) independently-published German data. All model predictions for an unscreened population were in line with German data observed prior to the introduction of cervical cancer screening (data available on request from authors).

3. Results

In the base-case analysis, different screening strategies led to an average gain of 56–91 undiscounted life days, and resulted in a 53–97% reduction in the risk of cervical cancer and a 61–99% reduction for cervical cancer mortality, as compared to no screening. HPV-based screening was more effective than cytology alone as it was associated with a 71–97% reduction (depending on screening intervals) in the risk of cervical cancer as compared to no screening. In contrast, strategies with Pap screening resulted in a 53–93% reduction in the risk of cervical cancer as compared to no screening (Fig. 2.). Compared to annual Pap screening, which is currently the recommended standard in Germany, biennial HPV testing was similarly effective (91–92% versus 93% risk reduction in cervical cancer).

In the base-case analysis, the discounted ICER of the various non-dominated screening strategies fell between 2600 Euro/LYG (cytology alone every five years) and 155,500 Euro/LYG (annual cytology from age 20 to 29 years and annual HPV at age 30 years and older) (Fig. 2.). Annual Pap cytology, the current recommended screening strategy in Germany was dominated by extended dominance, that is, it was dominated by a blend of HPV screening strategies (i.e. a combination of strategy 6 and strategy 16, see Fig. 2.). In particular, strategy 10, biennial HPV screening in women aged 30 years and older (with biennial Pap screening in women aged 20 to 29 years) was basically equally effective as the annual Pap screening (87.4 versus 88.7 undiscounted life days gained compared to no screening) and resulted in a discounted ICER of 28,400 Euro/LYG, which is cost-effective when compared to other well-accepted medical technologies. Adding Pap-Triage

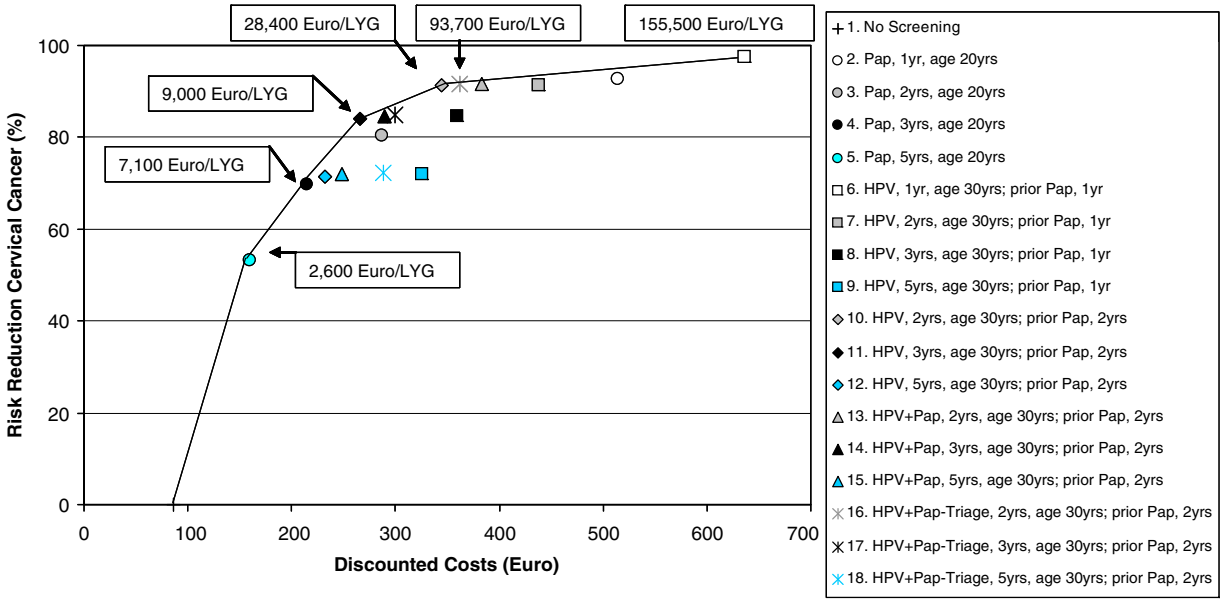

Fig. 2 – Cost-effectiveness Frontier: Risk reduction in cervical cancer (in%) versus discounted life time costs (in Euro). The ICER (in Euro/LYG) of non-dominated strategies are shown in boxes.

Table 4 – Undiscounted and discounted absolute and incremental life expectancy and costs (in Euro), and incremental cost-effectiveness ratios ICER (in Euro/LYG).

Strategy	Undiscounted Costs (Euro)	Undiscounted Life expectancy (years)	Discounted Costs (Euro)	Discounted Incr. costs (Euro)	Discounted Life expectany (years)	Discounted Incr. life expectancy (years)	Discounted ICER[b] (Euro/LYG)
1. No screening	339	67.31	87		28.83		
5. Pap, 5 years, Age: 20 years	396	67.46	159	73	28.86	0.0285	2600
4. Pap, 3 years, Age: 20 years	488	67.50	215	55	28.87	0.0078	7100
12. HPV, 5 years, Age: 30 years; prior [a] Pap, 2 years	487	67.51	232	18	28.87	0.0007	Ext. dominated
15. HPV + Pap, 5 years, Age: 30 years; prior [a] Pap, 2 years	525	67.51	248	16	28.87	0.0003	Ext. dominated
11. HPV, 3 years, Age: 30 years; prior [a] Pap, 2 years	578	67.53	266	18	28.87	0.0048	9000
3. Pap, 2 years, Age: 20 years	625	67.53	287	21	28.87	−0.0010	Dominated
18. HPV + Pap-Triage, 5 years, Age: 30 years; prior [a] Pap, 2 years	621	67.51	288	22	28.87	−0.0046	Dominated
14. HPV + Pap, 3 years, Age: 30 years; prior [a] Pap, 2 years	639	67.53	289	23	28.87	0.0002	Ext. dominated
17. HPV + Pap-Triage, 3 years, Age: 30 years; prior [a] Pap, 2 years	663	67.54	299	10	28.87	0.0001	Ext. dominated
9. HPV, 5 years, Age: 30 years; prior [a] Pap, 1 year	609	67.51	325	26	28.87	−0.0048	Dominated
10. HPV, 2 years, Age: 30 years; prior [a] Pap, 2 years	759	67.55	345	46	28.88	0.0025	28,400
8. HPV, 3 years, Age: 30 years; prior [a] Pap, 1 year	701	67.54	359	14	28.87	−0.0023	Dominated
16. HPV + Pap-Triage, 2 years, Age: 30 years; prior [a] Pap, 2 years	800	67.55	362	17	28.88	0.0002	93,700
13. HPV + Pap, 2 years, Age: 30 years; prior [a] Pap, 2 years	856	67.55	383	21	28.88	0.0000	Dominated
7. HPV, 2 years, Age: 30 years; prior [a] Pap, 1 year	883	67.55	438	77	28.88	0.0000	Ext. dominated
2. Pap, 1 year, Age: 20 years	1084	67.55	514	76	28.88	0.0005	Ext. dominated
6. HPV, 1 year, Age: 30 years; prior [a] Pap, 1 year	1394	67.56	637	123	28.88	0.0012	155,500

HPV: Human papillomavirus, ICER: incremental cost-effectiveness ratio, Incr.: incremental, LYG: life year gained, Pap: Papanicolaou test.

[a] Age 20 to 29 years.

[b] Rounded values.

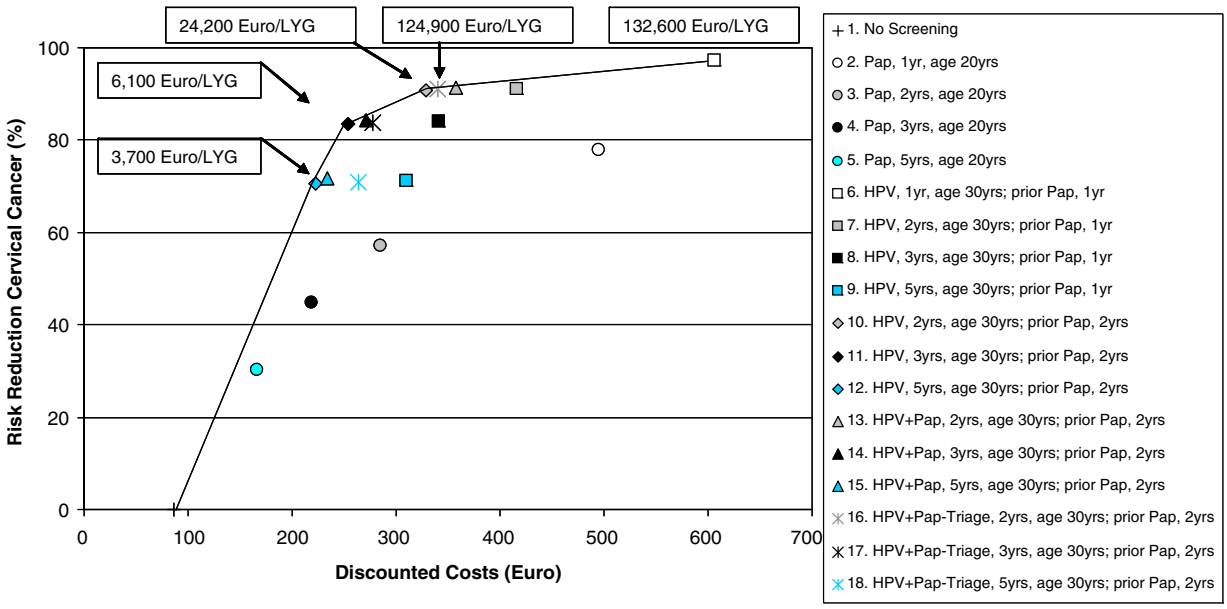

Fig. 3 – Scenario analysis with test characteristics from a German Screening trial (Petry et al.):[35] Risk reduction in cervical cancer (in%) versus discounted life time costs (in Euro).

of HPV-positives to this biennial HPV-based screening strategy (strategy 16) results in only 0.3 additional life days gained (88.7 life days gained compared to no screening) and an ICER of 93,700 Euro/LYG, requiring a higher willingness-to-pay. Moving from biennial to annual HPV screening (i.e. strategy 6: annual HPV testing in women aged 30 years and older and annual Pap screening in women aged 20 to 29 years) substantially increased the screening effort, slightly increases the effectiveness (91.0 life days gained compared to no screening), but results in a discounted ICER of 155,500 Euro/LYG.

Table 4 depicts the undiscounted and discounted life expectancy and lifetime costs as well as the discounted incremental cost-effectiveness ratios. In this base-case analysis, values for model parameters (e.g. test accuracy data, screening adherence) were selected conservatively against the new screening technology. Therefore, long-term effectiveness of (annual) Pap screening was overestimated in the base-case, and incremental effectiveness of HPV as compared to Pap screening was underestimated.

In a scenario analysis with test sensitivity and specificity values taken from a published German screening study and a Pap sensitivity much lower than in international studies and meta-analyses (46% for the detection of CIN3+ as compared to 72% in the base-case), HPV screening every one, two or three years was more effective than annual cytology (risk reduction for cervical cancer: 97%, 91%, and 84%, respectively, versus 78% for annual Pap). HPV screening every five - years was more effective than biennial Pap screening. From the cost-effectiveness perspective, all cytology alone screening strategies were dominated by HPV-based screening strategies (Fig. 3.). HPV screening in women aged 30 years or older in screening intervals of two and three years and biennial Pap screening in women aged 20 to 29 years were considered to be cost-effective, as they had discounted ICER of 24,200 Euro/LYG and 6100 Euro/LYG, respectively.

In sensitivity analyses, variation in HPV test costs, screening adherence, screening start age, reduction in HPV-incidence and the annual discount rate influenced the results (see Table 5). After doubling HPV test costs, biennial screening with a combination of HPV- and Pap-testing in women aged 30 years and older (and biennial Pap screening in women age 20 to 29 years) was the most efficient strategy with a discounted ICER of 46,800 Euro/LYG. In this analysis annual Pap cytology was not dominated, and had a discounted ICER of 90,200 Euro/LYG. With increased screening adherence (>75%), a longer screening interval would be more efficient, because the benefit of a small screening interval decreases with increasing screening adherence (see Fig. 4). However, with a low screening adherence (<45%), a shorter screening interval would be more effective and cost-effective. HPV screening in women aged 30 years or older preceded by biennial Pap screening in women aged 20 to 29 years remained the preferred strategy in these sensitivity analyses.

With decreasing HPV-incidence, the discounted ICER of all strategies increased (see Fig. 5). If HPV-incidence decreased by more than 70%, triennial HPV screening in women aged 30 years and older (and biennial Pap screening in women aged 20 to 29 years) would become the preferred strategy. The discounted ICER of all strategies increased with an increasing annual discount rate. With an annual discount rate of 7% or greater, triennial HPV screening in women aged 30 years and older (and biennial Pap screening in women aged 20 to 29 years) should be the preferred strategy. Increasing the starting age of screening from 20 to 25 years caused no relevant loss in effectiveness but resulted in lower costs. Thus, an optimal strategy in Germany may be biennial HPV testing in women aged 30 years and older (and biennial Pap screening in women aged 25 to 29 years) with a discounted ICER of 23,400 Euro/LYG. Adding Pap-Triage for HPV-positive women to this biennial HPV screening strategy results in a discounted

Table 5 – Summary of relevant sensitivity analyses results: Discounted incremental cost-effectiveness ratios[b] (Euro/LYG).

Strategy	Base-case	50% HPV test cost	200% HPV test cost	0% Discount rate	5% Discount rate	10% Discount rate	5% Screening adherence	75% Screening adherence	95% Screening adherence	20% Reduction in HPV-incidence	70% Reduction in HPV-incidence	90% Reduction in HPV-incidence
1. No Screening												
5. Pap, 5 years, Age: 20 years	2600	2500	2600	380	6200	37,600	Ext. dominated	3100	3500	3200	8300	21,000
4. Pap, 3 years, Age: 20 years	7100	Dominated	7200	Dominated	14,300	70,000	Ext. dominated	12,600	19,300	8600	20,800	53,900
12. HPV, 5 years, Age: 30 years; prior[a] Pap, 2 years	Ext. dominated	Ext. dominated	Dominated	2100	Ext. dominated	Ext. dominated	Ext. dominated	Ext. dominated	27,400	Ext. dominated	Ext. dominated	Ext. dominated
15. HPV + Pap, 5 years, Age: 30 years; prior[a] Pap, 2 years	Ext. dominated	Dominated	Ext. dominated	Ext. dominated	Ext. dominated	Ext. dominated	Dominated	Ext. dominated	Ext. dominated	Ext. dominated	Ext. dominated	Ext. dominated
11. HPV, 3 years, Age: 30 years; prior[a] Pap, 2 years	9000	5100	Dominated	3300	18,100	91,200	Ext. dominated	18,800	34,000	11,000	27,200	74,000
3. Pap, 2 years, Age: 20 years	Dominated	Dominated	15,700	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
18. HPV + Pap-Triage, 5 years, Age: 30 years; prior[a] Pap, 2 years	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
14. HPV + Pap, 3 years, Age: 30 years; prior[a] Pap, 2 years	Ext. dominated	Dominated	41,600	Ext. dominated	Ext. dominated	Ext. dominated	Ext. dominated	Ext. dominated	Ext. dominated	Ext. dominated	Ext. dominated	Ext. dominated
17. HPV + Pap-Triage, 3 years, Age: 30 years; prior[a] Pap, 2 years	Ext. dominated	Ext. dominated	Dominated	Ext. dominated	Ext. dominated	Ext. dominated	Ext. dominated	Ext. dominated	Ext. dominated	Ext. dominated	Ext. dominated	Ext. dominated
9. HPV, 5 years, Age: 30 years; prior[a] Pap, 1 year	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
10. HPV, 2 years, Age: 30 years; prior[a] Pap, 2 years	28,400	20,100	Dominated	12,500	48,000	158,300	1200	91,100	235,500	34,200	81,200	217,900
8. HPV, 3 years, Age: 30 years; prior[a] Pap, 1 year	Dominated	Dominated	Dominated	Ext. dominated	Dominated	Dominated	Dominated	Dominated	Dominated			
16. HPV + Pap-Triage, 2 years, Age: 30 years; prior [a] Pap, 2 years	93,700	73,400	Dominated	44,500	152,200	465,000	Dominated	270,500	631,000	107,700	221,400	562,900
13. HPV + Pap, 2 years, Age: 30 years; prior[a] Pap, 2 years	Dominated	Dominated	46,800	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
7. HPV, 2 years, Age: 30 years; prior[a] Pap, 1 year	Ext. dominated	Ext. dominated	Dominated	Dominated	Ext. dominated	Ext. dominated	Ext. dominated	Dominated	Dominated	Ext. dominated	Ext. dominated	Ext. dominated
2. Pap, 1 year, Age: 20 years	Ext. dominated	Ext. dominated	90,200	Ext. dominated	Ext. dominated	Ext. dominated	Ext. dominated	Ext. dominated	Dominated	Ext. dominated	Ext. dominated	Ext. dominated
6. HPV, 1 year, Age: 30 years; prior [a] Pap, 1 year	155,500	125,000	470,300	64,900	278,000	1,075,400	2200	683,700	2,216,000	187,000	441,100	1,170,700

HPV: Human papillomavirus, ICER: incremental cost-effectiveness ratio, Incr.: incremental, LYG: life year gained, Pap: Papanicolaou test.

[a] Age 20–29 years.

[b] Rounded values.

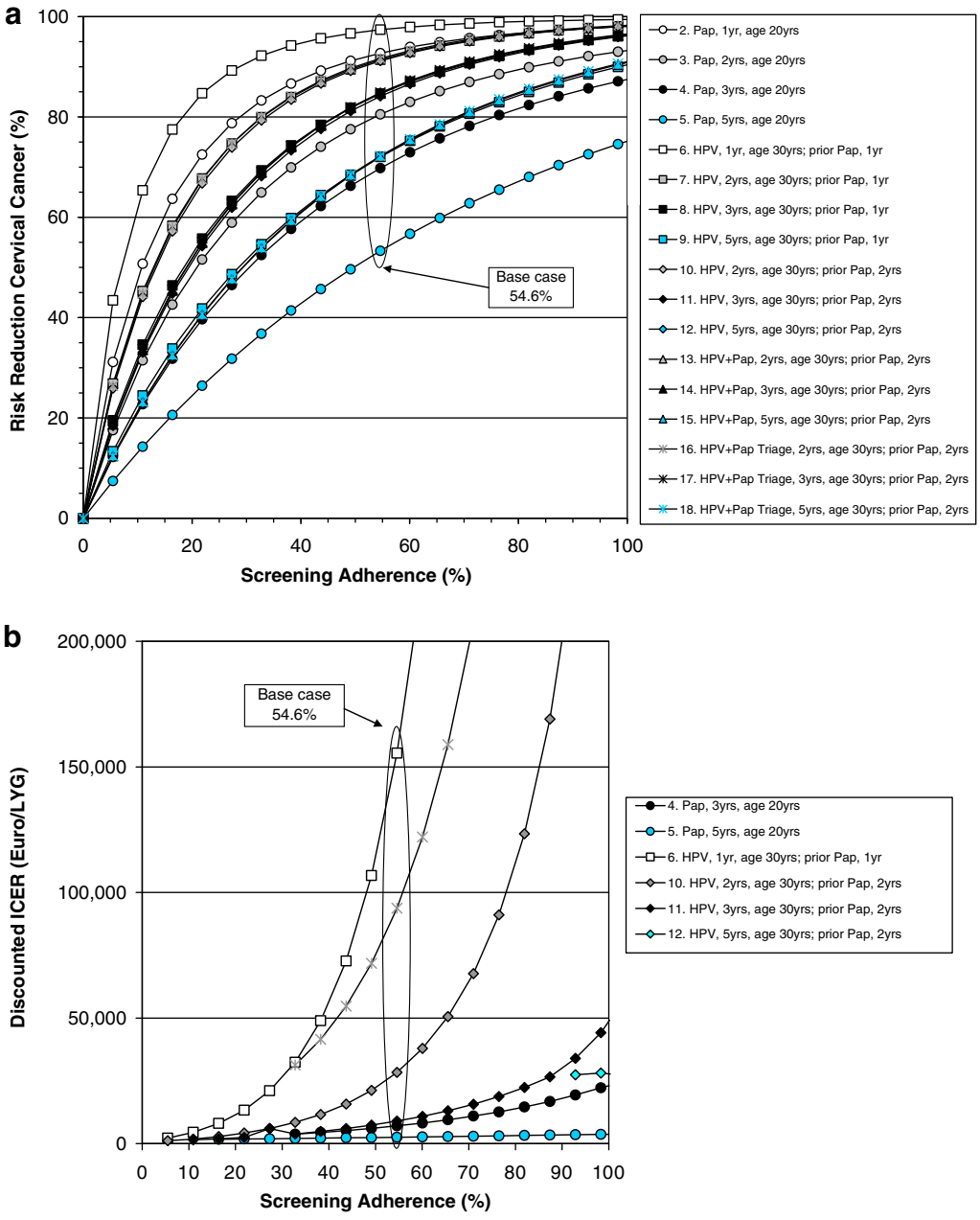

Fig. 4 – Sensitivity analyses on screening adherence: Risk reduction in cervical cancer (4a) and incremental cost-effectiveness ratios of non-dominated strategies (4b).

ICER of 87,200 Euro/LYG. Annual HPV screening in women aged 30 years and older (and biennial Pap screening in women aged 25 to 29 years) results in a discounted ICER of 123,500 Euro/LYG.

4. Discussion

Based on our analyses, primary HPV screening for cervical cancer is more effective and efficient than cytology when considering long-term outcomes such as life expectancy, risk of cervical cancer, and mortality due to cervical cancer. If HPV testing for primary cervical cancer screening were introduced in Germany, an extension of the screening interval to at least two years could be considered. Based on results from the base-case and sensitivity analyses of this study, biennial HPV screening in women aged 30 years and older with biennial Pap screening in women aged 25 to 29 years may be the optimal screening strategy, with a discounted ICER of 23,400 Euro/LYG. In the case of greater screening adherence or poorer Pap sensitivity, which is a likely circumstance in HPV vaccinated populations or in regions with low Pap screening performance, even HPV screening just once every three years could be safe and cost-effective.

Our findings are consistent with the results of other published modelling studies,[16,44–56] suggesting that HPV screening alone or in combination with cytology is effective and cost-effective when screening intervals are designated at every two or three years. However, most international studies

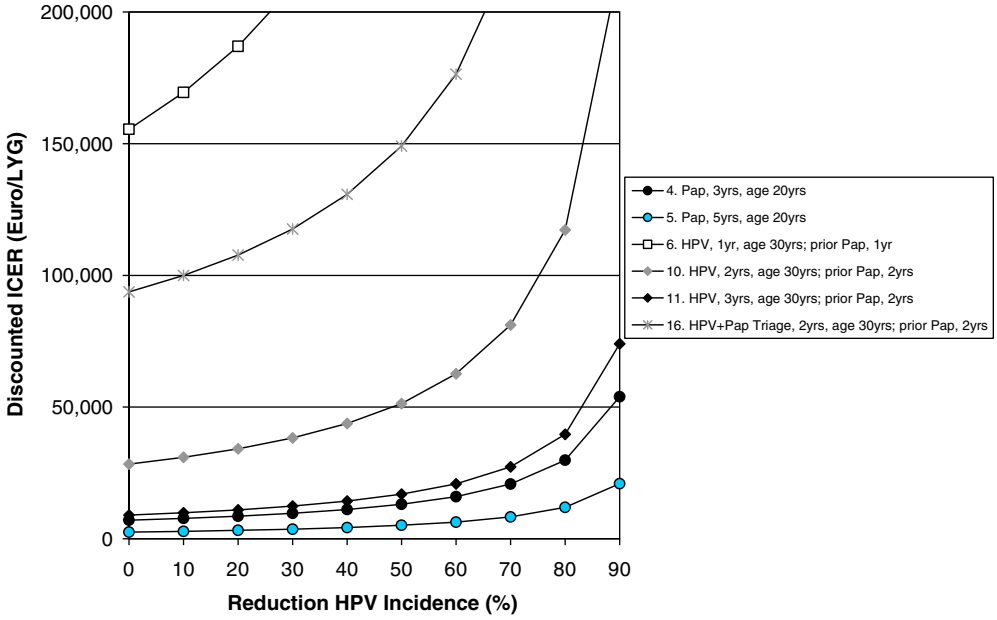

Fig. 5 – Sensitivity analysis on HPV-incidence: incremental cost-effectiveness ratios of non-dominated strategies.

did not include annual cytology in their evaluation.[57,58] Therefore, the results of most international models were of limited use in the German decision context. Only one modelling study[59] evaluated annual cytology and a strategy involving HPV testing and Pap-Triage for HPV-positive women. However, this study evaluated a combination of HPV and cytology screening and HPV screening with Pap-Triage for HPV-positive women, but not HPV testing alone. Triennial HPV testing in women aged 30 years and older with Pap-Triage for HPV-positive women preceded by cytology from age 21 to 29 years and from age 25 to 29 years was considered cost-effective as these strategies had discounted ICER of 78,000 and 53,000 USD/QALY gained, respectively.

A specific strength of our study is that we systematically combined the best available evidence from short-term clinical trials and meta-analyses with long-term observational studies and validated our decision model against real world German cancer registry data. We included resource utilisation, costs, and screening adherence data for the German health care context. This is a typical example of a situation in which clinical trials alone cannot offer a meaningful answer and must be complemented by decision-analytic modelling.[60]

Our study has several limitations. First, there were no empirical quality-of-life data, which could have been additionally implemented into the model. As such, long-term effectiveness was based on life expectancy instead of quality-adjusted life expectancy. Since screening results in a relatively small average gain in life expectancy, changes in quality-of-life due to psychological distress associated with the communication of screening results or adverse events of pre-cancer treatment may significantly affect the estimated cost-effectiveness ratios.[61,62] Second, due to lack of detailed data, age-specific adherence rates were assumed to be an average adherence in every screening round independent of prior screening history. No data on more complex adherence patterns were available. In sensitivity analyses, the screening adherence influenced the ICER of the different screening strategies. Third, our decision model did not consider heterogeneity of the population with respect to different HPV types and did not include separate states for women treated for precancerous lesions. However, the bias within the model is conservative or against HPV screening.[63–65] Fourth, modelling results evaluating the impact of an HPV vaccination on the screening programme are limited. As such, a model containing HPV type-specific health states is necessary and, in order to consider immunity and transmission dynamics, population based dynamic models are also needed.[63] Our sensitivity analysis on HPV-incidence suggests that HPV screening might be still cost-effective even in vaccinated populations with low HPV prevalence if performed at intervals of three years or greater. However, in vaccinated populations with a lower prevalence of precancerous lesions, the screening test accuracy may be lower as compared to non-vaccinated populations. This was not considered in our analysis. Fifth, clinical practice patterns were derived from guidelines and clinical expert estimations in order to incorporate more realistic health care data. Sixth, only direct medical costs from the perspective of the health care system were considered. Inpatient costs were underestimated, biasing the results against HPV screening. However, in sensitivity analyses, cost of cancer treatment had no influence on decision results.

In conclusion, based on our analyses, HPV-based primary screening for cervical cancer is more effective than cytology and can be considered cost-effective if performed at intervals of two years or greater. With the introduction of HPV-based primary screening in Germany, the screening interval could be extended to two years for women with average risk. Because our results were based upon a conservative modelling approach, the incremental effectiveness and cost-effectiveness of HPV screening may be even more favourable in reality and the screening interval may be extended to three years for women who are not at high risk. However, prior to

encouraging such an extension of the screening interval, the effect of these longer intervals on screening adherence and attendance at gynaecological checkups should be carefully considered. The implementation of an organised screening programme for quality-controlled introduction of HPV-screening and -vaccination with continued systematic outcomes evaluation is recommended.

Future research is needed to acquire evidence-based information on adherence patterns and the impact of screening results on quality-of-life. This research should include decision-analytic evaluation of the different, integrated screening strategies in mixed vaccinated and non-vaccinated populations and of different practice patterns with respect to diagnostic work-up and treatment after initial screening results.

Conflict of interest statement

All authors have completed a unified conflict of Interest declaration form and declare that no company had supported the submitted work. The Institution of G.S., P.S., N.M., U.S. had support from the German Agency for HTA at the German Institute for Medical Documentation and Information (DAHTA@DIMDI), an Institute of the German Federal Ministry of Health, for conducting the submitted work.

K.L., P.A., J.E., A.K., J.W. had no conflict of interests. The other authors declared the following relationships in the previous 3 years: (1) the Institution of G.S., P.S., N.M., U.S. received travel support from Qiagen for scientific meeting attendance in the previous 3 years and is currently being funded by the Institute of Quality and Efficiency in Health Care (IQWiG), Germany, for conducting an evidence-based benefit assessment of HPV-based screening; (2) T.M. received travel funding and honoraria for consultancy (Sanofi Pasteur); J.W. received payment for board membership (SPMSD), K.-U.P. received travel funding (Qiagen, MTM) and payment for advisory board membership (Roche Diagnostics, MTM); P.H. received honoraria for lectures (HPV test companies), and was involved in research studies from HPV-related companies. The authors declare no other relationships that may be relevant to the submitted work.

Funding

This health technology assessment was commissioned and funded by the German Agency for HTA at the German Institute for Medical Documentation and Information (DAHTA@DIMDI), an Institute of the German Federal Ministry of Health (Grant no. HTA 41-08). The authors had complete and independent control over study design, analysis and interpretation of data, report writing and publication, regardless of results.

Contributors

U.S. was the principle investigator and G.S. the co-investigator of this health technology assessment. U.S. was responsible for the overall supervision. G.S. coordinated and supervised the data extraction; she developed the decision-analytic model, performed the analyses and wrote the first draft of the submitted work. P.S. and N.M. performed literature search, and extracted model data. G.S., P.S., N.M., and U.S. interpreted model analyses results and discussed them with K.-U.P. and P.H. as well as with other experts from the panel. K.L., P.A., J.W. were responsible for the economic data calculations. K.-U.P. and J.E. supported the work with original data. All authors contributed to the writing of the final draft of the paper, participated in revising it and approved the final version. U.S. is the guarantor.

Licence agreement

Acknowledgements

We thank the members of our expert panel for providing us with original data for the model and important information as well as for the review and discussion of certain topics within the project: Prof. Dr. Dieter Hölzel, Munich Cancer Registry of the Munich Cancer Centre, Clinic Grosshadern, Ludwig-Maximilians-University, Munich, Germany; Dr. Roland Stabenow, Common Cancer Registry of the Federal States Berlin/Brandenburg/Mecklenburg-Vorpommern/Sachsen-Anhalt/Sachsen/Thüringen, Berlin, Germany; Dr. Christa Stegmaier, Saarland Cancer Registry, Saarbrücken, Germany; Prof. Dr. Achim Schneider, M.P.H, University Clinic Benjamin Franklin, Gynaecology, Campus Benjamin Franklin, Berlin; Prof. Dr. Hermann Brenner, MPH, Department of Epidemiology, German Centre for Research on Ageing (DZFA), University of Heidelberg, Heidelberg, Germany.; Dr. Stefanie Klug, M.P.H., Institute for Medical Biometry, Epidemiology and Informatics, University of Mainz, Germany.; Jeremy Goldhaber-Fiebert, Ph.D., Center for Health Policy/CPCOR, Stanford University, Stanford, CA, USA; Prof. Sue Goldie, MD, M.P.H., Harvard Center for Risk Analysis, Harvard School of Public Health, Boston, MA, USA.; Jane Kim, Ph.D., Harvard Center for Risk Analysis, Harvard School of Public Health, Boston, MA, USA.; Dr. Evan Myers, MD, Department of Obstetrics and Gynaecology, Center for Clinical Health Policy Research-Evidence-Based Practice Center and Division of General Internal Medicine, Duke University, Durham, NC, USA; Prof. Dr. Chris Meijer, Dept of Pathology Vrije Universiteit Medical centre, Netherlands; Prof. Dr. Ulrich Schenck, Institute for Cytology of the Bavarian Cancer Society, Technical University of Munich, Germany; PD Dr. Volker Schneider, International Academy for Cytology; Prof. Dr. Georg Marckmann, M.P.H., Institute for Ethics and History of Medicine, University of Tübingen, Germany.; Dr. Jörn Knöpnadel, National Department for Health Care Quality, National Association of Statutory Health Insurance Physicians, Berlin, Germany; Dr. Marc Arbyn, Scientific Institute of Public Health, Coordinator, Unit of Cancer Epidemiology Scientific Institute of Public Health; Prof. Dr. Jack Cuzick,

Cancer Research UK, Wolfson Institute of Preventive Medicine, London; Dr. Wilhelm Oberaigner, Institute for Clinical Epidemiology TILAK and Tumor Registry; Innsbruck, Austria and ONCOTYROL – Center for Personalized Cancer Medicine, Innsbruck, Austria.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2011.03.006.

REFERENCES

1. Anttila A, Ronco G. Description of the national situation of cervical cancer screening in the member states of the European Union. Eur J Cancer 2009.
2. Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG) e.V. Interdisziplinäre S2k-Leitlinie für die Prävention, Diagnostik und Therapie der HPV-Infektion und präinvasiver Läsionen des weiblichen Genitale: Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG) e.V. 2008.
3. Husmann G, Kaatsch P, Katalinic A, et al. Krebs in Deutschland 2005/2006: Häufigkeiten und Trends. Berlin: Robert Koch-Institut; 2010. URL: http://www.rki.de/cln_151/nn_199884/DE/Content/GBE/Gesundheitsberichterstattung/GBEDownloadsB/KID2010,templateId=raw,property=publicationFile.pdf/KID2010.pdf.
4. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens – Part B: biological agents. *Lancet Oncol* 2009;**10**(4):321–2.
5. Cuzick J, Arbyn M, Sankaranarayanan R, et al. Overview of human papillomavirus-based and other novel options for cervical cancer screening in developed and developing countries. *Vaccine* 2008;**26**(Suppl 10):K29–41.
6. Siebert U, Sroczynski G, Hillemanns P, et al. The German Cervical Cancer Screening Model: development and validation of a decision-analytic model for cervical cancer screening in Germany. *Eur J Public Health* 2006;**16**(2):185–92.
7. Beck JR, Pauker SG. The Markov process in medical prognosis. *Med Decis Making* 1983;**3**(4):419–58.
8. Hunink M, Glasziou P. *Decision making in health and medicine. Integrating evidence and values*. Cambridge, UK: Cambridge University Press; 2001.
9. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making* 1993;**13**(4):322–38.
10. Bearman DM, MacMillan JP, Creasman WT. Papanicolaou smear history of patients developing cervical cancer: an assessment of screening protocols. *Obstet Gynecol* 1987;**69**(2):151–5.
11. Canfell K, Barnabas R, Patnick J, Beral V. The predicted effect of changes in cervical screening practice in the UK: results from a modelling study. *Br J Cancer* 2004;**91**(3):530–6.
12. Hildesheim A, Schiffman MH, Gravitt PE, et al. Persistence of type-specific human papillomavirus infection among cytologically normal women. *J Infect Dis* 1994;**169**(2):235–40.
13. Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med* 1998;**338**(7):423–8.
14. Koutsky LA, Holmes KK, Critchlow CW, et al. A cohort study of the risk of cervical intraepithelial neoplasia grade 2 or 3 in relation to papillomavirus infection. *N Engl J Med* 1992;**327**(18):1272–8.
15. Legood R, Gray A, Wolstenholme J, Moss S. Lifetime effects, costs, and cost effectiveness of testing for human papillomavirus to manage low grade cytological abnormalities: results of the NHS pilot studies. *Bmj* 2006;**332**(7533):79–85.
16. Mandelblatt JS, Lawrence WF, Womack SM, et al. Benefits and Costs of Using HPV Testing to Screen for Cervical Cancer. *JAMA* 2002;**287**(18):2372–81.
17. Moscicki AB, Shiboski S, Broering J, et al. The natural history of human papillomavirus infection as measured by repeated DNA testing in adolescent and young women. *J Pediatr* 1998;**132**(2):277–84.
18. Munoz N, Kato I, Bosch FX, et al. Risk factors for HPV DNA detection in middle-aged women. *Sex Transm Dis* 1996;**23**(6):504–10.
19. Myers ER, McCrory DC, Nanda K, Bastian L, Matchar DB. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. *American Journal of Epidemiology* 2000;**151**(12):1158–71.
20. Syrjanen K, Kataja V, Yliskoski M, et al. Natural history of cervical human papillomavirus lesions does not substantiate the biologic relevance of the Bethesda System. *Obstet Gynecol* 1992;**79**(5(Pt 1)):675–82.
21. van Oortmarssen GJ, Habbema JD. Epidemiological evidence for age-dependent regression of pre-invasive cervical cancer. *Br J Cancer* 1991;**64**(3):559–65.
22. Vessey MP, Villard-Mackintosh L, McPherson K, Coulter A, Yeates D. The epidemiology of hysterectomy: findings in a large cohort study. *Br J Obstet Gynaecol* 1992;**99**(5):402–7.
23. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. Empfehlungen zur Diagnostik und Therapie der HPV-Infektion des weiblichen Genitale. Nr. 015/027 ed; 2003. leitlinien.net (09.10.2009).
24. Deutsche Krebsgesellschaft e. V. (DKG) und Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG). Interdisziplinäre S2-Leitlinie für die Diagnostik und Therapie des Zervixkarzinoms. Deutsche Krebsgesellschaft e. V. 2004.
25. Gemeinsamer Bundesausschuss (G-BA). Methoden zur Früherkennung des Zervixkarzinoms. (http://www.g-ba.de/downloads/40-268-107/2006-12-19_-KFU-HPV-Zervix_TGr.pdf). 2006.
26. Tumorzentrum München. Manual. Empfehlungen zur Diagnostik, Therapie und Nachsorge: Zervixkarzinom.: Tumorzentrum München an den Medizinischen Fakultäten der Ludwig-Maximilians-Universität und der Technischen Universität 2004.
27. Statistisches Bundesamt. Sterbetafel 2004-2006. www.-genesis.destatis.de/genesis/online/logon. 2007.
28. Statistisches Bundesamt. Statistisches Jahrbuch 2008. Wiesbaden: Statistisches Bundesamt 2008.
29. Schneider A, Hoyer H, Lotz B, et al. Screening for high-grade cervical intra-epithelial neoplasia and cancer by testing for high-risk HPV, routine cytology or colposcopy. *Int J Cancer* 2000;**89**(6):529–34.
30. Deutsche Krebsgesellschaft e. V. (DKG) und Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG). Interdisziplinäre S 2-Leitlinie für die Diagnostik und Therapie des Zervixkarzinoms.: Deutsche Krebsgesellschaft e. V. 2004.
31. Kerek-Bodden H, Altenhofen L, Brenner G, Franke A. Durchführung einer versichertenbezogenen Untersuchung zur Inanspruchnahme der Früherkennung auf Zervixkarzinom in den Jahren 2002, 2003 und 2004 auf der Basis von Abrechnungsdaten. Berlin: Zentralinstitut für die kassenärztliche Versorgung in der Bundesrepublik Deutschland 2008.
32. Arbyn M, Sasieni P, Meijer C, et al. Chapter 9: Clinical applications of HPV testing: a summary of meta-analyses. *Vaccine* 2006;**24**(Suppl 3). S3/78–89.

33. McCrory DC, Matchar DB. Evaluation of cervical cytology – systematic review. Agency for Health Care Research and Quality (AHRQ) 1999.
34. Nanda K, McCrory DC, Myers ER, et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. *Ann Intern Med* 2000;**132**(10):810–9.
35. Petry KU, Menton S, Menton M, et al. Inclusion of HPV testing in routine cervical cancer screening for women above 29 years in Germany: results for 8466 patients. *Br J Cancer* 2003;**88**(10):1570–7.
36. Mitchell MF, Schottenfeld D, Tortolero-Luna G, Cantor SB, Richards-Kortum R. Colposcopy for the diagnosis of squamous intraepithelial lesions: a meta-analysis. *Obstet Gynecol* 1998;**91**(4):626–31.
37. Bundesamt S. Mikrozensus Deutschland 2003. 2008; Available from: www.destatis.de.
38. Statistisches Bundesamt. Online-Auftritt des statistischen Bundesamtes. 2009.
39. Gold MR, Siegel JE, Russell LB, Weinstein MC. *Cost-Effectiveness in Health and Medicine*. New York: Oxford University Press Inc.; 1996.
40. IQWiG. Entwurf einer Methodik für die Bewertung von Verhältnissen zwischen Nutzen und Kosten im System der deutschen gesetzlichen Krankenversicherung. Version 2.0: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) 2009.
41. Eichler HG, Kong SX, Gerth WC, Mavros P, Jonsson B. Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? *Value Health* 2004;**7**(5):518–28.
42. McCabe C, Claxton K, Culyer AJ. The NICE cost-effectiveness threshold: what it is and what that means. *Pharmacoeconomics* 2008;**26**(9):733–44.
43. Rothgang H, Niebuhr D, Wasem J, Gress S. The National Institute for Clinical Excellence (NICE). *Gesundheitswesen* 2004;**66**(5):303–10.
44. Bidus MA, Maxwell GL, Kulasingam S, et al. Cost-effectiveness analysis of liquid-based cytology and human papillomavirus testing in cervical cancer screening. *Obstet Gynecol* 2006;**107**(5):997–1005.
45. Cuzick J, Beverley E, Ho L, et al. HPV testing in primary screening of older women. *Br J Cancer* 1999;**81**(3):554–8.
46. Goldie SJ, Kim JJ, Myers E. Chapter 19:Cost-effectiveness of cervical cancer screening. *Vaccine* 2006;**24**(Suppl 3): S3/164–170.
47. Goldie SJ, Kim JJ, Wright TC. Cost-effectiveness of human papillomavirus DNA testing for cervical cancer screening in women aged 30 years or more. *Obstetrics and Gynecology* 2004;**103**(4):619–31.
48. Kim JJ, Wright TC, Goldie SJ. Cost-effectiveness of alternative triage strategies for atypical squamous cells of undetermined significance. *Jama* 2002;**287**(18):2382–90.
49. Kim JJ, Wright TC, Goldie SJ. Cost-effectiveness of human papillomavirus DNA testing in the United Kingdom, The Netherlands, France, and Italy. *J Natl Cancer Inst* 2005;**97**(12):888–95.
50. Kulasingam SL, Kim JJ, Lawrence WF, et al. Cost-effectiveness analysis based on the atypical squamous cells of undetermined significance/low-grade squamous intraepithelial lesion Triage Study (ALTS). *J Natl Cancer Inst* 2006;**98**(2):92–100.
51. Kulasingam SL, Myers ER, Lawson HW, et al. Cost-effectiveness of extending cervical cancer screening intervals among women with prior normal pap tests. Obstet Gynecol. 2006;107(2 Pt 1):321-8.
52. Mittendorf T, Petry KU, Iftner T, Greiner W, von der Schulenburg JM. Economic evaluation of human papillomavirus screening in Germany. *Eur J Health Econ. [Article]* 2003;**4**(3):209–15.
53. Sherlaw-Johnson C, Philips Z. An evaluation of liquid-based cytology and human papillomavirus testing within the UK cervical cancer screening programme. *Br J Cancer* 2004;**91**(1):84–91.
54. van Ballegooijen M, n Marle ME, Warmerdam PG, et al. Present evidence on the value of HPV testing for cervical cancer screening: a model-based exploration of the (cost-)effectiveness. *Br J Cancer* 1997;**76**(5):651–7.
55. Berkhof J, Coupé V, Bogaards J, et al. The health and economic effects of HPV DNA screening in The Netherlands. *Int J Cancer* 2010;**127**(9):2147–58.
56. Vijayaraghavan A, Efrusy M, Mayrand M, Santas C, Goggin P. Cost-effectiveness of high-risk human papillomavirus testing for cervical cancer screening in Québec, Canada. *Can J Public Health* 2010;**101**(3):220–5.
57. Mittendorf T, Nocon M, Roll S, et al. HPV-DNA-Diagnostik zur Zervixkarzinomfrüherkennung. Schriftenreihe Health Technology Assessment, Bd 58. Köln: DAHTA@DIMDI; 2007.
58. Mühlberger N, Sroczynski G, Esteban E, et al. Cost-effectiveness of primarily human papillomavirus-based cervical cancer screening in settings with currently established Pap screening: a systematic review commissioned by the German Federal Ministry of Health. *Int J Technol Assess Health Care* 2008;**24**(2):184–92.
59. Goldhaber-Fiebert JD, Stout NK, Salomon JA, Kuntz KM, Goldie SJ. Cost-effectiveness of cervical cancer screening with human papillomavirus DNA testing and HPV-16, 18 vaccination. *J Natl Cancer Inst* 2008;**100**(5):308–20.
60. Siebert U. When should decision-analytic modeling be used in the economic evaluation of health care? [Editorial]. *Eur J Health Econ* 2003;**4**(3):143–50.
61. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, et al. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. *Lancet* 2006;**367**(9509):489–98.
62. McCaffery K, Waller J, Nazroo J, Wardle J. Social and psychological impact of HPV testing in cervical screening: a qualitative study. *Sex Transm Infect* 2006;**82**(2):169–74.
63. Goldie SJ, Goldhaber-Fiebert JD, Garnett GP. Chapter 18: Public health policy for cervical cancer prevention: the role of decision science, economic evaluation, and mathematical modeling. *Vaccine* 2006;**24**(Suppl 3). S3/155–163.
64. Goldie SJ, Kuntz KM. A potential error in evaluating cancer screening: a comparison of 2 approaches for modeling underlying disease progression. *Med Decis Making* 2003;**23**(3):232–41.
65. Siebert U, Zietemann V, Sroczynski G. [Pharmacogenomics Bias – Systematic Distortion of Study Results by Genetic Heterogeneity]. *GMS Health Technol Assess. [HTA-Kurzfassung]* 2008;**4**(Doc03):1–7.
66. Cuzick J, Clavel C, Petry KU, Meijer CJ, Hoyer H, Ratnam S, et al. Overview of the European and North American studies on HPV testing in primary cervical cancer screening. *Int J Cancer* 2006;**119**(5):1095–101.