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IJC
International Journal of Cancer

The health and economic effects of HPV DNA screening in the Netherlands

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We studied the health and economic effects of human papillomavirus (HPV) DNA testing in cervical screening using a simulation model. The key data source was a Dutch longitudinal screening trial. We compared cytological testing with repeat cytology (for borderline/mildly abnormal smears) to HPV testing with cytology triage (for HPV-positive smears), combination testing (combined HPV and cytology) and cytological testing with HPV triage (for borderline/mildly abnormal smears). We varied the screening interval from 5 to 10 years. The main outcome measures were the number of cervical cancer cases, the number of quality-adjusted life years (QALYs), and the incremental cost-effectiveness ratio (ICER). The base-case estimates were accompanied with ranges across 118 calibrated parameter settings (calibration criteria: cervical intraepithelial neoplasia 2/3, cancer and mortality rates). In comparison to 5-yearly cytology, 5-yearly HPV testing with cytology triage gave a reduction in the number of cancer cases of 23% (range, 9–27%). The reduction was 26% (range, 10–29%) for combination testing and 3% (range, −1 to 8%) for cytology with HPV triage. For strategies with primary HPV testing, the model also estimated a reduction in cancer cases when the screening interval was extended to 7.5 years. Five-yearly cytology with HPV triage and 5 to 7.5-yearly HPV testing with cytology triage were cost effective for the base-case settings and the majority of calibrated parameter settings (ICER below Dutch willingness-to-pay threshold of €20,000/QALY). Our model indicates that HPV testing with cytology triage is likely to be cost effective. An extension of the screening interval may be considered to control costs.

Since the implementation of screening, the incidence of cervical cancer has markedly decreased in developed countries. A further reduction is anticipated in the future as vaccines are now available that protect against infection with HPV types 16 and 18.[1–3] Because the HPV vaccines only have a prophylactic effect, they are expected to be the most effective when given before the start of sexual activity. For older nonvaccinated women, screening will remain the most important instrument for cervical cancer prevention.

Key words: human papillomavirus, cervical cancer, screening, mathematical model, cost-effectiveness
Conflict of interest: C.J.M. is a member of the advisory board of Qiagen. P.J.S. has provided occasional consultation to Roche and Gen-Probe.
Grant sponsor: The Netherlands Organisation for Health Research and Development; **Grant number:** ZONMW grant 50-50110-96-474
DOI: 10.1002/ijc.25211
History: Received 22 Jun 2009; Accepted 7 Jan 2010; Online 28 Jan 2010
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The primary screening modality presently used in cervical screening is the Pap test. Although this test has formed the basis for successful screening programs (*e.g.*, in the UK, Finland, Sweden and The Netherlands), its sensitivity is limited and the use of a more sensitive test such as the human papillomavirus (HPV) DNA test[4,5] may lead to a further reduction in the cervical cancer incidence. Several longitudinal trials have been started in the last 10 years, comparing the Pap test to the HPV test or a combination of both tests.[6–11] The first analyses have demonstrated that HPV testing in women more than 30 years of age detects more high-grade cervical intraepithelial neoplasia or cancer (CIN2+) than cytology and that the CIN2+ risk is lower after an HPV-negative result at the previous screening round than after negative cytology. These results suggest that an extension of the screening interval may be considered when HPV testing is implemented.[8,12] The trials have also shown that HPV testing is likely to yield an increase in the colposcopy referral rate. This provides another reason to reassess the length of the screening interval upon implementation of HPV testing.

The main aim of this study is to predict the effect of HPV testing in combination with an increase in the screening interval on the number of cervical cancer cases, the number of quality-adjusted life years (QALYs) and costs. For this purpose, we incorporated the results of the Population-Based

SCreening study Amsterdam (POBASCAM) trial[12] in a mathematical Markov model for cervical disease.[13,14] Model parameters that could only be weakly identified from available data sources were varied and calibrated against CIN2+ detection rates, cervical cancer incidence rates and mortality rates. To inform decision makers, we performed cost-effectiveness analyses.

Material and Methods

Base-case settings

We constructed a Markov model of the natural history of high-risk HPV infections and cervical cancer. In the model, predictions were obtained *via* microsimulation of health states at 6-month intervals. We made the following assumptions. Infection with high-risk HPV is necessary to develop CIN2+, whereas CIN grade 1 (CIN1) may also be caused by low-risk HPV.[15,16] Spontaneous regression of the HPV infection is possible and does not depend on age.[17,18] After viral clearance, women are susceptible to a new infection of the same HPV genotype. This means that type-specific clearance does not lead to natural immunity against reinfection with the same type. The progression rate from HPV infection to CIN grade 3 (CIN3) is age-dependent and 2.5-fold higher above age 30 than at young age.[19] Regression from CIN3 to state Well is possible. The probability of progressing from state CIN3 to cervical cancer increases with the duration of CIN3[20–23] and as a consequence the mean time to progress from CIN3 to cancer is longer than the mean time to regress from CIN3 to Well. We modeled the increasing cancer hazard by formulating a model where CIN3 progresses to cancer *via* states CIN3 (II) and CIN3 (III). The data used for estimating the disease parameters in the base model are shown in Table 1.[6,12,14,17–22,24–41] A key data source was the POBASCAM trial, a longitudinal screening trial of 44,102 women receiving either HPV DNA testing with cytological testing (intervention group) or cytology only (control group).[6,12,24] HPV DNA testing was performed by GP5+/6+ PCR[41] and conventional glass slides were used for cytological examination. The HPV infection clearance and progression rates in the model were obtained directly from the POBASCAM study[18,25] and the age-specific HPV incidence rates were set such that the age-specific HPV prevalences in the model and POBASCAM study[26] were equal.

The model accurately reproduced the age-specific CIN2/3 detection rates in the POBASCAM study (5-year age cohorts, cytology arm, goodness-of fit $\chi^2(7) = 10,632$, p-value $= 0.16$). The model gave an acceptable fit to the age-specific cancer incidence rates reported in The Netherlands in 1999–2003[35] (Fig. 1, dotted line and bold black lines).

Calibrated models

Some features of our model could be only weakly identified from our data but may have a substantial impact on the results: (*i*) the durations between the health states, (*ii*) the screening participation and the association with high-risk groups and (*iii*) the absolute sensitivity of colposcopy/biopsy and screening. We varied model parameters that were related to (*i*), (*ii*) or (*iii*) and calibrated the predictions on observed age-dependent CIN2+ detection rates, cancer incidence rates and mortality rates.

Starting from the base-case setting (Table 1), we constructed 9 new parameter settings denoted by A1–A9. The mean duration from HPV infection to CIN3 was increased from 3 (base-case setting) to 4 years by setting the probability of directly switching from HPV infection to CIN3 (without visiting CIN1 and CIN2) to 0 (A1). The mean duration from HPV infection to CIN3 was further increased to 6 years by multiplying the probabilities of the transitions CIN1-CIN2, CIN1-Well, CIN2-CIN3 and CIN2-Well by 0.5 (A2). The mean duration between CIN3 and cancer FIGO1 was lowered from 15 (base-case setting) to 11 years by multiplying the probability of the transition CIN3(III)-cancer FIGO1 by 2 (A3) and was increased to 23 years by multiplying the probability of the transition CIN3(III)-cancer FIGO1 by 0.5 (A4). The mean FIGO1 to FIGO2+ duration was increased from 10 (base-case setting) to 15 years by multiplying the FIGO1 – FIGO2+ transition probability by 0.67 (A5). The proportion of screening refusers was increased from 10 (base-case setting) to 20% (A6). A negative association between screening participation and the risk of HPV infection was incorporated by multiplying the base-case risk of HPV infection by 3 in screening refusers[42] (A7). The sensitivity of colposcopy/biopsy was lowered from 100% (base-case setting) to 75% for CIN1/2, 85% for CIN3 and 95% for cancer[43] (A8). The absolute sensitivities of cytology and the HPV DNA test (base-case settings) were multiplied by 90% (A9).

Parameter settings A1–A9 may poorly fit the CIN2+ detection, cancer incidence and mortality rates because they have been obtained by changing parameter values without further calibration. We tuned the parameters as follows. For settings A1–A4 and A6–A9, the probabilities of transitions CIN0-CIN1 and CIN3-CIN3(II) were tuned to improve the fit of the model. For parameter setting A5, the FIGO1 symptom probability was used as a tuning parameter. The tuning process was guided by a calibration lack-of-fit measure. This measure was based on the following relative sum of squares

$$\frac{\sum_i (\hat{y}_i - y_{\mathrm{obs},i})^2}{\sum_i (\hat{y}_{\mathrm{base},i} - y_{\mathrm{obs},i})^2}$$

where $y_{\mathrm{obs},i}$ is the observed data of the i-th age cohort, $\hat{y}_{\mathrm{base},i}$ is the prediction obtained under the base-case parameter setting and $\hat{y}_i$ is the prediction under A1–A9. We formulated separate relative sums of squares for the CIN2+ rate (POBASCAM study, age 30–60 years, cytology arm), the cancer incidence rate in The Netherlands (data 1999–2003, age 10–80 years) and the mortality rate in The Netherlands (data 1999–2003, age 10–80 years), and the calibration lack-of-fit

Table 1. Model parameters, screening characteristics, quality of life and costs

Natural history parameters	Transition probability (1 cycle = 6 months)	References
Progression from		6,12,17–21,23–35
Well to HPV infection[1]	0.003–0.1	
HPV infection directly to CIN3[1]	0.002–0.010	
HPV infection to CIN1[1]	0.02–0.10	
CIN1 to CIN2	0.5/3	
CIN2 to CIN3	0.5/3	
CIN3 to CIN3 (II)	0.4/2	
CIN3 (II) to CIN3 (III)	0.5/14	
CIN3 (III) to cancer FIGO1	1/14	
Cancer FIGO1 to FIGO2+	0.6/12	
Well to HPV-negative lesion	0.003	
Regression from		
HPV infection to Well	0.36	
CIN1 to Well	0.5/3	
CIN2 to Well	0.5/3	
CIN3 to Well	0.6/2	
CIN3 (II) to Well	0.5/14	
CIN3 (III) to well	0	
HPV-negative lesion to Well	0.6	
Clinical manifestion of		
Pre-cancer	0	
Cancer FIGO1	0.033	
Cancer FIGO2+	0.3	
Screening characteristics	**Parameter values**	**References**
Proportion of women participating in screening	90%	12,23,36,37
Attendance rate per screening round	80%	
Attendance rate at repeat testing	90%	
Proportion of abnormal cytology in		
CIN0, HPV−	0.02	
CIN0, HPV−, 6 months after abnormal cytology	0.10	
CIN0, HPV+	0.15	
CIN1	0.40	
CIN2	0.50	
CIN3	0.75	
Proportion of HPV-positive samples in		
Women with HPV infection	94%	
Women without HPV infection	0%	
Sensitivity of colposcopically directed biopsy	100%	
Utilities	**Quality of life (duration)**	
Positive screening test result	0.97 (1 month)	38–40
CIN1 treatment	0.97 (6 months)	
CIN2/3 treatment	0.93 (6 months)	
CIN2/3 residual	0.93 (6 months)	

Table 1. Model parameters, screening characteristics, quality of life and costs (Continued)

Natural history parameters	Transition probability (1 cycle = 6 months)	References
Detection of FIGO1	0.65 (6 months)	
Detection of FIGO2+	0.55 (6 months)	
Follow-up FIGO1	0.97 (4.5 years)	
Follow-up FIGO2+	0.85 (4.5 years)	
Costs	**Costs (€) (index 2007)**	
Screening		14,34,36
Laboratory costs: first (conventional) cytology test	21.00 per sample	
Repeat cytology test	25.60 per sample	
HPV test (GP5+/6+ PCR[41])	33.10 per sample	
General Practitioner costs: baseline test(s)	11.30 per visit	
Repeat tests	21.20 per visit	
Regional organization costs	10.80 per visit	
Invitation/evaluation costs	5.90 per invitation	
Traveling/time costs	7.80 per visit	
Diagnosis, treatment, follow-up		
CIN0	344	
CIN1	1,474	
CIN2	1,707	
CIN3	1,856	
FIGO stage 1	9,192	
FIGO stage 2+	10,830	
Palliative care	43,525 $\leq$ 50 years	
	31,024 50 – 70 years	
	13,206 $\geq$ 70 years	

[1]The reported ranges reflect the variation with age.

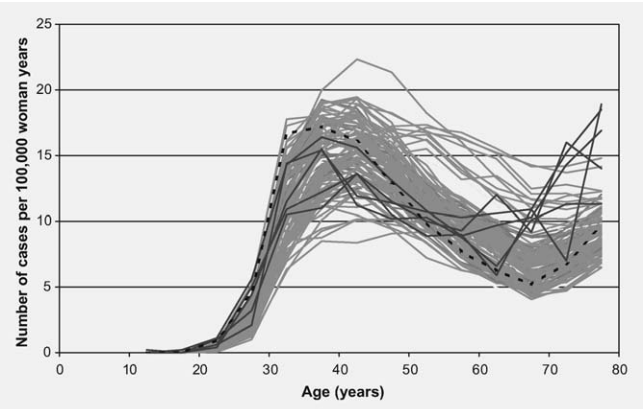

Figure 1. Cancer incidence rates: base-case model rates (dotted), rates under 118 calibrated parameter settings (grey) and incidence rates in the Netherlands in years 1999–2003 (black).

was defined as the maximum of the 3 relative sums of squares. Five-year age cohorts were used for the calculation of the relative sum of squares. For each parameter setting A1–A9, a grid search identified the values of the tuning parameters for which the calibration lack-of-fit was minimized.

After having tuned A1–A9, we had 9 calibrated parameter settings $\hat{\theta}_1, \ldots, \hat{\theta}_9$ in addition to base-case setting $\hat{\theta}_0$. Subsequently, we created new parameter settings $\tilde{\theta}$ by applying $\tilde{\theta} = \left(\frac{\hat{\theta}_1}{\hat{\theta}_0}\right)^{\delta_1} \times \cdots \times \left(\frac{\hat{\theta}_9}{\hat{\theta}_0}\right)^{\delta_9} \times \hat{\theta}_0$ with δ_i ($i = 1, \ldots, 9$) a 0–1 variable. The total number of parameter settings was $2^9 = 512$ by setting each δ_i equal to 0 and 1. In a final calibration step, we only accepted settings $\tilde{\theta}$ for which the calibration lack-of-fit was less than 1.5. In general, this means that a parameter setting is accepted only if it is not more than 50% worse than the base-case setting in predicting the CIN2+ detection rates, cancer rates and mortality rates. One hundred and eighteen parameter settings were accepted. Figure 1 gives an impression of the variation in cancer incidences among the 118 calibrated parameter settings (gray lines).

Baseline and follow-up results of the POBASCAM trial

To check whether the model could reproduce the results from the POBASCAM trial,[12] we programed the

POBASCAM intervention and control strategy in our model. The CIN3+ rate ratios (intervention versus control group) estimated by the model (base-case parameter setting) were 1.29 at the baseline round and 0.66 at the subsequent round. The ranges over the calibrated parameter settings were 1.20–1.32 at the baseline round and 0.59–0.86 at the subsequent round. The corresponding CIN3+ rate ratios in POBASCAM were 1.70 (95% CI: 1.15–2.51) and 0.45 (95%CI: 0.28–0.72).

HPV testing strategies

We compared (*i*) the current Dutch cytological screening strategy to (*ii*) HPV testing with cytological triage for HPV positive women, (*iii*) combination testing (combined HPV and cytology testing as primary screening instrument) and (*iv*) cytological testing with HPV triage for borderline/mild dyskaryosis (equivalent to ASC-US/LSIL[44]).

The current strategy (*i*) is to screen women aged 30–60 years at 5 year intervals by cytology. Colposcopy is recommended if cytology is at least moderate dyskaryosis and repeat cytology if cytology is borderline/mild dyskaryosis. For HPV testing with cytology triage, strategy (*ii*), colposcopy is recommended if the sample is HPV positive and cytologically abnormal (borderline/mild dyskaryosis or worse) and repeat cytology is recommended if the sample is HPV positive and cytologically normal. For the combination testing strategy (*iii*), colposcopy is recommended if cytology is at least moderate dyskaryosis or if the sample is HPV positive and cytologically abnormal. Repeat cytology is recommended if the sample is HPV positive and cytologically normal or if the sample is HPV negative and cytology is borderline/mild dyskaryosis. Strategies (*i*), (*ii*) and (*iii*) have the same protocol for repeat testing. Cytological testing is performed at 6 and 18 months with a recommendation for colposcopy after an abnormal test. If a woman has a screening outcome different from the outcomes described earlier, the woman is referred for routine screening. Cytology with HPV triage strategy (*iv*) does not have repeat testing. The difference between (*iv*) and current cytological screening protocol (*i*) is that women with borderline/mild dyskaryosis are referred for either colposcopy or routine screening based on the HPV triage test. If the triage test is cytology (strategy *ii*), a glass slide for cytological examination is cocollected. If the triage test is HPV DNA (strategy *iv*), a women is reinvited for HPV testing.[14] We set the number of screening rounds for HPV testing strategies at 7, 6, 5 and 4 corresponding to screening intervals of 5, 6, 7.5 (2×7 and 2×8 years) and 10 years, respectively.

Costs and health state utilities

The unit costs and health state utilities are presented in Table 1. We included traveling and production loss costs (societal perspective) and indexed all costs and effects at year 2007. The costs of screening, diagnosis and treatment have already been published[14,34,36] and were updated using the consumer price index. We obtained the utilities from international publications.[38–40]

Analyses

We analyzed a simulated cohort of 4,000,000 women. We simulated the health of each woman from 10 till 100 years of age and counted health outcomes and costs from 30 years of age. The outcomes include the number of cervical cancers, the number of detected CIN2+, the number of colposcopies, costs, the number of QALYs obtained by summing health utilities over time and the incremental cost-effectiveness ratio (ICER) of a new strategy compared to the current strategy (5-yearly cytology). The ICER is the ratio of the difference in costs and the difference in QALYs. For computing the ICERs, we discounted QALYs and costs at the Dutch rates of 1.5% and 4%.[45] A strategy was considered cost effective if the ICER did not exceed the Dutch willingness-to-pay threshold of €20,000/QALY.

We calculated ranges of the model estimates across 118 calibrated parameter settings to illustrate the uncertainty around the base-case estimates. Furthermore, in univariate sensitivity analyses, we studied the effect of varying one parameter on the ICER while holding the other parameters at their base-case settings. Starting from the base-case parameter setting, we recalculated the ICERs after having changed the CIN2/3 treatment costs (base-case setting ± €500), the cancer treatment costs (base-case setting ± €5,000), the HPV testing costs (base-case setting ± €10), the sensitivity and specificity of the HPV test to detect an HPV infection (base-case setting −3%[24]), the guidelines for costs calculation (1, no discounting, 2, UK guidelines: 3.5% discounting for costs and effects; health care costs only) and the utilities [life years (LYs) instead of QALYs].

We also carried out an incremental cost-effectiveness analysis.[46] We included a strategy in the incremental analysis only if it did not do worse than 5-yearly cytological screening in terms of QALYs. We first ordered the included strategies according to costs. Next, we selected the nondominated strategies. A strategy was nondominated if no weighted combination of other strategies existed for which the same number of QALYs could be achieved at lower costs. In the incremental analysis, we calculated the ICERs by taking the ratio of the differences in costs and in QALYs for 2 adjacent nondominated strategies.[46] To avoid confusion, we denoted the ICER comparing a nondominated strategy to 5-yearly cytology by $ICER_1$ and denoted the ICER comparing a nondominated strategy to the adjacent nondominated, less expensive strategy by $ICER_2$.

Results

Health effects

The estimated effect of HPV testing on the number of cancer cases is presented in Figure 2. Replacing current screening (5-yearly cytology) by HPV screening with cytology triage led to a percentual reduction in the number of cancer cases of 23% (range, 9–27%). The reduction in number of cancer cases was 26% (range, 10–29%) for combination testing and

Table 2. New strategies versus 5-yearly cytology: changes in undiscounted costs (€ per woman) under base-case parameter setting

Screening strategy	Screening interval (years)	Screening costs	Diagnosis and treatment costs	Indirect costs	Total costs
Cytology only	5	Current strategy			
HPV with cytology triage	5	57.8 (56.8; 58.2)	17.5 (17.5; 57.6)	4.4 (4.1; 7.3)	79.7 (79.7; 121.3)
	6	17.1 (16.1; 17.3)	14.4 (13.3; 47.3)	−1.5 (−1.8; 0.8)	30.0 (28.7; 64.1)
	7.5	−22.9 (−23.5; −22.6)	12.7 (9.7; 40.1)	−7.4 (−7.6; −5.7)	−17.7 (−20.8; 10.5)
	10	−64.7 (−65.4; −64.3)	16.8 (9.6; 31.4)	−13.9 (−14.1; −12.9)	−61.8 (−69.1; −46.9)
Combined HPV with cytology	5	151.8 (148.1; 152.2)	23.4 (23.4; 64.2)	6.7 (6.5; 9.5)	181.9 (180.1; 223.5)
	6	97.4 (94.3; 97.7)	17.0 (17.0; 52.8)	0.4 (0.2; 2.7)	114.8 (114.8; 151.3)
	7.5	44.1 (41.6; 44.2)	14.9 (13.9;41.4)	−5.7 (−6.0; −4.0)	53.2 (52.2; 79.0)
	10	−11.5 (−13.3; −11.3)	16.6 (10.3; 32.9)	−12.5 (−12.9; −11.6)	−7.5 (−13.7; 8.0)
Cytology with HPV triage	5	−5.1 (−5.5; −2.8)	5.3 (3.3; 19.5)	−0.1 (−0.2; 1.7)	0.1 (−1.4; 18.0)
	6	−37.3 (−37.9; −35.1)	8.9 (2.0; 15.8)	−5.8 (−5.8; −4.4)	−34.2 (−41.1; −24.1)
	7.5	−69.0 (−69.4; −66.8)	13.7 (1.9; 19.2)	−11.3 (−11.5; −10.3)	−66.6 (−78.5; −59.4)
	10	−102.0 (−102.4; −99.8)	28.8 (3.7; 31.8)	−17.4 (−17.9; −16.6)	−90.6 (−113.5; −85.6)

Values in parenthesis indicate cost ranges across 118 calibrated parameter settings.

3% (range, −1 to 8%) for cytology with HPV triage. Both HPV screening with cytology triage and combination testing showed a cancer reduction for screening intervals of 5, 6 and 7.5 years. Cytology with HPV triage showed an increase in the number of cancer cases for screening intervals more than 5 years. The results were similar for number of deaths from cervical cancer (not shown).

In comparison to 5-yearly cytology, the number of CIN2+ showed a percentual increase of 31% (range, 23–48%) for 5-yearly HPV with cytology triage, 34% (26–52%) for 5-yearly combination testing and 1% (−1 to 8%) for 5-yearly cytology with HPV triage. The number of CIN2+ per colposcopy referral showed a decrease of 21% (range, 18–25%) for 5-yearly HPV with cytology triage, 30% (22–32%) for 5-yearly combination testing, and 10% (9–14%) for 5-yearly cytology with HPV triage. When extending the interval to 10 years, the reductions in the number of CIN2+ per colposcopy referral were 14% (13–16%) for HPV with cytology triage, 21% (19–22%) for combination testing and 5% (3–11%) for cytology with HPV triage.

Economic effects

The change in costs per woman obtained when replacing current cytological screening by a strategy with HPV testing is presented in Table 2. HPV testing with cytology triage led to cost savings for screening intervals 7.5 to 10 years and combination testing led to cost savings for screening interval 10 years. Implementation of 5-yearly cytology with HPV triage was approximately cost neutral. The diagnosis and treatment costs of HPV testing with cytology triage and combination testing showed a nonmonotonic trend with increasing intervals. The reason for this is that the rise in cancer treatment costs outweighed savings from diagnosing and treating fewer CIN2/3.

The results of the cost-effectiveness analysis for the base-case parameter setting are presented in Figure 3*a*. The change in discounted costs (vertical axis) is plotted against the change in discounted QALYs (horizontal axis) obtained by comparing a new strategy to 5-yearly cytology. Strategies in the South-East quadrant as well as strategies in the North-East quadrant that fall below the willingness-to-pay threshold line are cost-effective ($ICER_1 \leq$ €20,000/QALY) HPV testing with cytology triage and combination testing were cost effective for intervals 5, 6 and 7.5 years. Cytology with HPV triage was cost effective for interval 5 years. The estimates of $ICER_1$ are also presented in Table 3 with the cost-effective strategies given in boldface. For strategies with a low $ICER_1$ for the base-case parameter setting, the predicted number of QALYs and costs under 118 calibrated parameter settings are presented in Figure 3*b*. The $ICER_1$s of combination testing strategies exceeded the willingness-to-pay threshold of €20,000/QALY for the majority of parameter settings. The $ICER_1$s of 5-yearly cytology with HPV triage and 5 to 7.5-yearly HPV testing with cytology triage were below the threshold for the majority of parameter settings.

In Table 3, the results of univariate sensitivity analyses are presented. Cost-effective strategies are given in boldface. Five to 7.5-yearly HPV testing with cytology triage and 5-yearly cytology with HPV triage were cost effective for all situations. Note that lowering the HPV test sensitivity by 3% had a small, inconsistent effect on $ICER_1$ because the decrease in

Table 3. ICER comparing a new strategy to 5-yearly cytology ($ICER_1$)

			Change in CIN1/3 costs		Change in cancer treatment costs		Change in HPV testing costs		HPV test features		Discount rates		
Screening strategy	Interval (years)	Base-case	−€500	+€500	−€5000	+€5000	−€10	+€10	Change in Spec −3%	Change in Sens −3%	0% for effects and costs	3.5% for effects and costs, health care costs only	LY instead of QALY
HPV with cytology triage	5	**9,305**	**7,632**	**10,978**	**9,823**	**8,787**	**5,397**	**13,213**	**10,842**	**9,335**	**6,728**	**17,907**	**9,088**
	6	**6,138**	**4,326**	**7,950**	**6,682**	**5,595**	**1,646**	**10,630**	**7,769**	**6,417**	**3,360**	**12,363**	**5,985**
	7.5	**878**	**<0**	**3,227**	**1,506**	**249**	**<0**	**7264**	**2,894**	**443**	**<0**	**3,002**	**844**
	10	–[1]	–	–	–	–	–	–	–	–	–	–	–
Combined HPV with cytology	5	**16,303**	**14,658**	**17,948**	**16,829**	**15,778**	**12,868**	**19,739**	**17,883**	**15,426**	**13,581**	32,075	**15,940**
	6	**12,444**	**10,896**	**13,992**	**12,948**	**11,939**	**9,063**	**15,825**	**13,865**	**12,227**	**9,826**	24,823	**12,240**
	7.5	**11,088**	**9,161**	**13,016**	**11,660**	**10,517**	**6,610**	**15,567**	**12,916**	**10,299**	**7,015**	23,362	**10,840**
	10	22,452	**102**	44,801	25,125	**19,778**	**<0**	89,416	107,770	**9512**	<0		**13,659**
Cytology with HPV triage	5	**3,955**	**78**	**7,077**	**4,512**	**3,397**	**2,846**	**5,064**	**4,055**	**1,802**	**118**	**5,660**	**3,785**
	6–10	–	–	–	–	–	–	–	–	–	–	–	–

ICERs were calculated for the base-case parameter setting and settings which differed from the base-case with regard to CIN1-3 treatment costs, cancer treatment costs, HPV testing costs, specificity and sensitivity of the HPV test (to detect an HPV infection), discount rates or utilities. Cost-effective strategies are given in bold ($ICER_1 \leq$ €20,000/QALY).
[1]Change in number of QALYs < 0.

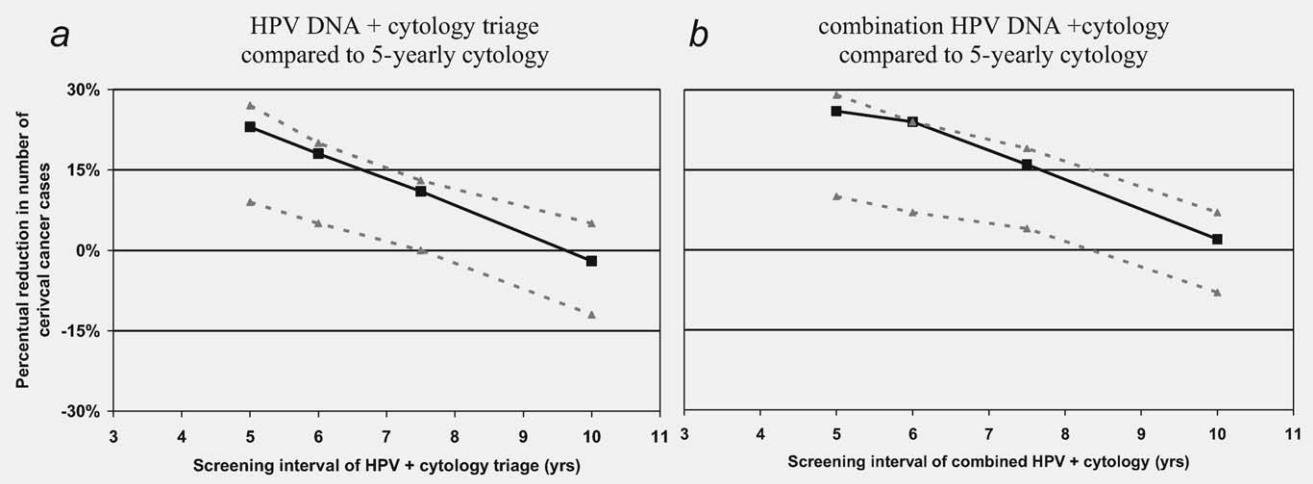

Figure 2. Percentual reduction in the number of cervical cancer cases obtained when replacing 5-yearly cytology by HPV with cytology triage (panel a) and combined HPV with cytology (panel b); base-case estimate (black) and range of estimates across calibrated parameter settings (grey).

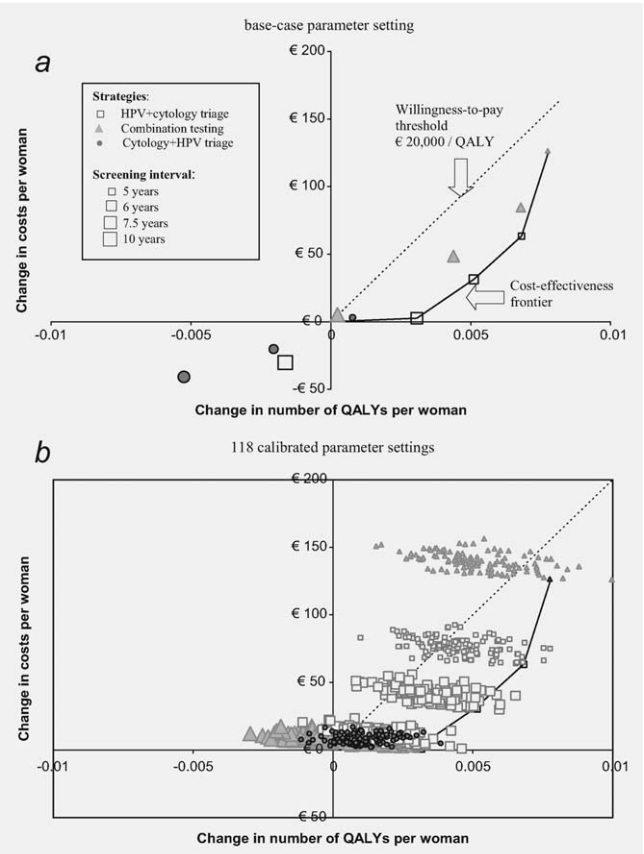

Figure 3. Cost-effectiveness plane: change in costs and number of QALYs per woman obtained when comparing a new strategy to 5-yearly cytology. Discount rates: 1.5% for QALYs and 4% for costs; base-case outcomes (panel a) and outcomes under 118 calibrated parameter settings (panel b).

number of QALYs was accompanied by a decrease in costs. In additional analyses, we estimated that a zero gain in number of QALYs was obtained for 7.5-yearly HPV testing (with cytology triage) when the HPV test sensitivity was 86% and a zero gain was obtained for 6-yearly HPV testing when the HPV test sensitivity was 78%. We also calculated that if the 3 percent decrease in HPV test sensitivity was accompanied with a 5 percent increase in sensitivity of cytology,[24] the $ICER_1$s of 5 to 7.5 yearly HPV testing with cytology triage, 6 and 7.5 yearly combination testing, and 5 yearly cytological testing with HPV triage would stay below €20,000/QALY. The $ICER_1$s of combination testing strategies exceeded the Dutch threshold of €20,000/QALY if the UK guidelines were used (3.5% discounting for QALYs and costs, health care perspective). However, the $ICER_1$s remained below the UK threshold of £30,000/QALY (≈ €36,000/QALY).

The results of the incremental analysis are also presented in Figure 3*a*. The nondominated strategies are in the lower right corner of the North East quadrant and are the connecting points of the cost-effectiveness frontier. The ICERs of the nondominated strategies when ordered according to costs and compared to the adjacent, less expensive strategy ($ICER_2$) were: €878/QALY for 7.5-yearly HPV with cytology triage, €14,077/QALY for 6-yearly HPV with cytology triage, €18,800 for 5-yearly HPV with cytology triage and €67,095 for 5-yearly combination testing. The $ICER_2$ of 5-yearly combination testing exceeded the willingness-to-pay threshold of €20,000/QALY.

Discussion

HPV16/18 vaccination is not likely to provide great benefits to women of 30 years and older as they may already have been infected once and also receive cervical screening.[47] For this large group of unvaccinated women, we evaluated the health and

economic effects of implementing HPV DNA testing in the cervical screening program. Our model identified HPV testing with cytology triage as the optimal screening strategy. Strategies with a screening interval more than 7.5 years were not cost effective.

Several modeling studies exist in which the implementation of HPV DNA testing has been evaluated.[39,48–56] The use of the HPV DNA test, most often studied as a combination test (HPV DNA and cytology), has been supported by the majority of those studies. Our study focused on the question how HPV testing should be implemented in the cervical screening program. A strong point of our model is that the key parameters were directly obtained from the longitudinal POBASCAM trial.[12] However, some parameters could still not be well-identified. Therefore, in addition to base-case results, we presented ranges under 118 parameter settings that were obtained by calibrating the model estimates on the CIN2+ detection rates in the POBASCAM study, the nationwide cancer incidence rates and the mortality rates. There is a growing interest in the concept of selecting calibrated parameter settings among modelers[53,57] because prospective information cannot be collected on the transition from CIN3 to cervical cancer. Our study showed that there was a large variation in the effect of HPV DNA screening on cancer over the 118 calibrated parameter settings. This underlines that the results from modeling efforts should be cautiously interpreted.

A limitation of our calibration study is that we did not change the structure of the natural history model. In particular, in all calibrated models, we assumed that after viral clearance, a woman was susceptible to a new infection of the same HPV genotype and natural immunity was not acquired. We set the mean time to viral clearance of transient infections at 1 year for all 118 calibrated parameter settings[18]and set the HPV incidences such that the modeled age-specific HPV prevalences reproduced the prevalences reported in the POBASCAM study.[26] A model with natural immunity is likely to have different HPV incidence and clearance rates than a model without natural immunity and a negative association between the viral clearance rate and the degree of natural immunity has been reported.[58] The probable implication of a negative association between clearance and immunity is the following. A model with a low viral clearance rate tends to have a low HPV incidence in order to reproduce the reported HPV prevalences. A low HPV incidence, on its turn, is associated with a high long-term negative predictive value of the HPV test for CIN3 in which case the use of HPV DNA testing in combination with an extended screening interval seems justifiable. Therefore, we think that our cost-effectiveness calculations will remain favorable to HPV DNA screening also when natural immunity is incorporated in the model.

An important issue is the expected decrease in screening efficiency and increase in costs when implementing HPV testing. Our model predicted only a modest decrease in the number of CIN2+ per colposcopy referral when cytology was used as a triage tool for HPV-positive samples. This is in line with other studies that recommend HPV testing with cytology triage for women older than 30 years.[59,60] Our model also predicted that if we replace cytology by HPV with cytology triage without extending the screening interval, the annual costs would increase by approximately €80 per woman (this corresponds to an increase in annual nationwide costs of €8 million). This increase can be largely ascribed to the estimated costs of the HPV test which are in our model about €10 higher than the costs of a cytological examination. Therefore, HPV testing with cytology triage in combination with a screening interval extension of 1 to 2.5 years may be considered to control the anticipated increase in costs.

The cost-effectiveness results are favorable for HPV testing because HPV testing is assumed to be considerably more sensitive than cytology to detect cervical lesions. There is much empirical evidence that the clinical sensitivity of the HPV test is high. Our study was based on the GP5+/6+ PCR test. Its sensitivity for detection of CIN2+ was retrieved from the POBASCAM study being 94.1% (95% CI: 91.7–95.9%).[24] The sensitivity estimate is consistent with meta-analytical estimates of 97.9% (95% CI: 95.9–99.9%)[5] and 96.1% (95% CI: 94.2–97.4%).[4] In addition, in 2 recent prospective screening trials, the sensitivities were 97.3% (95% CI: 90.7–99.7%)[10] and 94.6% (95% CI: 84.2–100).[61] In the majority of HPV screening studies, the FDA approved Hybrid Capture 2 test (Qiagen®) has been used for HPV testing. This test has similar clinical sensitivity and specificity as the GP5+/6+ PCR test[62] and the 2 tests cost about the same.[14] Therefore, a model based on the Hybrid Capture 2 test is expected to give similar cost-effectiveness predictions as our model.

In several randomized implementation trials, the intention-to-treat effectiveness of HPV DNA testing for detection of CIN3+ appeared to be somewhat lower than expected on the basis of published HPV test sensitivities.[8,63] This may be due to incomplete follow-up of HPV-positive, cytologically normal women as some women do not show up at repeat testing or do not have a colposcopy after referral.[64] In our model, we assumed an attendance rate at repeat testing of 90%. As a repeat testing strategy, we only considered repeat cytological testing at 6 and 18 months. This repeat testing strategy is currently used in the Dutch screening program for women with borderline/mild dyskaryosis at baseline. Because cytology has an excellent specificity,[5] it also seems suitable for monitoring HPV-positive women. It may, however, be desirable to use only 1 repeat test for HPV-positive cytologically normal women to minimize loss to follow-up and screening burden.[65] Several suggestions have been done in the literature. An acceptable colposcopy rate may be attained when women are referred for colposcopy if they show HPV type-persistence at the repeat test.[60] The assessment of type-persistence should be done after at least 6 months to determine clearance of transient infections.[18] Furthermore, typing of HPV16 and HPV18 at baseline or at the repeat test may be considered as those types are associated with a strongly increased CIN2+ risk.[25,66] Finally, protein and methylation markers[67,68] have been suggested for further

stratification of HPV-positive women. We think that there are several ways to efficiently manage HPV-positive women. Any potential strategy should be evaluated on detected number of high-grade lesions, costs and colposcopy rate computed from large cohort studies before implementation can take place.

To conclude, our model indicates that HPV testing with cytology triage is a cost-effective alternative to cytological screening. The increase in costs anticipated when implementing HPV testing can be controlled by extending the screening interval.

Acknowledgements

The authors are grateful to Dr. Dirk van Niekerk for reading and discussing the manuscript. The work of J.A.B. was funded by The Netherlands Organisation for Health Research and Development (ZONMW grant 50-50110-96-474). Author Contributions: J.B., V.M.C. and C.J.M. designed the study. J.B. performed the analyses and wrote the manuscript together with V.M.C., J.A.B. and C.J.M. F.J.K. and C.J.M. gave input on the role of the general practitioner, the pathologist and the organization of cervical screening. T.J.H. gave input on the role of the gynecologist. P.J.S. and C.J.M. provided the data from the POBASCAM trial. All authors critically reviewed the article and approved of the final version.

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