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Natural history and screening model for high-risk human papillomavirus infection, neoplasia and cervical cancer in the Netherlands

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A simulation model is presented that assumes that persistent infection with high-risk human papillomavirus (hrHPV) is a necessary cause of cervical cancer. For the estimation of the model parameters, data of recent Dutch follow-up studies were reanalyzed. The predicted incidences of cervical cancer, cervical intraepithelial neoplasia (CIN1, CIN2 and CIN3) and abnormal cytology were validated with nationwide figures and population-based screening results. The model predicted a lifetime risk for cervical cancer of 2.9% with a peak at age 48 years. The predicted lifetime risk dropped to 0.4% when attending cervical screening. For women who were not hrHPV infected at 30 years, the lifetime risk was 1.6%. Sensitivity analyses were performed to check natural history assumptions that were only weakly identified from available data sets. The incidence of CIN3 observed with screening appeared a useful clinical end point as the predicted incidence was robust against changes in the sensitivity of cervical cytology and the duration to CIN3. The model can be used to study the health-economic benefits that can be achieved in nationwide screening when including an hrHPV test.

Key words: cervical neoplasms; cytology; cost effectiveness; human papillomavirus; longitudinal studies; models; screening

Population-based screening is regarded as an effective method for reducing the incidence of invasive cervical cancer. Epidemiologic studies report that in countries where cytologic screening has been implemented, the incidence of cervical cancer has shown a larger decrease than in countries without screening.[1,2] Although many countries subscribe to the necessity of screening, each country has its own screening program and different opinions about the optimal program remain.

Because persistent infection with the high-risk human papillomavirus (hrHPV) is the key causative agent of cervical cancer,[3,4] many recent and ongoing longitudinal studies have examined whether a test for detection of hrHPV in addition to cytologic inspection increases the efficacy of screening.[5–9] Combined screening (hrHPV and cytology) leads to an earlier detection of women who are at risk for developing high-grade lesions[10] and has a higher sensitivity for the detection of high-grade lesions.[11] However, hrHPV testing also induces extra screening costs so that the determination of the optimal screening scenario involves an elaborate cost-effectiveness analysis.

An attractive way to study the efficacy of different screening scenarios is simulation modeling.[12–16] Simulation enables us to combine the results of several studies, compare a large number of scenarios and provides an assessment of the costs and effectiveness in preventing cancer. A simulation model requires the specification of an underlying natural history model that describes health trajectories of women in an unscreened population. We present a natural history model for women in the Netherlands between 30 and 80 years of age and apply the model to predict the incidence of neoplasia and cervical cancer in an unscreened and screened population. The model predictions are validated with nationwide and population-based data.

Material and methods

Markov model

We developed a Fortran90 (Salford Software, Manchester, UK) program that simulates health trajectories of a cohort of women on the basis of the Markov model.[17] This model contains a number of health states among which transitions are possible at discrete points in time. The transitions are governed by an age-dependent transition probability matrix. The transitions take place at six-month intervals. The intake age is set at 30 years, which is the age at which women receive the first screening invitation in the Netherlands. Cervical abnormalities developed at an earlier age are captured by specifying an intake distribution for the health states. The model is depicted in Figure 1. The states of the Markov model are pathologic health states that may be different from cytomorphologic classifications observed at screening.

Assumptions

The key assumption of the model is that invasive cervical cancer cannot develop without a persistent hrHPV infection.[3,4] Lower-grade preinvasive lesions (CIN1/2) may be caused by a low-risk HPV infection or another type of infection, whereas all high-grade lesions (CIN3) are caused by an hrHPV infection. Clearance of an hrHPV infection may precede regression of the lesion in which case an hrHPV-negative lesion is observed.[18] The incidence of hrHPV infection is age-dependent but progression and regression of a CIN lesion and clearance of hrHPV are not.[8,18,19]

Data for estimation

The incidence and clearance of hrHPV infection, the incidence and regression of hrHPV-negative lesions, the probability of cervical abnormalities at the first screening age and the sensitivity of cervical cytology were calculated from the POBASCAM study, a population-based, randomized controlled screening trial of 44,102 Dutch women between 30 and 60 years of age.[8] This study contains 2 arms: in the control arm, referral for colposcopy follows current screening in the Netherlands and depends only on the cytologic result, whereas referral in the intervention arm may also depend on hrHPV status (presence of hrHPV was tested with GP5+6+ PCR−EIA[20]). For the estimation, only the intervention data were used. To determine the CIN3 incidence, long-term follow-up data of 2,250 women with normal cytology at intake[10,21] were examined and the progression and regression incidences of hrHPV-positive lesions were estimated from cohort studies of hrHPV-positive women with abnormal cytology at intake.[18,19,22,23] Registry data were used to compute the survival probabilities,[24] the incidences of hysterectomy and other cause of death[25] and the duration of cervical cancer FIGO stage 1.[26] The progression rate of CIN3 to cervical cancer and the detection rate of cervical cancer were obtained from data collected outside the Netherlands.[27–32] The estimates of the model parameters are presented in Table I. A detailed description of the estimation is given below.

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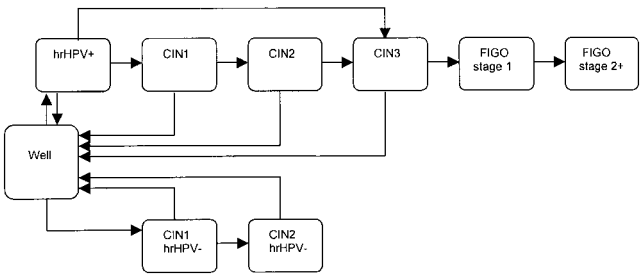

FIGURE 1 – Flow chart representation of the natural history model. The states benign hysterectomy, survivor of cervical cancer, death by cervical cancer and death by other cause are left out.

Data for validation

The incidence of invasive lesions was validated with registry data.[33] The number of preinvasive and invasive lesions detected by cytologic screening and the prevalence of abnormal cytology were validated with data from the POBASCAM control arm and nationwide screening results.[34] The applicability of the model in a non-Dutch setting was examined by comparing model predictions to German[9] and British[6] screening results.

Intake probabilities

At the first screening age of 30 years, some participants had already developed lesions.[35] The POBASCAM data yielded the following intake probabilities: CIN0 (hrHPV+ 0.07 and hrHPV− 0.87) CIN1 (hrHPV+ 0.01 and hrHPV− 0.01), CIN2 (hrHPV+ 0.008 and hrHPV− 0.002), CIN3 (hrHPV+ 0.018 and hrHPV− 0.001) and FIGO stage 1 cervical cancer (hrHPV+ 0.0004 and hrHPV− 0.0000).

Clearance and age-dependent incidence of hrHPV infection

The 6-month hrHPV clearance (from hrHPV+ to Well in Fig. 1) was estimated from follow-up data of 290 women in the POBASCAM study that had normal cytology and an hrHPV-positive test (GP5+6+ PCR-EIA[20]) at baseline. After 6 months, 37% of the women had cleared the hrHPV infection (95% confidence interval [CI] 28–46), which is consistent with published percentages of 39%[36] and 36%.[37] The viral clearance did not depend on age. The incidence of hrHPV infection was estimated by a stochastic difference equation[38] in which the hrHPV-positivity of normal smears after 6 months (y(+6)) is predicted from the current hrHPV-positivity (y), the 6-month incidence of clearing hrHPV (α) and the 6-month incidence of acquiring hrHPV (β). The equation has the following structure: $y(+6) = (1-\alpha)\, y + \beta$. We set the clearance incidence α equal to 37% in which case β can be estimated by least squares. We further assumed that the infection rate β changes at age 35 and 40 years and remains constant for women aged 41 years and over. As shown in Figure 2, the stochastic difference equation accurately fitted the observed prevalences of hrHPV in normal smears. The estimated 6-month incidences were 0.017 (95% CI 0.013–0.022) for age 30–34 years, 0.010 (95% CI 0.008–0.013) for age 35–39 years and 0.007 (95% CI 0.006–0.009) for age 40+ years.

Progression of hrHPV-positive women

The model allows for lesions that develop from CIN0 to CIN3 within 6 months after hrHPV infection. Such rapidly progressive lesions without distinguishable phases of CIN1/2 have been mentioned in the literature.[39–41] The 6-month incidence of CIN3 after hrHPV infection was set at 0.01 and the 6-month incidence of a progressive CIN1 lesion was set at 0.025. By combining the 6-month incidences of direct and indirect progression from CIN0 to CIN3, it follows that the CIN0–CIN3 duration is 2.5 years and the probability of progressing to CIN3 after hrHPV infection is 0.073. The progression probability of 0.073 is consistent with a long-term CIN3 incidence of 0.099 (95% CI 0.042–0.156) after hrHPV infection calculated from follow-up data of 2,250 Dutch women[21] with normal or borderline smear at baseline. Other studies reported long-term cumulative incidences of 0.077[5] and 0.069.[7] The chosen incidence of 0.01 for rapidly progressive lesions implies that 29% of the CIN3 lesions developed directly from CIN0. This percentage is consistent with a follow-up study[7] where 23% (95% CI 10–35) of the CIN3 lesions found within 4 years after a normal smear were detected in the first time interval of 9 months.

The probabilities of progressing from CIN1 to CIN3 and from CIN2 to CIN3 were set at 0.25 and 0.50, respectively, and are consistent with probabilities of progressing to CIN3 of 0.40 (95% CI 0.24–0.56) after an hrHPV-positive mild dyskaryosis smear and 0.52 (95% CI 0.31–0.73) after an hrHPV-positive moderate dyskaryosis smear.[19] The progression probabilities are also consistent with probabilities of 0.30 (95% CI 0.11–0.49; end point CIN2/3) and 0.16 (95% CI 0.00–0.33; end point CIN3) computed from a longitudinal study of 34 hrHPV-positive Dutch women with histologically confirmed CIN1 at baseline.[23] Furthermore, the CIN1–CIN3 progression probability of 0.25 is comparable to an estimate of 0.28 obtained by adjusting a pooled international figure[27] for hrHPV status at intake. We set the mean time to progress from CIN1–CIN3 at 2 years, which is comparable to a reported estimate of 1.8 years.[23]

Regression of hrHPV-positive CIN lesions

Regression of hrHPV-positive CIN lesions involves 2 transitions, hrHPV clearance and regression of the lesion. These transitions may be completed simultaneously or at different points in time. It has been shown that the mean time to hrHPV clearance is slightly shorter than the mean time to cytologic regression,[18] which indicates that some hrHPV-negative CIN3 lesions are regressive lesions. Viral clearance times that exceed the cytologic regression times have been observed as well[23] and may for instance be caused by multiple hrHPV infections or acquisition of hrHPV. We illustrate the discrepancy between the time to viral clearance (negative on GP5+6+ PCR-enzyme immunoassay) and to cytologic regression (first of 2 successive normal smears) in Figure 3, where durations are plotted of 65 women with abnormal cytology (mild, moderate or severe dyskaryosis) and an hrHPV-positive test at baseline.[18] Some women show viral clearance and cytologic regression at the same time point (on diagonal in Figure 3), but the time interval between the transitions can be more than 3 years. The sizes of the 3 different patterns were estimated by the percentages of dots on, above and below the diagonal yielding 30% simultaneous clearance and regression, 40% first viral clearance and 30% first cytologic regression. The estimated average time of achieving both viral clearance and regression of the lesion was 1.5 years.

Residual CIN2/3 lesion

The estimated probability of a residual CIN2/3 lesion after treatment of CIN2/3 in the Netherlands is 0.16 (95% CI 0.11–0.21).[22]

Progression to invasive cancer

Forty percent of the women are assumed to progress from CIN3 to micro-invasive cancer, which is consistent with the literature[27] and progression rates used in other models.[12,15] The mean duration to micro-invasive cancer after onset of the lesion was set at 12 years in order to match with published estimates of 11.8 years,[28] 12 years[30] and 13.3 years.[29] To accurately describe the variability around the mean duration, 2 intermediate tunnel states (Pre1FIGO1 and Pre2FIGO1 in Table I) were included.[17] In a model with 2 intermediate states, 40% of the invasive carcinomas develop within 10 years after hrHPV infection. Similar percentages were reported by others.[28,29] The predicted proportion of invasive carcinomas that develop within 3 years after hrHPV infection is 0.7% and is consistent with a published estimate of 1.1% (95% CI 0.4–1.7).[42]

TABLE I – NATURAL HISTORY MODEL PARAMETERS

Health state		Six-monthly transition probability	Mean duration (years)
Origin	New		
Well	hrHPV infection		
	30–34 years	0.017	
	35–39 years	0.010	
	40+ years	0.007	
	hrHPV-negative CIN lesion		
	CIN1	0.002	
	CIN2	0.0002	
	CIN3	0	
HrHPV infected	CIN1	0.10	1.0
	CIN3	0.01	
	Well	0.37	
CIN1 and hrHPV infected	CIN2	0.25	1.0
	Pre-well[1]	0.25	
CIN2 and hrHPV infected	CIN3	0.25	1.0
	Pre-well[1]	0.25	
CIN3 and hrHPV infected	Pre-1FIGO1	0.20	1.0
	Pre-well[1]	0.30	
hrHPV-negative lesion	Well	0.51	1.0
Pre-1FIGO1	Pre-2FIGO1	0.104	4.8
Pre-2FIGO1	Undetected FIGO stage 1	0.104	4.8
Undetected FIGO stage 1	Undetected FIGO stage 2+	0.048	6.3
	Detected FIGO stage 1	0.032	
Undetected FIGO stage 2+	Detected FIGO stage 2+	0.30	1.7

[1]Pre-well incorporates 3 states: well; clearance of hrHPV infection but no regression of CIN lesion; and regression of the CIN lesion but no clearance of hrHPV infection. If different from state Well, Pre-well connects only with Well.

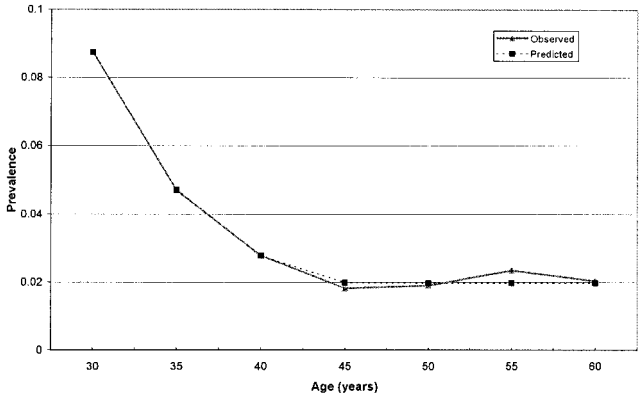

FIGURE 2 – Prevalence of hrHPV in normal smears. The observed smears were collected in the POBASCAM study.[8] The presence of hrHPV was tested with GP5+6+ PCR-EIA.[20]

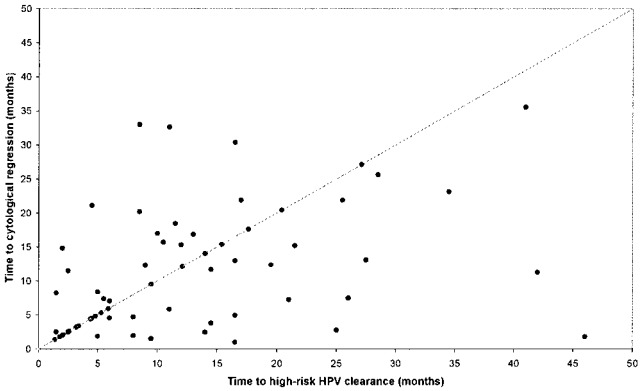

FIGURE 3 – Time to cytologic regression (first of 2 successive normal smears) against the time to hrHPV clearance (negative on GP5+6+ PCR-EIA).[20] The data comprise follow-up results of 65 women with an hrHPV-positive abnormal smear (mild, moderate or severe dyskaryosis) at intake.[18]

Progression from FIGO stage 1 to stage 2+

The duration to FIGO stage 2+ was estimated at 6.3 years on the basis of Dutch data collected before the introduction of nationwide screening.[26] Other models[12,15] used similar durations.

Detection of cancer

The annual symptom probabilities were computed by simulation on the basis of UK screening and cancer incidence data,[31,32] yielding estimated 6-month symptom probabilities during FIGO stage 1 and stage 2+ of 0.048 and 0.30. The estimates were insensitive to changes in the sensitivity of cytology (varied from 70–90%) and are comparable to symptom rates used in other models.[12,14,15]

HrHPV-negative lesions

It is assumed that hrHPV is the only causative agent for a CIN3 lesion but that CIN1 and CIN2 lesions may be caused by other types of infections, including low-risk HPV (Fig. 1). Analogous to the estimation of hrHPV incidence, the 6-month cumulative incidence of an hrHPV-negative CIN lesion was estimated by fitting a stochastic difference equation[38] on the POBASCAM intervention data. The estimated 6-month incidences of an hrHPV-negative CIN1 and CIN2 lesion were 0.002 (95% CI 0.001–0.003) and 0.0002 (95% CI 0.0001–0.0003).

Survival probabilities

The 5-year relative survival probability for FIGO stage 1 in the Netherlands is 93% if younger than 45 years of age and 86% otherwise. For stage 2+, the 5-year relative survival probability is 43%.[24]

Screening model

In the Netherlands, women between 30 and 60 years of age are invited to cytologic screening at 5-year intervals. If the baseline PAP smear is borderline or mild dyskaryosis, the participant is recalled after 6 and 18 months and referred to a gynecologist if a

TABLE II – SENSITIVITY AND SPECIFICITY OF CONVENTIONAL PAP SMEAR FOR DETECTING CIN LESIONS: SETTINGS IN THE BASE-CASE MODEL AND THE HIGH- AND LOW-SENSITIVITY VARIANT

Threshold	Base-case		Sensitivity high		Sensitivity low	
	BMD[1]	>BMD	BMD	>BMD	BMD	>BMD
Specificity (%)	98.5	99.85	98.5	99.85	98.5	99.85
Specificity second smear (%)	90	99	90	99	90	99
Sensitivity (%)/threshold CIN1	50	20	65	25	40	20
CIN2	65	40	75	45	55	35
CIN3	80	50	85	55	70	50

[1]BMD, borderline or mild dyskaryosis (KOPAC classification: Pap2/3al).

second abnormal smear is found. If the baseline smear is moderate dyskaryosis or worse, the participant is referred to a gynecologist for colposcopic diagnosis. The cervical smears are read according to the KOPAC classification.[34,43,44] A comparison with the Bethesda 2001 classification is available.[34,43] The compliance rate at nationwide screening in the Netherlands is about 80%.[45] We assumed that 50% of the noncompliers are women who never attend screening.

The sensitivity and specificity are computed from the POBASCAM data and presented in Table II (base-case). A stratified estimator for the sensitivity was used where the strata are defined by the hrHPV status and cytology.[46] In this way, verification bias is avoided that arises because only some women are referred for colposcopy.[47] The sensitivities and specificities of abnormal cytology are comparable to figures in review studies.[11,48,49] Besides base-case estimates, high- and low-sensitivity estimates are presented.

Simulation analyses

Predictions were obtained by simulating health trajectories of 10,000,000 women without and with cytologic screening. The invasive and preinvasive part of the model were validated by comparing the predicted incidence of cervical cancer and the predicted screening results (detected lesions and abnormal cytology) to 95% confidence intervals calculated from the validation data sets. To construct the confidence intervals, a normal reference distribution was assumed for the logarithm of the statistic.

The robustness of the model predictions was examined by 1-way sensitivity analyses. Regarding the predicted incidence of cervical cancer, we varied the sensitivity of cytology (Table II), the incidence of hrHPV infection (−25 and +25%), the incidence of CIN3 after hrHPV infection (−25 and +25%) and the duration from CIN3 to FIGO stage 1 (−25 and +25%). Regarding the predicted screening results, we varied the sensitivity of cytology (Table II) and the CIN0–CIN3 duration after hrHPV infection (from 2.5 to 5 years).

Results

Predictions and validation

Cervical cancer in an unscreened population. The predicted preclinical and clinical incidences of cervical cancer in an unscreened population were unimodal functions with modes 40 and 48 years of age (Fig. 4). The predicted lifetime risk (summed until age 80 years) for clinical cervical cancer was 2.9% and the mortality risk was 1.1%. Forty percent of the clinical cases were in FIGO stage 1. For women who are not infected by hrHPV at age 30 years, the predicted lifetime risk for cervical cancer was 1.6%.

Preinvasive lesions and cervical cancer in a screened population. With cytologic screening, the predicted lifetime risk of cervical cancer dropped to 0.9% (compliance rate 80%) and to 0.4% for compliant women. Sixty percent of the predicted cases of cervical cancer were in FIGO stage 1. The average incidence of cervical cancer became 15.0 (per 100,000 women years) and is comparable to the observed incidence in the Netherlands, which dropped from 15.7 (95% CI 14.5–16.9) in 1989 to 13.6 (95% CI 12.6–14.7) in 1998.[33] The predicted incidence of cervical cancer had a peak-valley shape (Fig. 5): the minimum was attained for the age cohort 65–69 years, which indicates that the predicted protective effect of the last screening round at age 60 years is at least 5 years.

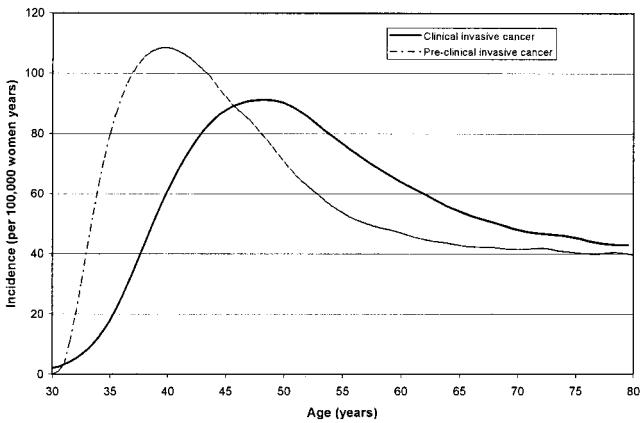

FIGURE 4 – Predicted incidence of preclinical and clinical cervical cancer in an unscreened population.

The percentage of hrHPV-positive CIN lesions was 45% for CIN1, 70% for CIN2 and 92% for CIN3. The predicted number of lesions detected by the baseline and first repeat smear of each screening round are presented in Table III. Except for the number of CIN1 lesions detected by the second smear, the predictions were within the POBASCAM 95% confidence bounds. The model further predicted that the percentage of smears that leads to the detection of CIN2/3 and cervical cancer were 0.7% and 0.04%. These percentages are consistent with nationwide figures of 0.6% (95% CI 0.5–0.7) and 0.04% (95% CI 0.03–0.06) in the year 2000.[34]

Cytology. The predicted prevalence of abnormal cytology was consistent with observed cytology in the year 2000 (Table IV).[34]

Sensitivity analyses

Cervical cancer in an unscreened population. The lifetime risk for cervical cancer changed +0.3 and −0.5% when changing the hrHPV incidence by +25 and −25%. The same percentage changes in lifetime risk were found when changing the CIN3 incidence by +25 and −25%. The main effect of varying the duration from CIN3 to FIGO stage 1 (−25 and +25%) was a shift in the age at which the incidence of cervical cancer peaks (−3 and +2 years for clinical invasive cancer).

Preinvasive lesions and cervical cancer in a screened population. The cervical cancer incidence with screening dropped to 13.5 per 100,000 women-years when increasing the sensitivity of cytology and raised to 17.7 per 100,000 women-years when decreasing the sensitivity of cytology (Fig. 5). The prediction under increased sensitivity remains consistent with the nationwide incidences in 1989 and 1998. Varying the hrHPV incidence or the

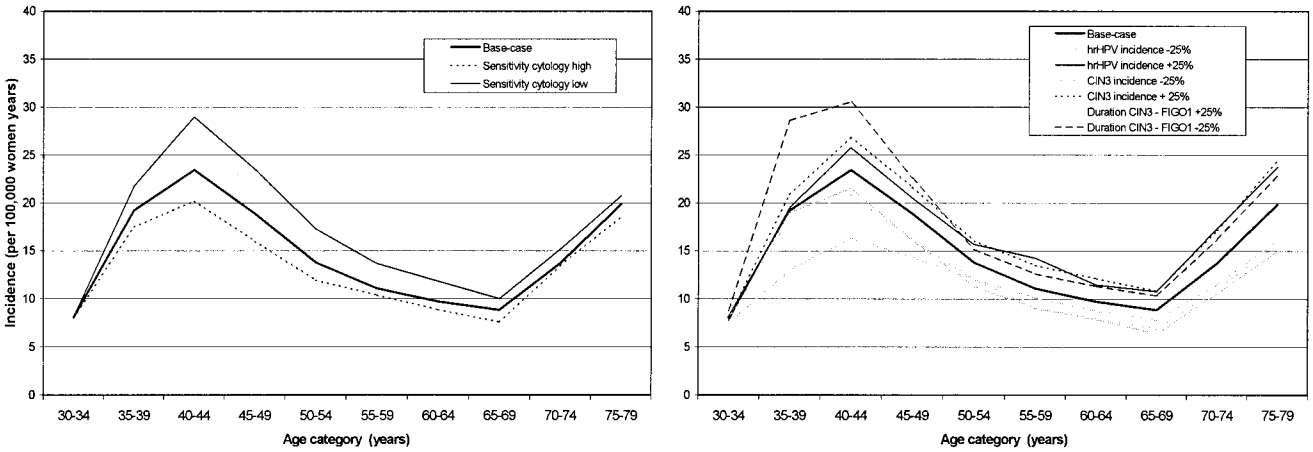

FIGURE 5 – Age-dependent incidence of clinical cervical cancer in a screened population (screening interval 5 years): prediction by the base-case model and by variants with a different sensitivity of cytology (see Table II) or a modified natural history parameter (hrHPV incidence ±25%, CIN3 incidence after hrHPV infection ±25%, duration CIN3-FIGO1 ±25%).

TABLE III – NUMBER OF LESIONS (CIN1, CIN2, CIN3, CERVICAL CANCER) DETECTED BY CYTOLOGIC SCREENING[1]

	CIN1	CIN2	CIN3	Cervical cancer
No. of lesions detected by baseline smear (% of baseline smears)				
Prediction by:				
Base-case model	0.05	0.10	0.36	0.03
Variant with increased sensitivity cytology	0.05	0.14	0.38	0.03
Variant with decreased sensitivity cytology	0.03	0.08	0.38	0.04
Variant with CIN0–CIN3 duration 5 years	0.08	0.16	0.34	0.03
POBASCAM estimate	0.07	0.13	0.44	0.01
95% CI	0.04–0.13	0.09–0.20	0.36–0.54	0.00–0.04
No. of lesions detected by second smear 6 months after baseline smear (% of baseline BMD[2] smears)				
Prediction by:				
Base-case model	4.2	2.5	7.9	0.7
Variant with increased sensitivity cytology	6.3	3.7	7.9	0.6
Variant with decreased sensitivity cytology	2.4	1.6	5.6	0.6
Variant with CIN0–CIN3 duration 5 years	7.2	3.7	7.0	0.7
POBASCAM estimate	7.3	3.6	6.6	0.4
95% CI	4.7–11.4	1.9–6.9	4.1–10.5	0.0–2.7

[1]Separate figures are presented for lesions found by the baseline smear (>BMD) of a screening round and by second smear after 6 months (≥BMD). Predictions are presented for the base-case model, variants with increased and decreased sensitivity of cytology (see Table II) and a variant with 5-year duration for CIN0–CIN3. The empirical figures (point estimate and 95 CI) are computed from POBASCAM data (control arm).–[2]BMD borderline or mild dyskaryosis (KOPAC classification: Pap2/3a1).

CIN3 incidence led to a mild incidence change of cervical cancer for women aged 40 years and over (Fig. 5) and varying the duration of CIN3 to FIGO stage 1 led to a substantial incidence change for women in the age cohort 35–39 years.

The percentage of hrHPV-positive lesions was robust against changes in the sensitivity of cytology but was slightly affected when increasing the CIN0–CIN3 duration from 2.5–5 years: in comparison to the base-case, the percentage of hrHPV-positive CIN lesions raised by 21% for CIN1 and 14% for CIN2. The predicted number of CIN1 and CIN2 became substantially smaller than the POBASCAM predictions when decreasing the sensitivity of cytology (Table III).

Cytology. The predicted prevalence of abnormal cytology at screening was fairly robust against changes in the sensitivity of cytology and the CIN0–CIN3 duration. Except for the model variant with decreased sensitivity of cytology, the predictions remained well covered by the 95% confidence intervals (Table IV).

International predictions. We examined whether the model can yield accurate predictions for the detected number of CIN lesions in the UK and Germany reported in the HART study[6] and Hannover/Tübingen study,[9] respectively. To be consistent with the UK screening model, we increased the sensitivity of cytology (Table II) and set the 5-year compliance rate at 85%.[6,50] The model predicted that the percentage of baseline smears that led to the detection of CIN2+ is 0.6% if intake is >BMD (HART 95% CI 0.4–0.7), 0.9% if intake is ≥BMD (HART 95% CI 0.6–1.0) and 0.3% if intake is PAP1, hrhPV+ (HART 95% CI 0.1–0.4). In Germany, annual cytologic screening is implemented, the compliance rate is about 50%,[51] and the sensitivity of cervical cytology for detecting CIN2+ is low.[9] Under these settings, the model predicted that the percentage of intake smears that leads to the detection of CIN2+ is 0.3% if intake is ≥BMD (Hannover/Tübingen 95% CI 0.2–0.5) and 0.2% if intake is PAP1, hrHPV+ (Hannover/Tübingen 95% CI 0.3–0.6). The number of CIN2+ lesions detected by a PAP1, hrHPV+ smear in the Hannover/Tübingen study is a bit low, which might be related to the use of different hrHPV tests (GP5+6+ and the HCII in the POBASCAM and the Hannover/Tübingen study, respectively). However, in general the predicted CIN2+ detection percentages are comparable to the HART and Hannover/Tübingen results.

TABLE IV – ANNUAL PREVALENCE OF ABNORMAL CYTOLOGY AT CERVICAL SCREENING[1]

PAP smear result (%)	Normal	BMD[2]	>BMD
Prediction by:			
Base-case model	96.8	2.4	0.8
Variant with increased sensitivity cytology	96.4	2.6	1.0
Variant with decreased sensitivity cytology	97.1	2.1	0.8
Variant with CIN0–CIN3 duration 5 years	96.4	2.7	0.9
Netherlands (year 2000) estimate	96.4	2.6	0.9
95% CI	95.7–97.2	2.5–2.8	0.8–1.0

[1]Predictions are presented for the base-case model, variants with increased and decreased sensitivity of cytology (see Table II) and a variant with 5-year duration for CIN0–CIN3. The empirical figures (point estimate and 95% CI) are computed from nationwide cytologic screening results in year 2000.[34] –[2]BMD, borderline or mild dyskaryosis (KOPAC classification: Pap2/3al).

The predicted percentage of abnormal cytology at baseline was 1.8% (95% CI 1.4–2.2) lower than in the HART study and 1.0% (95% CI 0.6–1.4) lower than in the Hannover/Tübingen study. The predicted UK percentage of abnormal cytology lies closer to the HART prediction when the specificity of cytology is lowered.

Discussion

Using a Markov simulation model, we predicted that the incidence of clinical cervical cancer without screening is a single-peaked function with a peak incidence at 48 years and a lifetime risk of 2.9% (summed until age 80 years). This prediction is consistent with the literature where peaks are reported between 44 and 49 years for European countries[52] and lifetime risks between 2.5% and 3.7%.[12,14,15,25,41] The predicted percentage of clinical cases in FIGO stage 1 is 40% and is consistent with a reported figure of 43%.[26] The predicted incidence of preclinical cervical cancer peaks at age 40 years. We further predicted that the lifetime risk of cervical cancer drops by 45% when not carrying hrHPV at age 30 years and drops by more than 80% when attending cervical screening.

An important aim of our study was to validate the model with regard to preinvasive and invasive lesions detected by cervical screening. We found that the predicted incidence of CIN3 and invasive cancer were comparable to the control arm of the POBASCAM study and were robust against changes in the sensitivity of cervical cytology and assumption about the development of CIN3 lesions. This is important for cost-effectiveness modeling because the incidences of CIN3 and invasive cancer are useful clinical effect measures. The model also yielded reasonable predictions for the number of CIN lesions detected in a British[6] and German[9] cohort study. This indicates that although most model parameters are estimated from Dutch cohort studies, the model can be applied to a non-Dutch population as well.

Several other models have been developed in which the human papillomavirus plays a key role.[12–16] The presented model is largely similar in structure but differs from previous models in the description of regression of CIN lesions. Instead of confining to simultaneous hrHPV clearance and lesion regression, the model allows for a serial regression process where hrHPV clearance precedes lesion regression. This assumption is supported by cohort studies[18,23] and offers an explanation for hrHPV-negative CIN2/3 lesions observed at screening. The model predicted that 8% of the CIN3 lesions were hrHPV-negative, which is consistent with reported figures of about 5%.[11,53] Nonetheless, in practice hrHPV-negative lesions may also be observed due to a technical error or integration of the virus.[3] This can be accounted for by specifying a technical sensitivity of the hrHPV test.[54] If the technical sensitivity is set lower than 100%, the predicted number of hrHPV-negative CIN3 lesions will be higher than 8%.

The main application of the model is in studying the cost-effectiveness of screening scenarios. An alternative to cytologic screening is combined screening (hrHPV and cytology), which has a higher sensitivity for detecting neoplasia but may be more expensive. Elaborate scenarios can be evaluated by the model, in particular, a scenario in which the referral of a borderline or mild dyskaryosis smear depends on the hrHPV test result as women with a positive hrHPV test result are more likely to develop CIN3.[18] A second important application of the model is in studying the plausibility of natural history assumptions. Information about the preinvasive part of the model is usually retrieved from cytology that has only a moderate sensitivity for detecting an underlying CIN lesion. By having integrated the natural history and screening model into one mathematical model, simulation analyses enable us to determine ranges for the natural history parameters that give plausible predictions for observed cytologic screening results. As an example, we showed how varying the duration between CIN0 and CIN3 affects the predicted number of detected lesions and compared these predictions with observed screening results.

The natural history model relies on etiologic assumptions that can easily be relaxed or modified when new data evidence becomes available. In the model, the incidence of hrHPV infection depends only on age. In practice, the incidence of hrHPV infection also depends on socio-economic features,[35] which correlate with proneness to attend screening. Therefore, a sensible generalization of the model is to have different hrHPV infection rates for compliant and noncompliant women. The model also does not distinguish between different types of hrHPV except for low-risk and high-risk types. It may be worthwhile to further differentiate hrHPV according to hrHPV type as the different hrHPV types do not have to be equally oncogenic and are not equally prevalent.[4] Differentiating with regard to hrHPV type also enables us to examine the cost-effectiveness of type-specific vaccines. A further limiting aspect of the present model is that it only includes persistent hrHPV infection as a causal factor for high-grade lesions and cervical cancer. However, hrHPV is a necessary but not sufficient cause of cervical cancer. The model can be refined by including information about genetic and epigenetic processes that drive the progression of preinvasive lesions to invasive cancer.[55]

In sum, the presented model was developed to study assumptions about the natural history of cervical cancer and to enable future cost-effectiveness analyses. Nationwide screening involves huge costs, and it is therefore important to determine whether the inclusion of an hrHPV test improves the efficacy of screening. This model enables us to make a careful evaluation of the health-economic benefits that can be achieved by using hrHPV-dependent referral policies.

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