Appendix S1. MISCAN-Cervix model description.

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1. Model purpose

Cervical cancer screening can be used as a strategy to reduce both cervical cancer incidence and cervical cancer mortality.[1-3] Cervical cancer screening has been implemented in many different ways across Europe. To assess the costs and effects of such screening programs one could monitor the existing programs or set up trials to evaluate different screening strategies. However, setting up large trials is expensive, needs a long follow-up time and might have ethical concerns. Also, the outcomes of such trials will be dependent on several factors, which might be different across countries, so the results might not be applicable to another country.

MISCAN-Cervix is a microsimulation model that is able to simulate a hypothetical population, including the development of cervical cancer. In these simulations, different screening strategies can be applied to quantify the effects of screening in this population.[4] Because the population characteristics in the model and their background risk for cervical cancer can be tailored to those of a specific country, it is possible to make country-specific estimations of costs and effects for different screening strategies. In this study, the model was set to represent the Dutch situation.

The three main aims of MISCAN-Cervix are:

1. To quantify the long-term harms, benefits, costs and cost-effectiveness of primary prevention and cervical cancer screening strategies.
2. To compare screening strategies, allowing the user to improve existing screening programmes as well as advising countries on the effects of implementing a cervical cancer screening programme.
3. To quantify the effects of removing barriers to screening, which can be used to prioritise which barriers should be removed first.

2. Model overview

The Microsimulation Screening Analysis (MISCAN) program was first developed in 1985 by the Department of Public Health of Erasmus MC University Medical Center in The Netherlands to evaluate the effects of screening on disease.[4] Since then, the MISCAN programme has been used to quantify the effects of screening for cancers of the breast, colon, cervix, prostate, and lung.[5-9]

MISCAN-Cervix, coded in Borland Delphi 7, is a stochastic, semi-Markov microsimulation model. In a microsimulation model, individuals are simulated one at a time instead of as proportions of a cohort. The advantage of this is that new events can be dependent on past events of that individual. The model is stochastic, which means that sequences of events are simulated by drawing from distributions of probabilities and durations instead of using fixed values. Therefore, the outcomes of the model are subject to random variation.

2.1. Model description

Figure S1 shows the basic structure of MISCAN-Cervix. The program consists of three main parts:

1. Demography part
2. Natural history part
3. Screening part

Input data for these parts is processed by the MISCAN program to generate individual life histories of women in a population. The program simulates both a situation without screening and a situation with the selected screening programme. The difference between the outcomes of those two scenarios is considered as the effect of screening. Al three parts are described further in the upcoming sections.

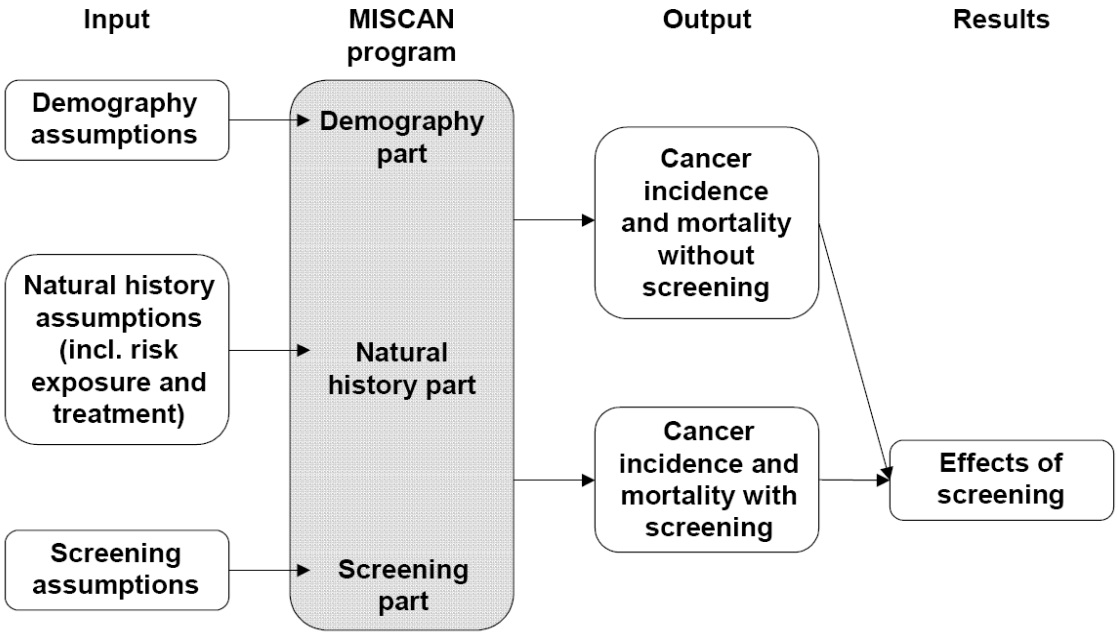

Figure S1. Basic structure of MISCAN-Cervix.

2.2. Demography part

MISCAN-Cervix simulates a female population. A specific life history is generated for each woman, including a date of birth and date of death from other causes than cervical cancer. Simulated women have a probability to have a hysterectomy for reasons other than cervical cancer, depending on the age and the birth year of the woman. In the model, women cannot become older than 100 years.

2.3. Natural history part

Figure S2 shows the natural history structure of MISCAN-CERVIX. In the static MISCAN model, several health states with corresponding durations and transition probabilities are defined.

Each woman starts at the 'Normal' state and has an age-specific risk of acquiring one or multiple infections with a high-risk type of the human papillomavirus (hrHPV). These hrHPV types can cause cancer and are detectable by the hrHPV-test. The model distinguishes between four categories of hrHPV types, based on their likeliness to cause cancer and efficacy of different vaccines against these types:

1. HPV-16
2. HPV-18
3. High risk types that are covered in the nonavalent vaccine (HPV-31/33/45/52/58)
4. Other high risk HPV types (HPV-35/39/51/56/59/66/68)

An acquired hrHPV infection will most likely regress, but may progress to a pre-invasive cervical intraepithelial neoplasia (CIN) grade 1, which may progress sequentially to CIN grade 2 and 3. Regression probabilities of pre-invasive lesions are dependent on age and lesion grade. A woman might also develop CIN lesions without the presence of hrHPV, although hrHPV-negative lesions will never progress to cancer.[10] A woman can have multiple lesions and hrHPV infections simultaneously, which may or may not progress independent of each other.[11]

A CIN3 lesion may progress to cervical cancer, which is modeled in five different stages according to the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) classification: FIGO stages 1A, 1B, 2, 3 and 4. Cancers classified as FIGO stage 1B and higher may be detected clinically (i.e., because of symptoms) before progressing to a higher stage. Screening may detect all pre-invasive and invasive lesions. Survival probabilities and durations until cervical cancer death depend on the stage and on the age at which the cancer is detected. A death is only counted as a cervical cancer death if the woman dies from cervical cancer before dying from other causes.

During the development of disease, a woman might die of other causes than cervical cancer at any moment. Also, a woman might have a hysterectomy for other reasons than cervical cancer at any moment, removing all prevalent hrHPV infections and CIN lesions. Women who have had a hysterectomy will no longer be at risk for acquiring an hrHPV infection or CIN lesion and will not be invited for screening any more.

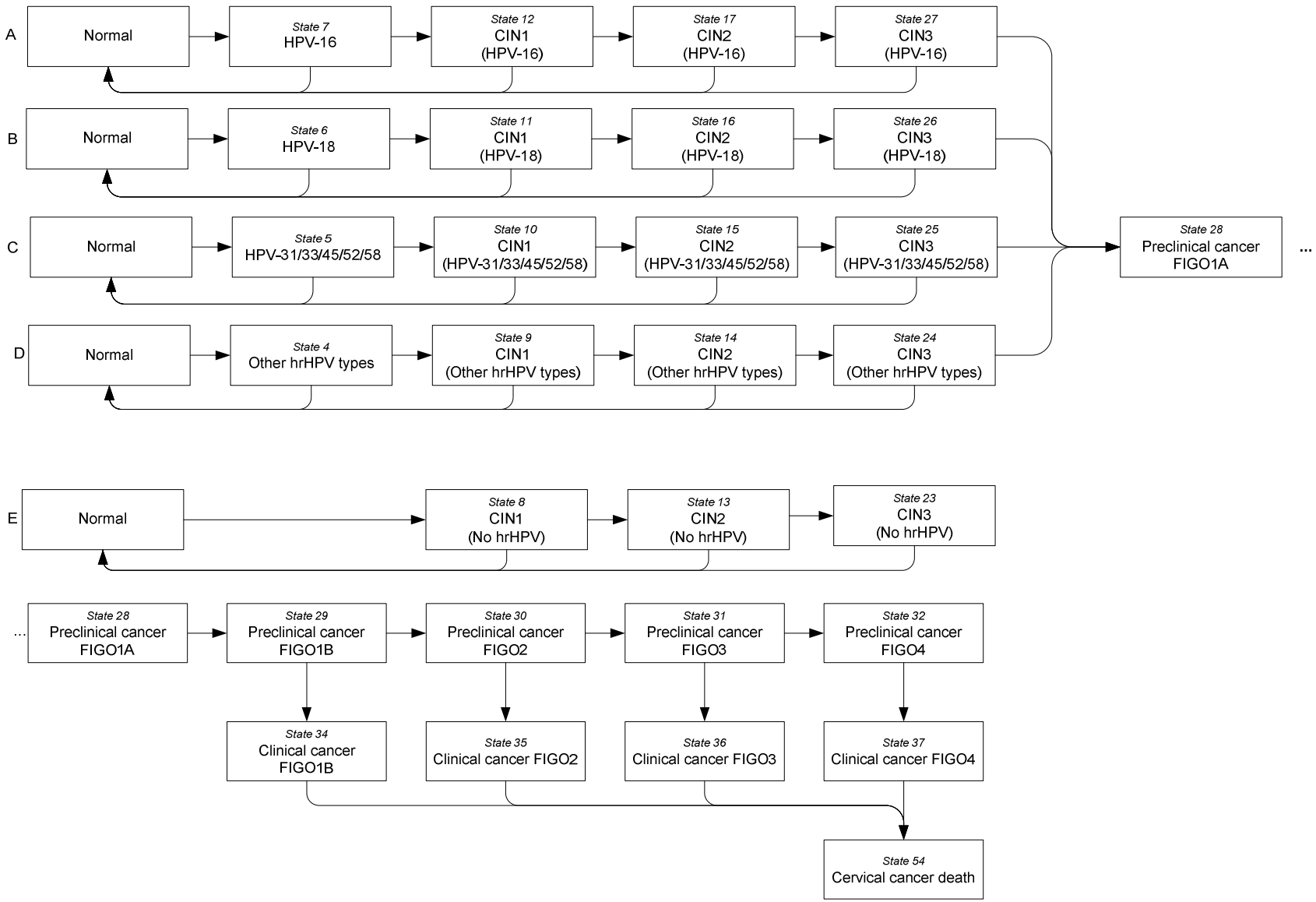

Figure S2. The natural history structure of MISCAN-Cervix.

(hr)HPV = (high-risk) human papillomavirus; CIN = cervical intraepithelial neoplasia; FIGO = International Federation of Gynaecology and Obstetrics.

If a woman acquires an hrHPV infection, the prevalence of disease is added to the original life history of this woman generated in the demography part, resulting in a life history with disease, as shown in Figure S3. In this case, the woman acquires two hrHPV infections. The first infection will progress to a CIN2 before the infection clears and the lesion regresses, while the second infection will progress to cervical cancer and cause a cervical cancer death. In the bottom line the original life history is combined with the natural history of cervical cancer. Here we see that the moment of death from cervical cancer occurs before the moment of death from other causes, altering the original moment of death. The difference between the original moment of death from other causes and the moment of death from cervical cancer is the number of life years lost due to cervical cancer.

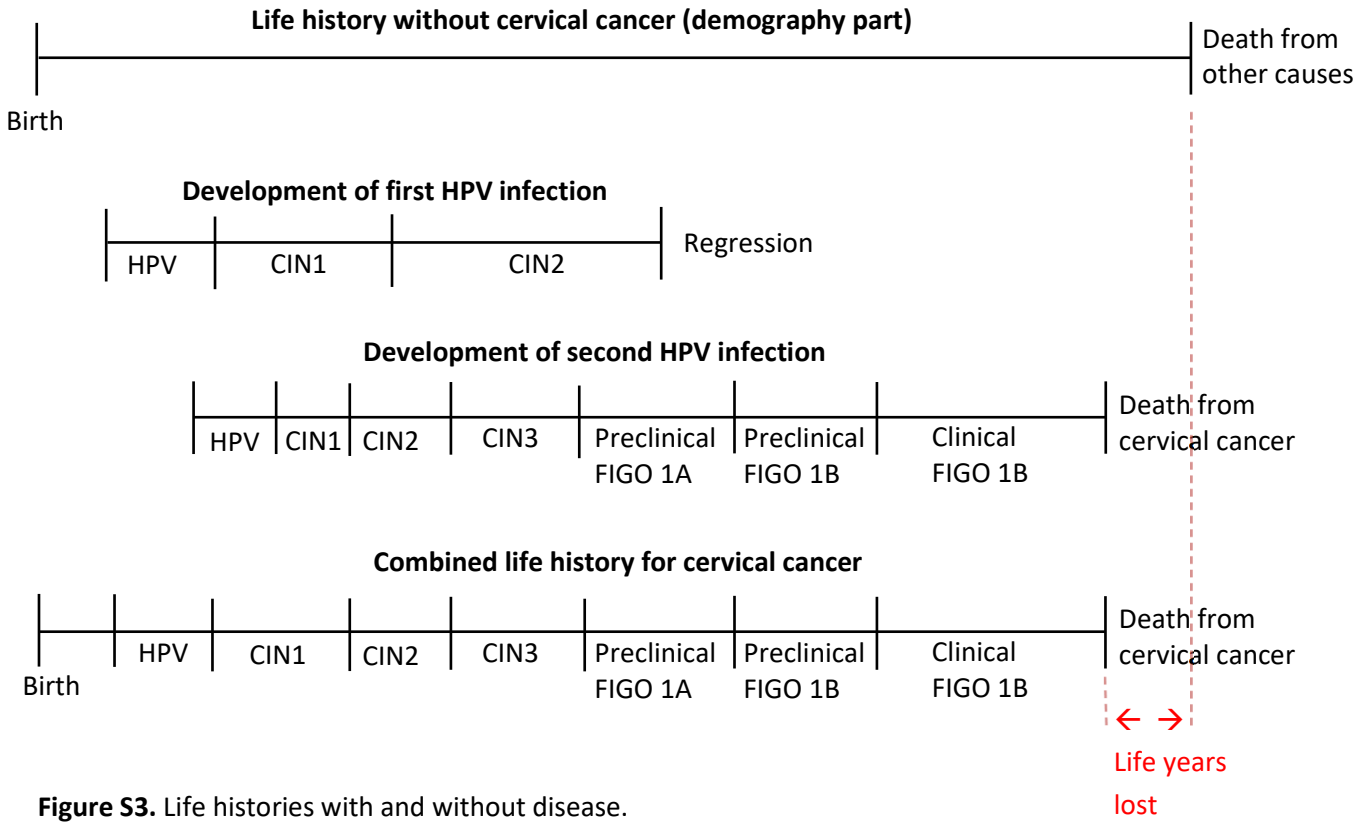

Figure S3. Life histories with and without disease.

HPV = human papillomavirus; CIN = cervical intraepithelial neoplasia; FIGO = International Federation of Gynaecology and Obstetrics.

2.4. Screening part

In the screening part of MISCAN-Cervix, screening strategies and screening behaviour are simulated. Women can be invited to participate in screening at specified ages. Depending on the test used and the highest prevalent lesion of a woman at the moment of the screening test, there is a probability of a positive test result. If the screening test is positive, a woman will be referred for either a triage test or a referral to colposcopy, depending on the applied strategy. When a woman is referred to colposcopy, all prevalent CIN lesions will be diagnosed and successfully removed/treated. In practice, low grade pre-invasive lesions (e.g. CIN1) might not be treated directly, but as these women will be monitored regularly and treated if the lesion progresses, these low grade lesions are considered as removed in the model.

As screen-detected cancers tend to have a better stage-specific survival than clinically detected cancers, detection of cervical cancer by screening in the model may prevent death from cervical cancer. However, if the death from cervical cancer is not prevented, the duration from the moment of detection until the moment of death from cervical cancer will not be different from clinically detected cancers.

The effect of screening on the life history of a woman is shown in Figure S4. In this case, the woman attends a screening intervention, removing the prevalent CIN lesions. The second hrHPV infection will not lead to cancer anymore and therefore, the woman will die at the original moment of death from other causes. The difference between the moment she would have died from cervical cancer and the moment she will now die of other causes is the screen effect and can be quantified as the number of life years gained.

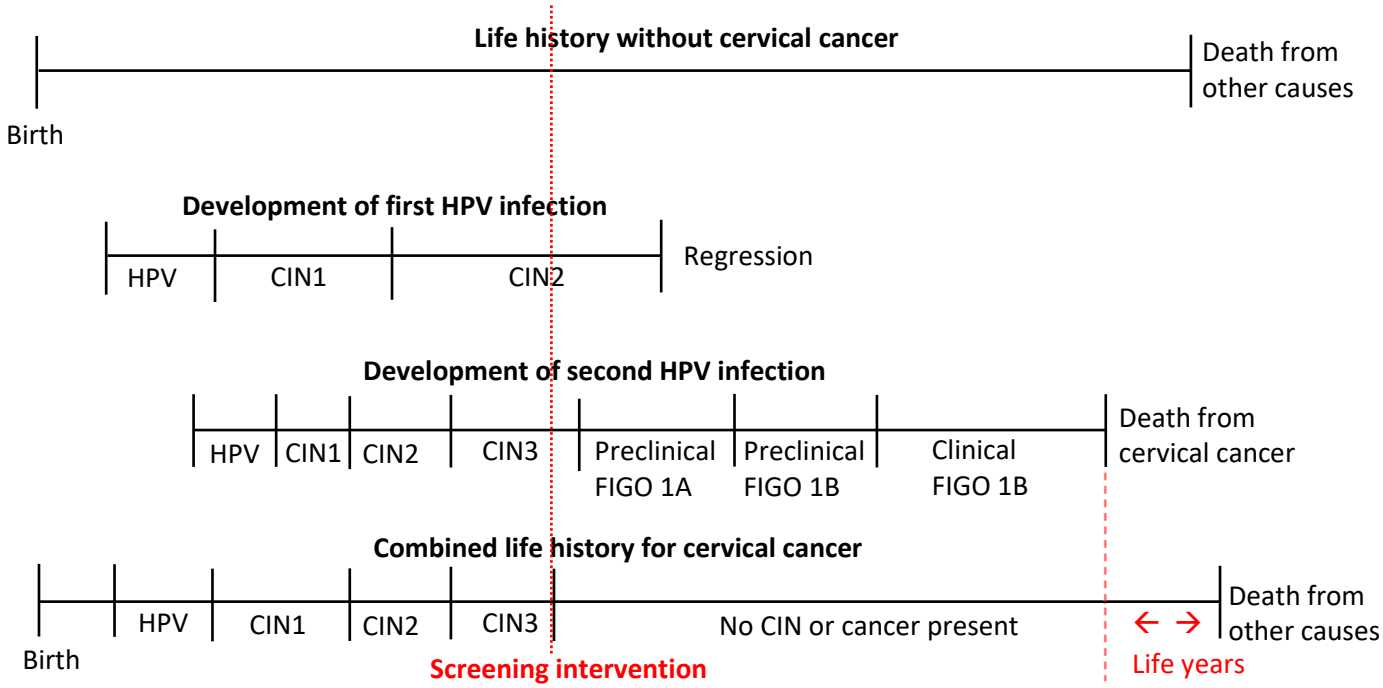

Figure S4. Life history with screening.

HPV = human papillomavirus; CIN = cervical intraepithelial neoplasia; FIGO = International Federation of Gynaecology and Obstetrics.

3. Model output

After the simulation is complete, several types of outcomes can be reported by the programme, such as:

3.1. Demographic or epidemiological outputs

1. Total number of life-years lived
2. Cervical cancer incidence rates by age group
3. Cervical cancer mortality rates by age group
4. Cervical cancer incidence counts by age group
5. Cervical cancer mortality counts by age group
6. Number of cervical cancer deaths per 100 000 women simulated lifelong

3.2. Screening outputs

1. Number of screen tests and triage tests by age group
2. Number of false positive referrals to colposcopy
3. Number of referrals to colposcopy by lesion grade and by age
4. Cervical cancer mortality reduction due to screening
5. Number of tests needed to prevent 1 cervical cancer incidence or death
6. Number of colposcopies needed to prevent 1 cervical cancer incidence or death
7. Life-years gained by screening

3.3. Undiscounted and discounted costs and QALY's

1. Costs of screening
2. Costs of diagnosis and treatment of disease
3. Costs of palliative care
4. Life-years gained compared to a no screening scenario
5. QALY's gained compared to a no screening scenario
6. Costs / life-year gained
7. Costs / QALY gained

4. Structural model assumptions

Several assumptions have to be made for each part of the model, either because data needed to directly calculate inputs are lacking or because complex processes needed to be simplified in order to be able to model them.

Making assumptions introduces uncertainty about the model outcomes. Therefore, model validation is used to test the model assumptions. During model validation, the model is set to simulate a 'real-life' situation, for example, a cohort study. The model outputs can then be compared with the outcomes of the real-world study that the model was trying to simulate. If differences in results cannot be explained by external reasons, such as underreporting of cause-specific deaths, the model parameter values are re-estimated. If this re-estimation of model parameters does not lead to a satisfying result, the model assumptions are reconsidered.

Also, sensitivity analyses are usually performed in which assumptions are varied which might be crucial for the conclusion of an analysis, to see if the conclusion still holds with these alternative assumptions.

4.1. Demography assumptions

The following demography assumptions were made, which affect the characteristics of the population without the presence of cervical cancer.

- One cohort is simulated with one life table. All women are born at the same time, but will die from cervical cancer or from other causes at different moments in time.
- In the model it is assumed that death from cervical cancer is independent from death from other causes. Whichever comes first determines the actual moment of death.

4.2. Natural history assumptions

Many characteristics of the natural history of cervical cancer cannot be observed because the disease starts to develop unnoticed. Once a diagnosis is made, it is in most cases unethical not to intervene. Therefore, assumptions have to made about the natural history of cervical cancer. These assumptions are based on expert opinion or derived from observed data such as detection rates. For an overview of the natural history part of the model, please see the natural history section of the model overview.

Human Papillomavirus

- Each woman has an age-specific risk of acquiring hrHPV infections.
- A woman can acquire multiple hrHPV infections during her lifetime, and these hrHPV infections may be present at the same time. The progression of these lesions are modelled independently, there is no interaction.
- If vaccination is introduced, there will be an age-specific relative reduction of the age-specific risk of acquiring hrHPV infections, depending on the vaccination type and vaccination coverage.
- Most hrHPV infections will clear naturally before progressing to cervical intraepithelial neoplasia (CIN).
- As described in the natural history section of the model overview, the model distinguishes four categories of hrHPV genotypes. The duration of hrHPV-infections and subsequent CIN lesions are assumed equal for all genotypes and independent of age. However, the progression probabilities from all pre-invasive health states are different between all genotypes and are dependent on age as well.
- If a woman has a hysterectomy because of cervical cancer or for other reasons than cervical cancer, all hrHPV infections are considered removed as well. No new hrHPV infections can be acquired.

Cervical Intraepithelial Neoplasia (CIN)

- Most CIN1 lesions will develop from an hrHPV infection
- Each woman has an age-specific risk of developing a CIN1 lesion in the absence of hrHPV.
- Progression probabilities for CIN lesions depend on lesion grade, age and hrHPV genotype. Most CIN1 lesions will clear before progression to CIN2. Those that progress to CIN2 will mostly clear before progression to CIN3. hrHPV-negative CIN3 will never progress to cancer.[10]
- If a woman has a hysterectomy because of cervical cancer or for other reasons than cervical cancer, all CIN lesions are considered removed as well. No new CIN lesions can be developed.

Cervical cancer

- Cervical cancer always develops following a hrHPV-positive CIN3 lesion.
- After the detection of cervical cancer, the woman has a hysterectomy. Therefore, we do not assume any possibility of having a recurrent cervical cancer.
- Preclinical FIGO1A does not cause symptoms yet and will therefore never be clinically detected. Preclinical FIGO1B or higher stages can be detected clinically in the absence of screening or can progress to a higher cancer stage (Figure S2).
- Durations of the different cancer stages do not depend on age or genotype
- Once a lesion has become cancer, progression probabilities to higher cancer stages depend on age, but are equal across genotypes.
- Clinically detected cervical cancer can either be cured or cause cervical cancer death. The probability to die from cervical cancer is dependent on the cancer stage and the age of the woman.
- If the woman is cured she will stay in the cancer state until death of other causes. If the women is not cured, she will die of cervical cancer within a maximum of 10 years after diagnosis.

Hysterectomy

- Women who do not have cervical cancer have an age-specific probability of getting a hysterectomy for reasons other than cervical cancer.
- A hysterectomy is assumed to remove all prevalent hrHPV infections and CIN lesions.
- Women who have had a hysterectomy will no longer acquire new hrHPV infections or develop new CIN lesions and will no longer be invited for screening tests

4.3. Screening assumptions

Several assumptions have to be made regarding the performance of the screening tests, the consequences of colposcopy and the screening behaviour of the women. For an overview of the screening part of the model, please see the screening part section of the model overview.

Terminology

- The screening strategy of an organised screening programme determines between which ages women are invited for screening, with which interval they are invited, which primary test is performed and which triage tests are performed after a positive primary test.
- A primary test is the initial screening test a woman is invited to. Based on the result of this test, the woman will be referred to colposcopy or triage testing.
- The primary test can either be cytology (checking for abnormal cells), hrHPV-test (checking for the presence of hrHPV) or a co-test, which is a combination of both.
- A triage test is a screening test that is performed after a woman has had a positive primary screening test, but before the decision is made whether or not to refer her for a colposcopy (e.g. a cytology test after a positive primary hrHPV-test). The triage test can be performed either directly after the primary test, or after a waiting period of several months or years, depending on the screening strategy.
- A colposcopy is a diagnostic exam by a gynaecologist to determine the presence of disease. This might include taking a biopsy.

Performance of the screening tests

- The probability of having a positive test result depends on the lesion grade and the hrHPV status of the woman for both cytology and the hrHPV-test.
- No differences in test characteristics are assumed for different hrHPV genotypes, both for cytology and the hrHPV-test.
- Systematic positive and systematic negative test results over time are possible for cytology for certain women, infections or lesions.

Screening behaviour

- Women invited to screening can either attend or not attend the primary screening test. The probability to attend is dependent on age. If a woman attends, she will do so exactly at the invited age.
- If a woman attends the primary test and is referred to triage testing or colposcopy, she might not adhere to this referral.

- If a scenario is simulated where the age ranges of the screening programme are extended compared to the current target ages, women in those newly targeted age groups will attend with the same probability as the closest age group that is invited in the current screening programme.

Colposcopy

- When a woman is referred to colposcopy, all prevalent CIN lesions will be diagnosed and removed/treated.
- Colposcopy is 100% accurate and will show the highest prevalent lesion.
- Women with a prevalent hrHPV infection but without a prevalent CIN will not be treated. The hrHPV infection may still progress to CIN after the colposcopy.
- As screen-detected cancers tend to have a better stage-specific survival than clinically detected cancers, detection of cervical cancer by screening in the model may prevent death from cervical cancer. However, if the death from cervical cancer is not prevented, the duration until death from cervical cancer will not be different from clinically detected cancers.

5. Model parameters

Next to the assumptions on the structure of the model, calculations or assumptions have to be made to determine the exact values of certain model parameters. In this section, we will describe the type of parameters that serve as inputs for the model and how the values of these parameters are determined. The parameters are categorised by the part of the model they belong to. Please see the model overview section above for more information about the model parts. Some parameters were calibrated. Please see the calibration section for more information about the calibration process.

5.1. Demographic part

The model simulates a cohort of 30 year-old women who are all born at the same date and have not been screened yet. Each woman in this cohort has a probability to die at each age as reported by Statistics Netherlands in The Netherlands for Dutch women in 2018, which results in a remaining life expectancy of 54.3 years.[12] Dutch age-specific hysterectomy probabilities by age were also obtained from the CBS for the most recent year available (2010).[13]

5.2. Natural history part

Background risk

The age-specific background risk for acquiring a hrHPV infection is calibrated to the hrHPV-prevalence as observed in the Dutch screening programme (see calibration section). The age-specific distribution of hrHPV infections over the four categories of genotypes is based on Coupe et al. 2008.[14] The background risk for acquiring a hrHPV infection for the 10% of the population that never attends screening ('never attenders') was previously found to be higher than that risk for the remaining 90% of the population that never attends screening.[7] In this calibration, the relative background risk of never attenders was estimated to be 2.6 compared to the rest of the population.

Progression probabilities of pre-invasive lesions

The age-specific probabilities that an hrHPV infection will progress to CIN1, CIN2, CIN3 or cancer are estimated during the calibration process using, among other sources, detection rates of the Dutch screening programme as a calibration target (see calibration section).

Probabilities of clinical detection of cancer

The age-specific probability that a FIGO1B, FIGO2 or FIGO3 cancer will be clinically detected before it progresses to a higher cancer stage is based on the calibration process during which the cancer stage distribution was the

main calibration target. FIGO1A is assumed not to give symptoms, so it will not be clinically detected, whilst FIGO4 cannot progress to a higher cancer stage, so will always be clinically detected at that stage.

Duration of health states

Most health states in the model have a duration, before transition to a next health state, that is drawn from a Weibull distribution. Most of these distributions have a Weibull shape parameter of 1, making them an exponential distribution (Table S1). The duration of clinical cervical cancer (states 34-37) and death from cervical cancer, if a woman is not cured, is assumed to be less than ten years and based on stage-specific survival data from the Dutch cancer registry (NKR).

Table S1. Durations of health states

Transition number*	From state*	To state*	Mean duration (years)	Weibull shape	Source
1	4. HPV-OHR	1. Normal	1	1	[15, 16]
2	4. HPV-OHR	9. HPV-OHR CIN1	1	1	[15, 16]
3	5. HPV-9V	1. Normal	1	1	[15, 16]
4	5. HPV-9V	10. HPV-9V CIN1	1	1	[15, 16]
5	6. HPV-18	1. Normal	1	1	[15, 16]
6	6. HPV-18	11. HPV-18 CIN1	1	1	[15, 16]
7	7. HPV-16	1. Normal	1	1	[15, 16]
8	7. HPV-16	12. HPV-16 CIN1	1	1	[15, 16]
9	8. NoHPV CIN1	1. Normal	1.5	1	[17]
10	8. NoHPV CIN1	13. NoHPV CIN2	1.5	1	[17]
11	9. HPV-OHR CIN1	1. Normal	1.5	1	[17]
12	9. HPV-OHR CIN1	14. HPV-OHR CIN2	1.5	1	[17]
13	10. HPV-9V CIN1	1. Normal	1.5	1	[17]
14	10. HPV-9V CIN1	15. HPV-9V CIN2	1.5	1	[17]
15	11. HPV-18 CIN1	1. Normal	1.5	1	[17]
16	11. HPV-18 CIN1	16. HPV-18 CIN2	1.5	1	[17]
17	12. HPV-16 CIN1	1. Normal	1.5	1	[17]
18	12. HPV-16 CIN1	17. HPV-16 CIN2	1.5	1	[17]
19	13. NoHPV CIN2	1. Normal	2	1	[17, 18]
20	13. NoHPV CIN2	23. NoHPV CIN3	2	1	[17, 18]
21	14. HPV-OHR CIN2	1. Normal	2	1	[17, 18]
22	14. HPV-OHR CIN2	24. HPV-OHR CIN3	2	1	[17, 18]
23	15. HPV-9V CIN2	1. Normal	2	1	[17, 18]
24	15. HPV-9V CIN2	25. HPV-9V CIN3	2	1	[17, 18]

25	16. HPV-18 CIN2	1. Normal	2	1	[17, 18]
26	16. HPV-18 CIN2	26. HPV-18 CIN3	2	1	[17, 18]
27	17. HPV-16 CIN2	1. Normal	2	1	[17, 18]
28	17. HPV-16 CIN2	27. HPV-16 CIN3	2	1	[17, 18]
29	23. NoHPV CIN3	1. Normal	5.7	0.84	Calibration
30	24. HPV-OHR CIN3	1. Normal	5.7	0.84	Calibration
31	24. HPV-OHR CIN3	28. FIGO1A	14.3	0.84	Calibration
32	25. HPV-9V CIN3	1. Normal	5.7	0.84	Calibration
33	25. HPV-9V CIN3	28. FIGO1A	14.3	0.84	Calibration
34	26. HPV-18 CIN3	1. Normal	5.7	0.84	Calibration
35	26. HPV-18 CIN3	28. FIGO1A	14.3	0.84	Calibration
36	27. HPV-16 CIN3	1. Normal	5.7	0.84	Calibration
37	27. HPV-16 CIN3	28. FIGO1A	14.3	0.84	Calibration
38	28. Preclinical FIGO1A	29. Preclinical FIGO1B	4	1	Calibration
39	29. Preclinical FIGO1B	34. Clinical FIGO1B	2.2	1	Calibration
40	29. Preclinical FIGO1B	30. Preclinical FIGO2	2.2	1	Calibration
41	30. Preclinical FIGO2	35. Clinical FIGO2	1.7	1	Calibration
42	30. Preclinical FIGO2	31. Preclinical FIGO3	1.7	1	Calibration
43	31. Preclinical FIGO3	36. Clinical FIGO3	1.7	1	Calibration
44	31. Preclinical FIGO3	32. Preclinical FIGO4	1.7	1	Calibration
45	32. Preclinical FIGO4	37. Clinical FIGO4	0.7	1	Calibration

* All possible states and transitions are graphically presented in Figure S2.

HPV=human papillomavirus OHR=Other high risk types 9V=HPV genotypes covered by the nonavalent vaccine, excluding HPV 16 and HPV18 CIN=Cervical intraepithelial neoplasia FIGO=Fédération Internationale de Gynécologie et d'Obstétrique..

5.3. Screening part

For this analysis, two screening programmes are modelled: the cytology screening programme as it was applied in The Netherlands until 2016 and the hrHPV-based programme that was implemented in The Netherlands in 2017.

In the modelled Dutch cytology programme, women aged 30–60 were screened five-yearly. Women with a High-grade Squamous Intraepithelial Lesion (HSIL) or worse were referred for colposcopy, while women with a lower grade positive cytology result were invited for a repeat test after six months using a co-test of cytology and hrHPV (Figure S5). In the hrHPV screening programme, women are still invited five-yearly at the ages 30–60, however the screening interval is extended to ten years for women testing negative for hrHPV at the ages of 40 or 50 and there is an extra invitation at the age of 65 for women testing hrHPV+ at age 60. After a positive hrHPV test, the sample is analysed with cytology after which a positive cytology leads to referral to colposcopy, while after a negative cytology women are invited for a repeat cytology test after six months (Figure S5). Women who are uncomfortable with taking a test at their general practitioner can request a hrHPV-sampling kit, although after a positive self-sample, the women still need a smear at their GP to perform the cytology on.

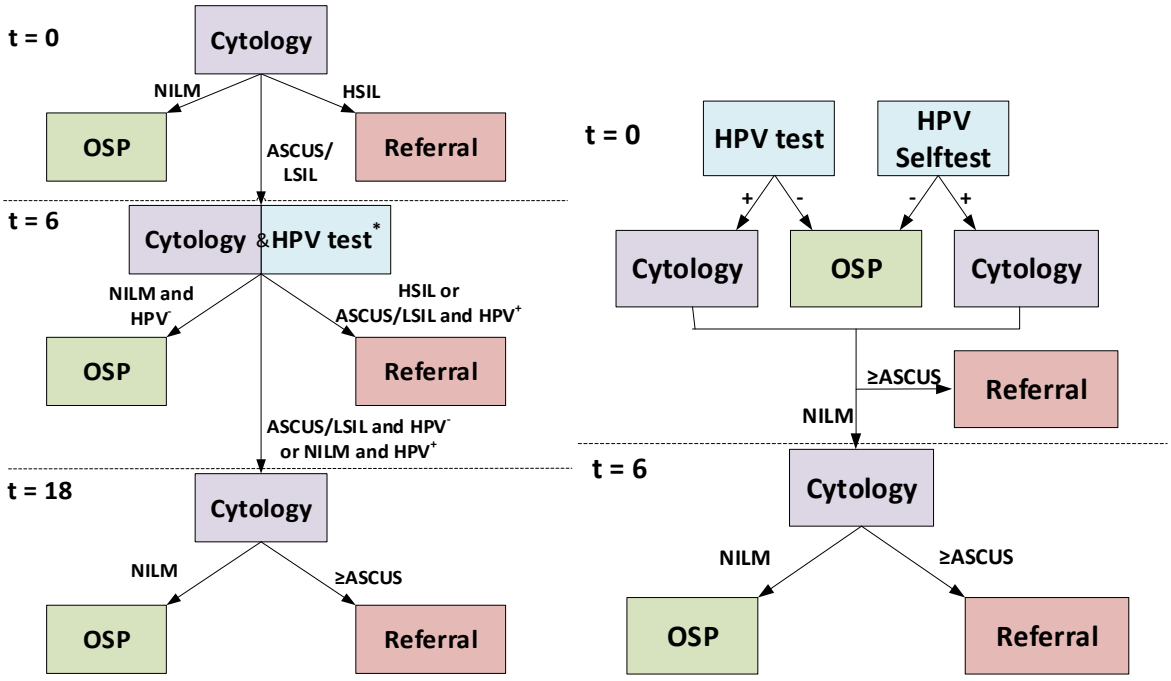

Figure S5. Triage in the cytology (left) and the hrHPV (right) screening programmes.

t = Time in months since primary test; OSP = Organised screening programme; HPV = Human papillomavirus; NILM = Negative for intraepithelial lesion or malignancy; ASC-US = Atypical squamous cells of undetermined significance; LSIL = Low-grade squamous intraepithelial lesion; HSIL = High-grade squamous intraepithelial lesion.

Screening behaviour

The age-specific probability to attend primary screening is based on observations in both the cytology and the hrHPV-based screening programme as well as the adherence to repeat testing or colposcopy in the triage. The probability to attend a primary cytology test was defined as the proportion of women eligible for screening in 2015 that attended before April 1 2016. The probability to attend a primary hrHPV-test was defined as the proportion of women eligible for screening in 2017 that attended before August 2018 either at their GP or by returning a self-sampling kit. The three months of longer follow-up for the hrHPV-based programme were added because the hrHPV-programme was starting up in 2017 and some delays in attendance might have occurred because of the implementation phase. We did not model any opportunistic screening activities outside the age ranges of the screening programmes. The adherence to repeat testing was defined as the proportion of women referred to repeat testing having a registered surveillance test within 6 months after the recommended date of the repeat test. The adherence to colposcopy was defined as the proportion of women referred to colposcopy having a registered cytology or histology result within 15 months after the referral date. The reason for this long follow-up is that it is standard practice in The Netherlands to not perform a biopsy at women having a low grade cytology result and a clear colposcopy, but to invite them for a repeat cytology after 12 months instead.

Self-sampling among previous never attenders

The proportion of self-samplers that now participates in screening, but would otherwise be never attenders is defined by the observed proportion of self-samplers that did not participate in the last two screening rounds according to the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA) database minus this proportion for women taking a smear at their GP:

P(NASS) = P(NoPrevScrSS) – P(NoPrevScrGP)

Where:

P(NASS) = The proportion of observed self-samplers that would otherwise be never attenders

P(NoPrevScrSS) = The proportion of self-samplers of whom no previous primary screen has been recorded for the last 10 years.

P(NoPrevScrGP) = The proportion of women taking a test at their GP of whom no previous primary screen has been recorded for the last 10 years.

Since women aged 30 or 35 were not invited at least twice before, the proportion of young women taking a self-sample that would otherwise be never attenders was assumed to be equal to the weighted average proportion of 40-60 year old women (Table S2)

Screening participation with extended intervals

In the first screening round after implementation, all women at the ages 45 and 55 were invited for screening, while in future rounds only those that tested hrHPV-positive in the previous round or did not participate the previous round will be invited. Therefore, fewer women will participate at those ages than currently observed in the first screening round (Table S2). Also, in this first screening round no women aged 65 were invited yet as they had to test hrHPV-positive at age 60 first. Therefore, we assumed the participation rate for women at age 65, who tested hrHPV-positive at age 60, to be the same as age 60:

$Att_{Sim}45$: $((1 - Att_{Obs}40) + (Att_{Obs}40 * HPV_{pos}40)) * Att_{Obs}45$

$Att_{Sim}55$: $((1 - Att_{Obs}50) + (Att_{Obs}50 * HPV_{pos}50)) * Att_{Obs}55$

$Att_{Sim}65$: $(Att_{Obs}60 * HPV_{pos}60)) * Att_{Obs}60$

Where:

Att_{Sim} = The simulated attendance in the population at the indicated age

Att_{Obs} = The observed attendance in the population at the indicated age in the first screening round

HPV_{pos} = The observed proportion of women testing hrHPV-positive at the indicated age in the first screening round

Att_{Obs} = The observed attendance at the indicated age in the first screening round

Table S2. Modelled screening behaviour by type of screening programme: base case assumptions

Screening behaviour	Cytology-based screening programme	hrHPV-based screening programme
*GP-test participation by age in all women of the Population**		
- 30 years	52.3%	43.4%
- 35 years	57.9%	49.3%
- 40 years	64.3%	56.4%
- 45 years	67.6%	15.6%**
- 50 years	70.4%	61.5%
- 55 years	69.6%	12.7%**
- 60 years	66.8%	60.3%
- 65 years	NA	3.1%***
*Self-sampling participation by age**		
- 30 years	NA	5.5%
- 35 years	NA	4.8%
- 40 years	NA	4.5%
- 45 years	NA	0.9%**
- 50 years	NA	4.6%
- 55 years	NA	1.0%**
- 60 years	NA	5.7%
- 65 years	NA	0.2%***
Adherence to cytology after a positive self-sample	NA	90.1%
Adherence to triage testing		
- 6 months after primary test	92.2%	77.1%
- 6 months after primary self-sample	NA	41.6%
- 18 months after primary test	67.3%	NA
Adherence to a referral for colposcopy after a		
- direct referral (ASC-US/LSIL)	NA	88.4%
- direct referral (HSIL)	97.0%	96.9%
- referral at 6 months after primary test	97.5%	88.4%
- referral at 6 months after primary test (HSIL)	97.5%	96.9%
- referral at 18 months after primary test	52.4%	NA

* Simulated participation rate in all women excluding those who have had a hysterectomy and those with a prevalent diagnosed cancer.
** Participation in the general population is much lower at ages 45 and 55 because significantly fewer women are invited for screening at these ages (i.e. only those who do not participate or test hrHPV-positive in the preceding screening round).
*** Participation in the general population is much lower at age 65 because significantly fewer women are invited for screening at this age (i.e. only those who test hrHPV-positive at age 65).
hrHPV = high-risk human papillomavirus; NA = not applicable; ASC-US = Atypical squamous cells of undetermined significance; LSIL = Low-grade squamous intraepithelial lesion; HSIL = High-grade squamous intraepithelial lesion.

Test characteristics

The test characteristics in MISCAN-Cervix are presented in Table S3. The probabilities of a cytology test being positive are calibrated based on detection rates and interval cancers. The calibration process is explained in more detail in the calibration section. Test characteristics for the hrHPV-test are based on literature. The sensitivity of the hrHPV test for hrHPV-positive women with a ≥CIN2 lesion was found to be 94% in the POBASCAM study.[19] The probability of a positive hrHPV-test in hrHPV-positive women with no CIN and hrHPV-positive women with a CIN 1 is based on a study of Rebolj and collegues using data from the Danish Horizon study.[20] The study presented concordance between the Hybrid Capture 2, cobas, CLART and Aptima hrHPV tests. We assumed that any prevalent hrHPV infection would be picked up by at least one of the four assays and defined the probability of a positive test result as the proportion of those total hrHPV infections that tested positive on the cobas hrHPV test.

Table S3. Test characteristics of the cytology test and the hrHPV-test by disease status

Test result and disease status	Probability of a positive test result
*Cytology ≥ASC-US in case of no prevalent hrHPV infection**	
- No CIN present	0.60%
- CIN1	41.24%
- CIN2	42.25%
- CIN3	85.80%
- Cervical cancer	85.09%
*Cytology ≥ASC-US in case of ≥1 prevalent hrHPV infection**	
- No CIN present	17.08%
- CIN1	41.24%
- CIN2	42.25%
- CIN3	85.80%
- Cervical cancer	85.09%
*Cytology ≥HSIL in case of no prevalent hrHPV infection**	
- No CIN present	0.04%
- CIN1	2.98%
- CIN2	12.19%
- CIN3	58.73%
- Cervical cancer	64.73%
*Cytology ≥HSIL in case of ≥1 prevalent hrHPV infection**	
- No CIN present	0.00%
- CIN1	2.98%
- CIN2	12.19%
- CIN3	58.73%
- Cervical cancer	64.73%
*Positive hrHPV-test**, in case of no prevalent hrHPV infection*	0%
*Positive hrHPV-test**, in case of ≥1 prevalent hrHPV infection*	
- No CIN present	55%
- CIN1	72%
- CIN2	94%
- CIN3	94%
- Cervical cancer	94%

* Probability to test positive the first time a women with this lesion present attends screening. 12% of the CIN lesions will be missed systematically over time.

**The same test characteristics are assumed for GP smears as for self-sampling kits

hrHPV = high-risk human papillomavirus; CIN = cervical intraepithelial neoplasia; ASC-US = Atypical squamous cells of undetermined significance; LSIL = Low-grade squamous intraepithelial lesion; HSIL = High-grade squamous intraepithelial lesion

6. Model calibration

The values of some model parameters in the parameter overview could either be based on observed data or on available literature. However, some other model parameters could not be derived from observational data (e.g. the age-specific background risk for acquiring an hrHPV-infection). Therefore, these parameter values needed to be calibrated.

In the calibration MISCAN-Cervix, a population is simulated for which high quality observational data is available over a time span of 10 years, including the screening behaviour of that population. In this case we used the Dutch female population in 2004-2013 and simulated their screening behaviour in the cytology programme.

The parameters that could not be derived from observational data or literature are estimated based on expert opinion or studies on similar parameters. The model runs with this set of parameter values after which the outputs of the model are compared with the observed data of that population on:

- Cervical cancer incidence by age
- Cervical cancer stage distribution by age
- HPV prevalence by age cytology result, lesion grade and genotype
- Detection rates.

Based on this comparison, the model inputs are adjusted using the Nelder-Mead algorithm. With these new inputs the model runs again where the calibration cycle starts again (Figure S6).[21] This cycle is repeated until the outputs of the model reflect the observed data well.

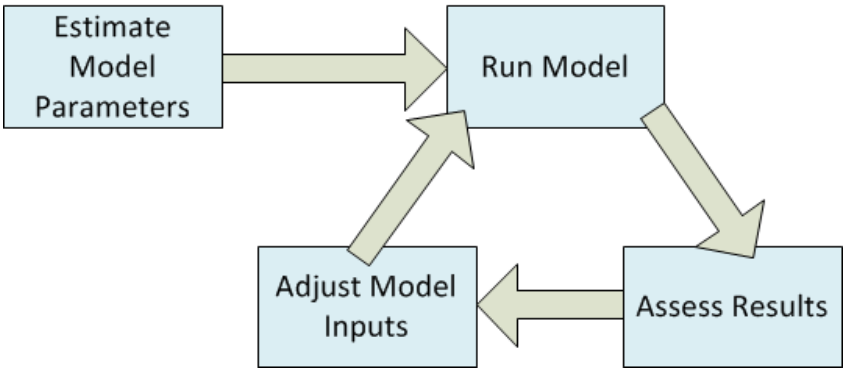

Figure S6. Calibration cycle.

6.1. Stepwise process

Due to the large number of parameters that need to be calibrated, we used a three-step approach.

Step 1

First, we isolated the infections that would progress to cancer, by setting all progression probabilities at 1. Than the parameters that are related to the development of cancer are calibrated on the cancer incidence, stage distribution and cancer detection rates. These durations and probabilities that are calibrated in step 1 are represented in Figure S7 by yellow ellipses and green ellipses respectively.

- Duration of progressive CIN3, including the shape of the corresponding Weibull distribution
- Duration of FIGO1A, FIGO1B, FIGO2, FIGO3 and FIGO4
- The probability that a cancer is clinically detected, before progressing to a higher stage, when in stage FIGO1B, FIGO2 or FIGO3. Please note that FIGO1A cancers are assumed not to give symptoms yet and FIGO4 cancers already reached the highest stage.

Also, test characteristics of cytology are calibrated that are related to cancer development.

- Sensitivity of cytology for CIN3
- Sensitivity of cytology for cervical cancer
- The probability of systematically missing a lesion at cytology.[22]

Lastly, the relative background risk of 'never attenders' is calibrated in this step as well.

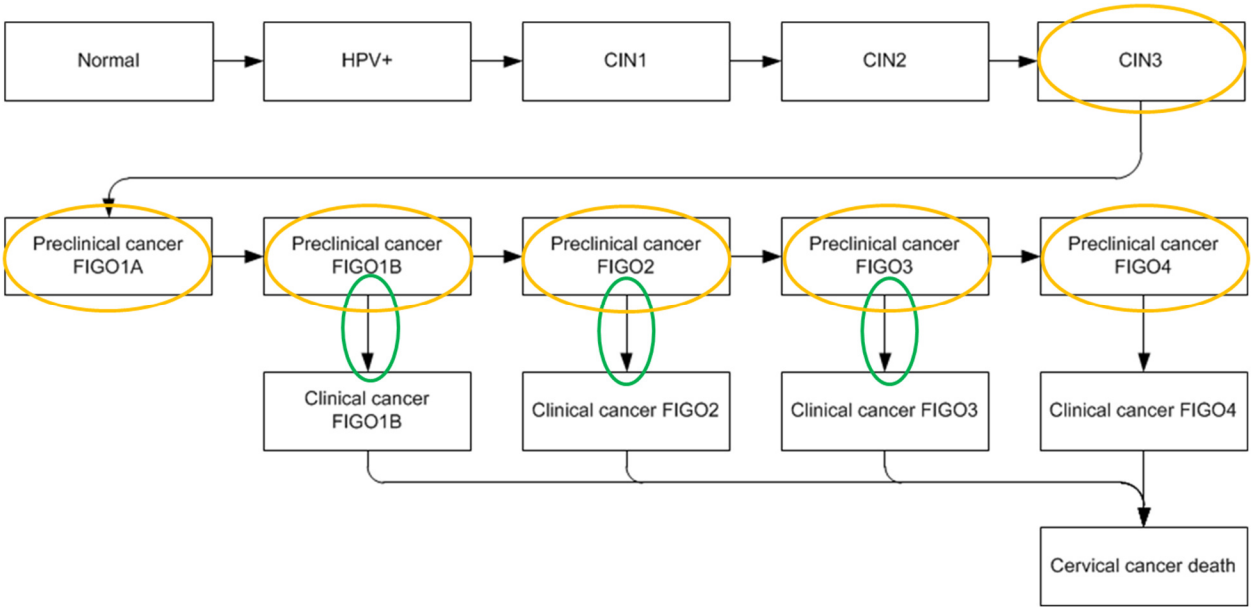

Figure S7. Calibrated durations and probabilities during step 1 of the calibration process.

HPV = human papillomavirus; CIN = cervical intraepithelial neoplasia; FIGO = International Federation of Gynaecology and Obstetrics.

Step 2

In the second step, we introduce clearance of hrHPV and regression of CIN lesions to the model to calibrate the parameters that are related to the development of precancerous lesions (Figure S8).

- Duration of regressing CIN3 (yellow ellipse)
- Hazard rate for an hrHPV infection
- Hazard rate for the development of a CIN1 in absence of hrHPV
- The age-specific probability of progression of hrHPV/CIN1/CIN2/CIN3 to a higher stage

Test characteristics calibrated in this step are:

- Sensitivity of cytology for CIN1
- Sensitivity of cytology for CIN2
- Probabilities of a positive cytology result in absence of CIN or hrHPV
- Probabilities of a positive cytology result in hrHPV-positive women in absence of CIN

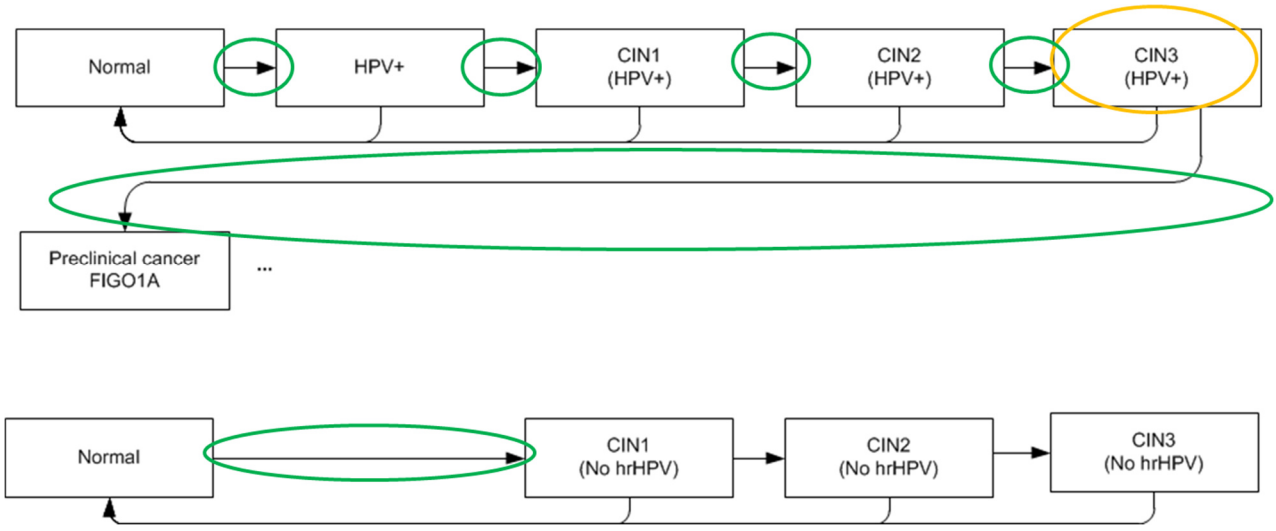

Figure S8. Calibrated durations and probabilities during step 2 of the calibration process.

HPV = human papillomavirus; CIN = cervical intraepithelial neoplasia; FIGO = International Federation of Gynaecology and Obstetrics.

Step 3

In the third and last step of the calibration process, the progression probabilities of hrHPV-infections and CIN lesions will be made type-specific to create the 5 disease pathways of the model. The reason that these probabilities need to be type-specific is that some types have been found to be more carcinogenic and therefore have a higher probability of progressing than others. As a starting point, all age-specific progression probabilities are assumed to be equal to those in the second step of the calibration, but a type-specific and disease stage-specific multiplication factor will be applied and adjusted by the Nelder-mead algorithm to obtain different progression probabilities by hrHPV-type, indicated by the green ellipses in Figure S9.

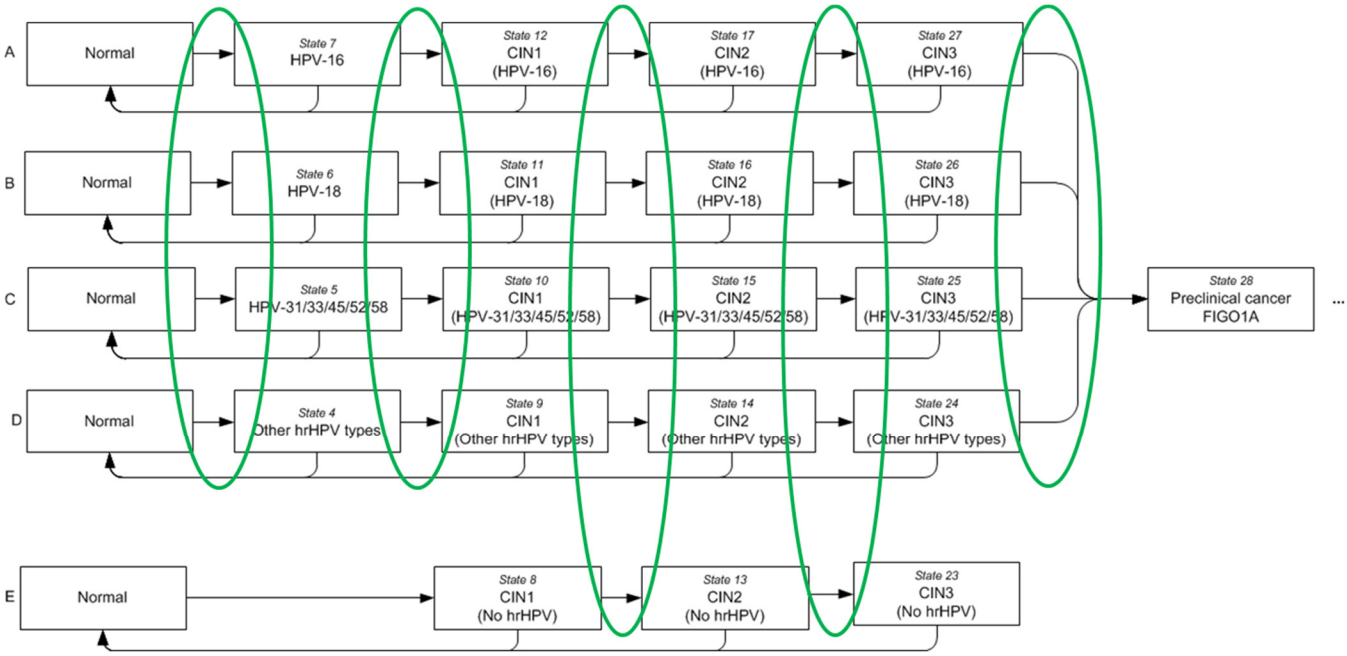

Figure S9. Calibrated probabilities during step 3 of the calibration process.

HPV = human papillomavirus; CIN = cervical intraepithelial neoplasia; FIGO = International Federation of Gynaecology and Obstetrics.

7. Calibration results

The Dutch MISCAN-Cervix model was calibrated to data from the Netherlands Cancer Registry (NCR) on age-specific and stage-specific cervical cancer incidence in the Netherlands in 2004-2013 (Figures S10 and S11). Detection rates from the organised screening programme are registered by PALGA and were used to calibrate the sensitivity of cytology and the progression probabilities of hrHPV and CIN (Figure S12). The age-specific hrHPV prevalence was calibrated to positivity rates as observed in the organised hrHPV screening programme between January 1st 2017 and March 31st 2018 (Figure S13). The observed hrHPV positivity rates for women under 30 was extrapolated based on hrHPV-prevalence in Finland.[23] The distribution over the different hrHPV-types was calibrated to a Dutch study of Coupe et al. in 2008 assessing the type-specific prevalence of >45 000 women (Figure S14).[14] Finally, the differences between hrHPV-types in progression probabilities of pre-invasive states were calibrated to Western-European data from a meta-analysis of Guan et al. in 2012 (Figure S15).[24] The calibration resulted in a good fit of the model predictions with the observed data (Figures S10-S15). Also, the model predictions on age-specific mortality fitted well with the observed age-specific mortality rates in the Netherlands from 2004-2013 from the NCR, which were not used to fit on during the calibration, showing the validity of the model (Figure S16).

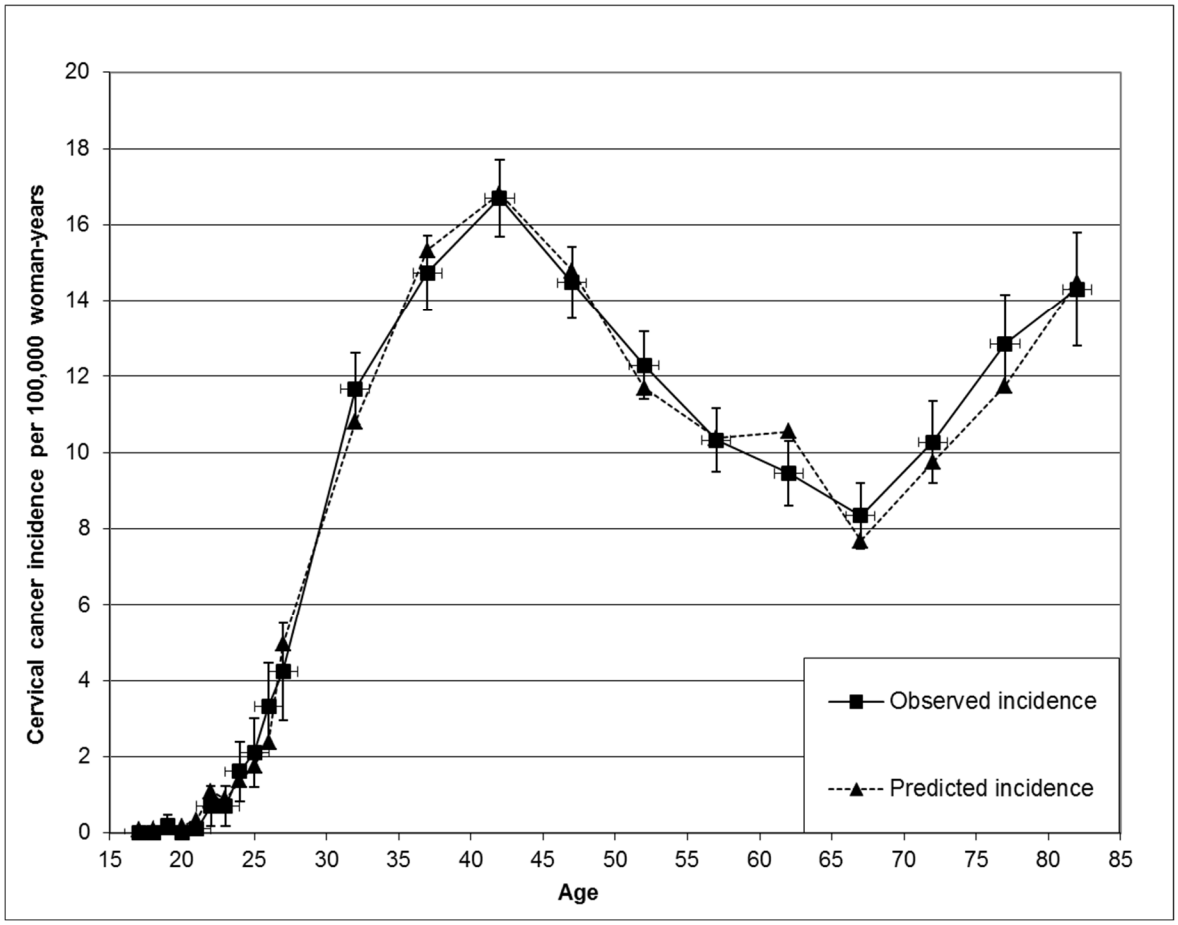

Figure S10. Model fit on age-specific cervical cancer incidence rates.

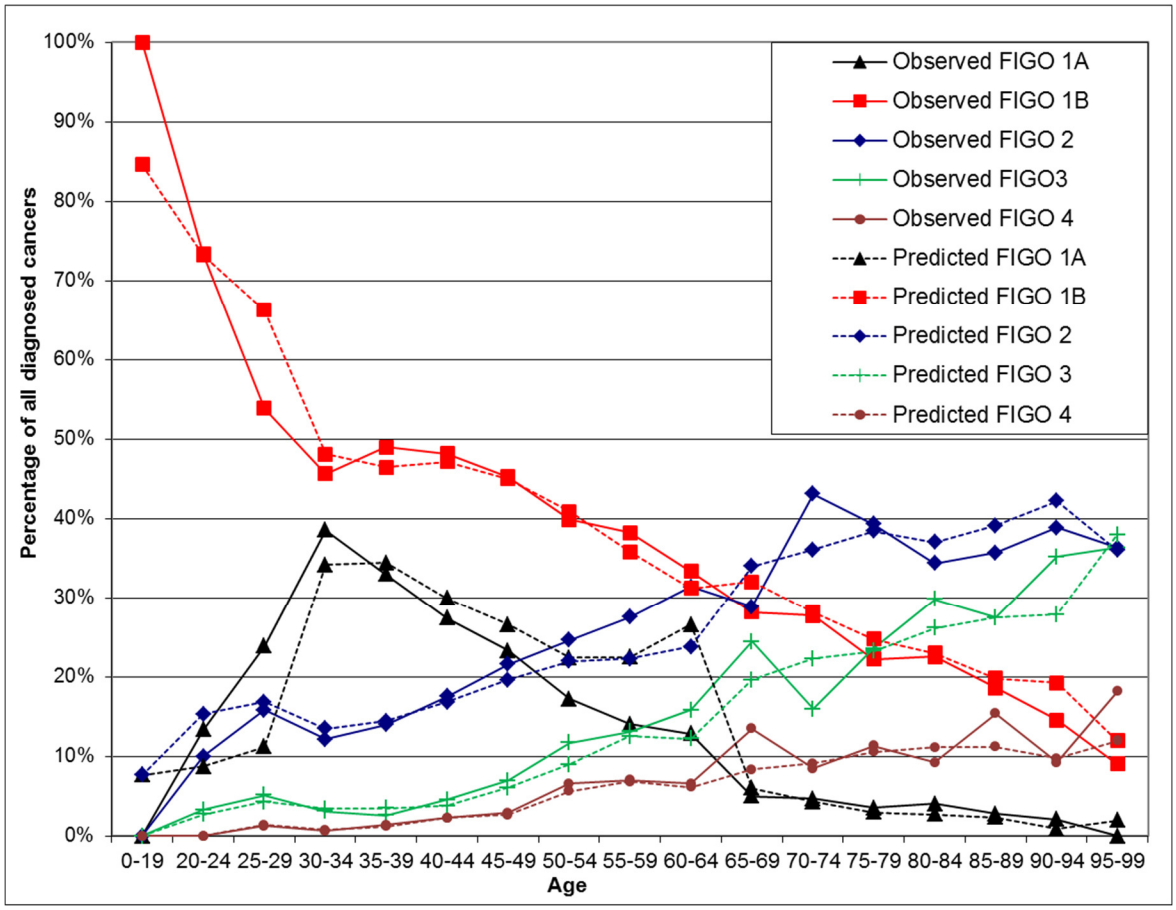

Figure S11. Model fit cervical cancer stage distribution by age.

FIGO = International Federation of Gynaecology and Obstetrics.

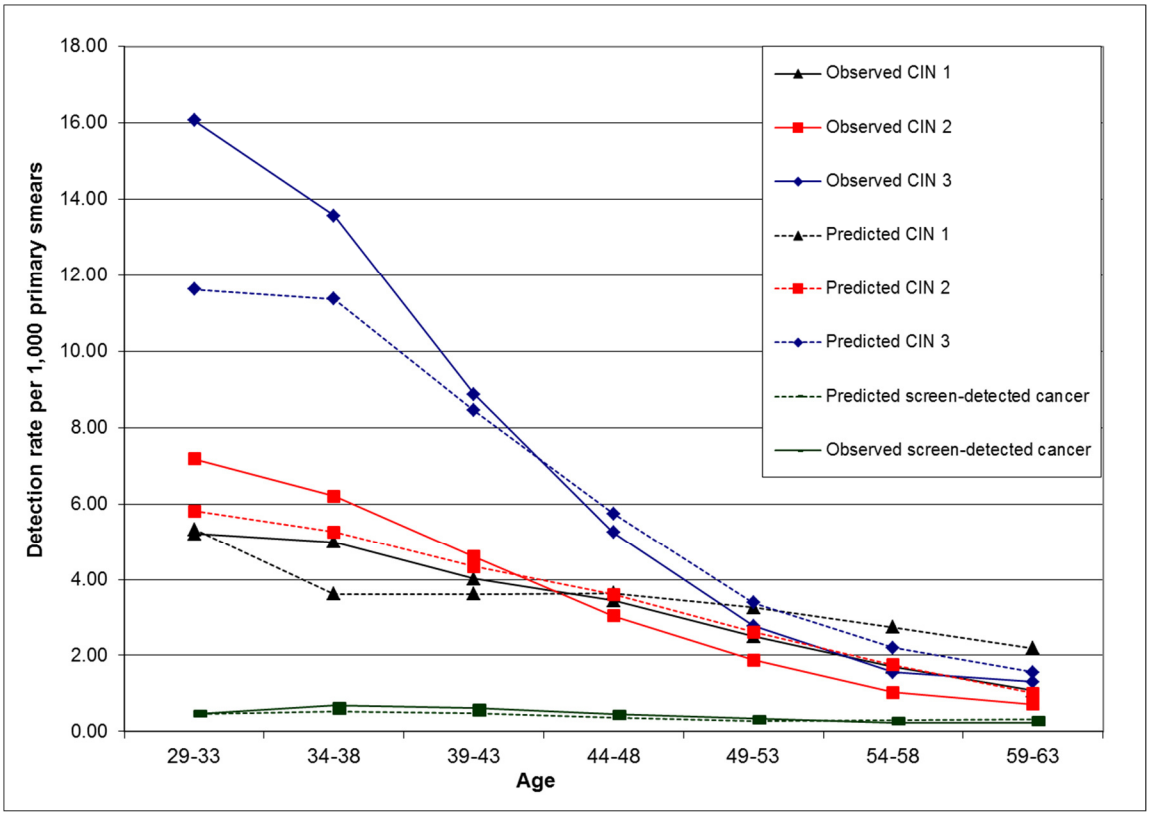

Figure S12. Model fit on age-specific detection rates rates.

CIN = cervical intraepithelial neoplasia.

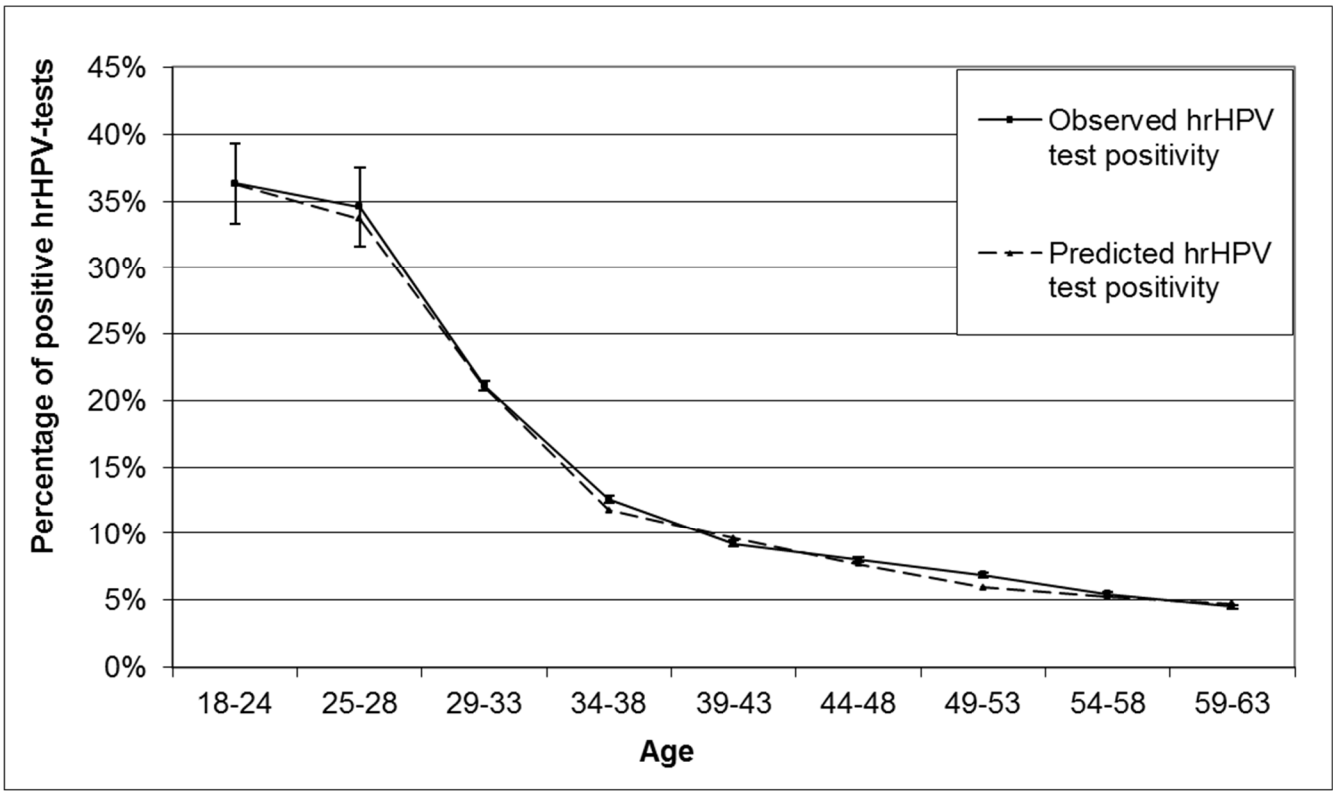

Figure S13. Model fit on age-specific hrHPV test-positivity rates.

hrHPV = high-risk human papillomavirus.

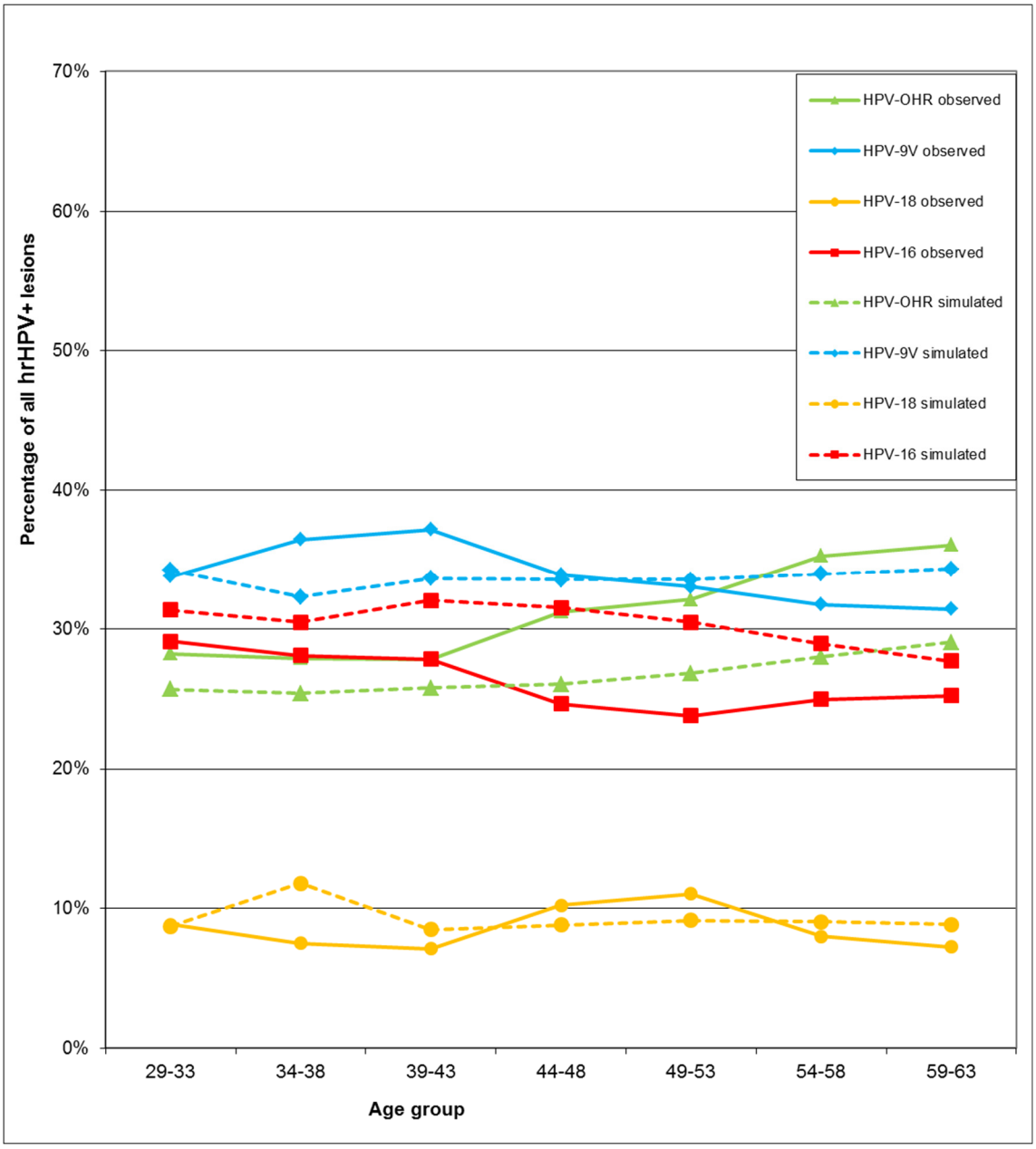

Figure S14. Model fit on age-specific hrHPV-type distribution among hrHPV-positive women.
(hr)HPV = (high-risk) human papillomavirus.

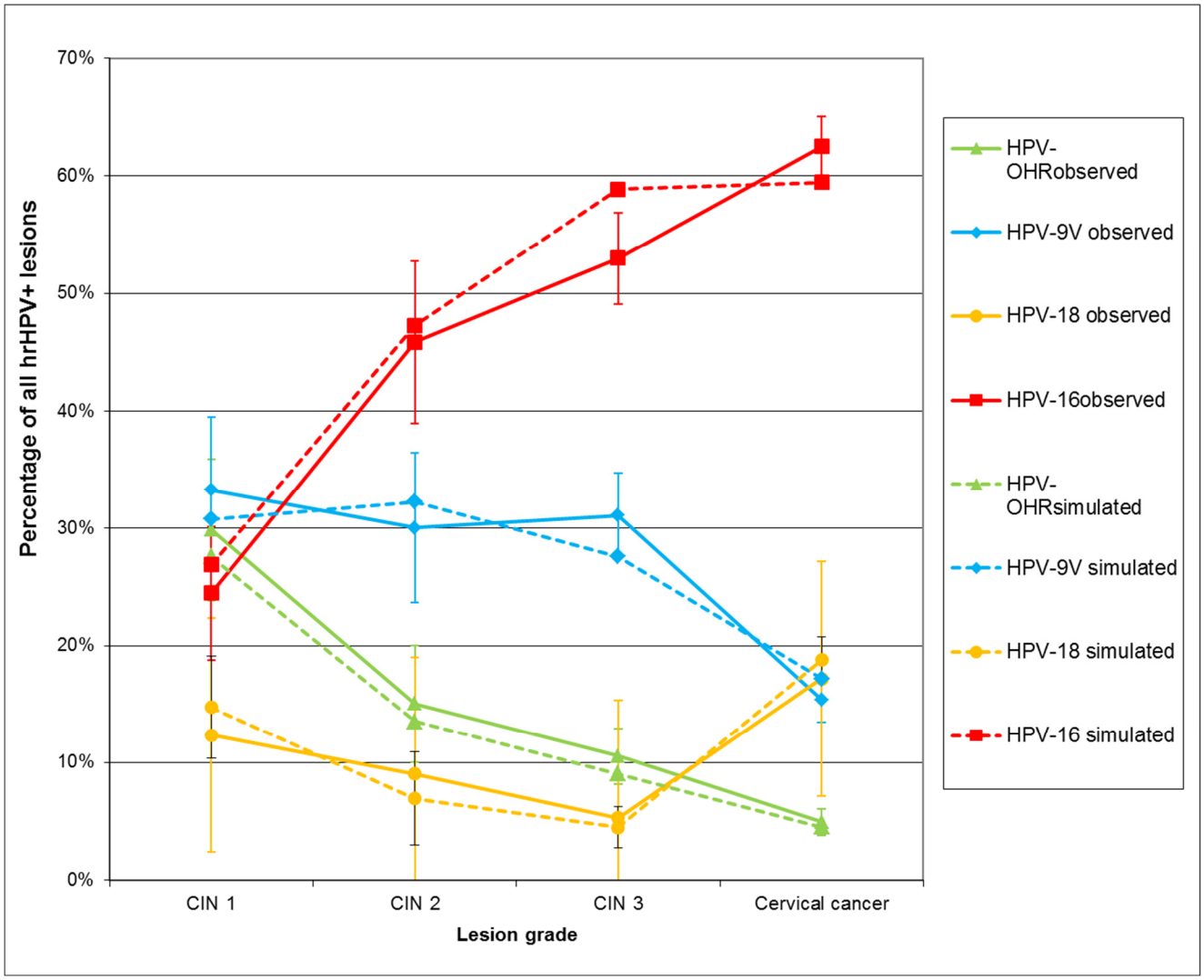

Figure S15. Model fit on lesion-specific hrHPV-type distribution among hrHPV-positive women.

(hr)HPV = (high-risk) human papillomavirus; CIN = cervical intraepithelial neoplasia.

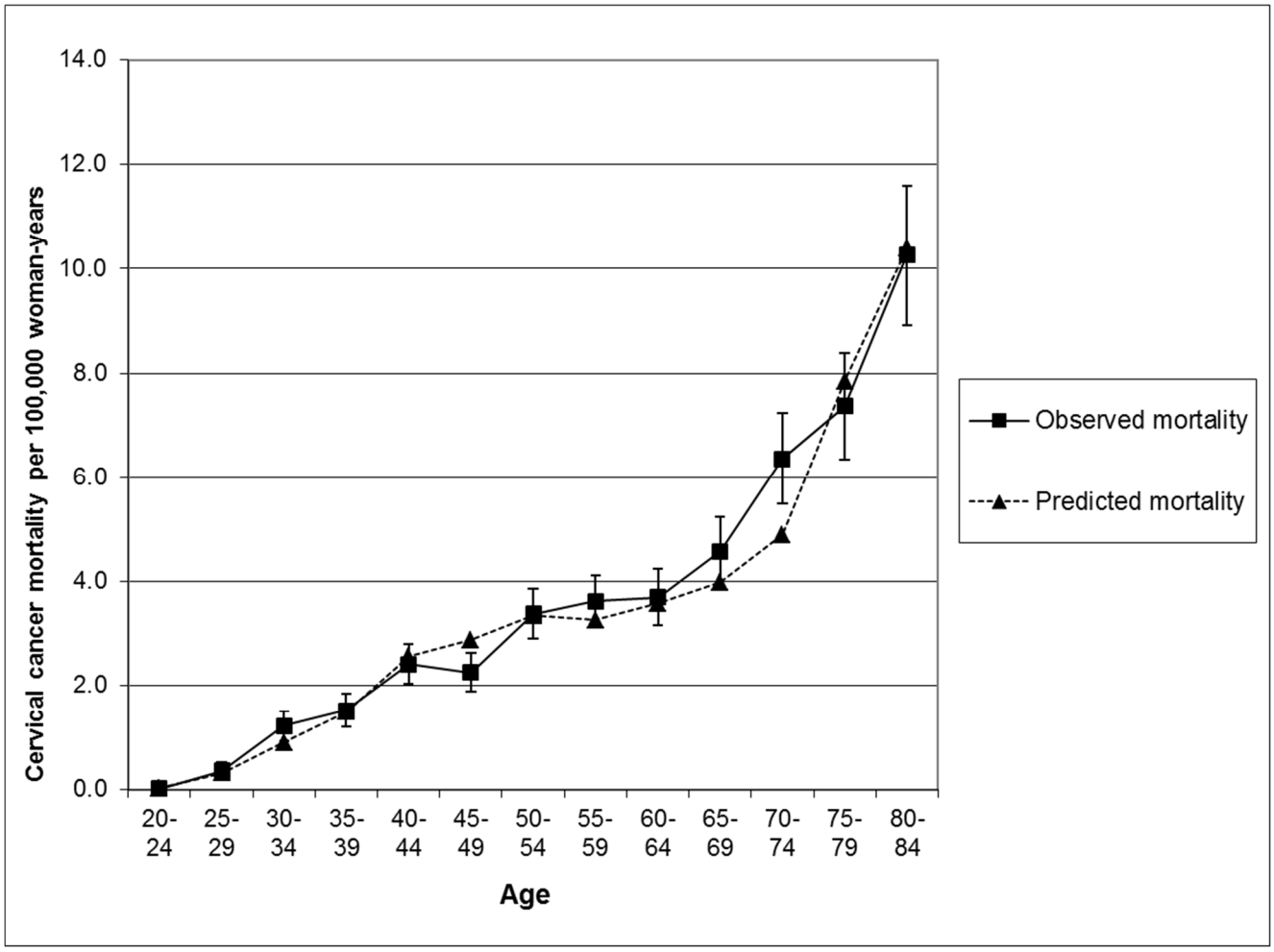

Figure S16. Model fit on age-specific mortality rates.

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