Description of MISCAN-cervix

Web Appendix accompanying 'A comparison of primary HPV to cytology cervical cancer screening in different European settings: A cost-effectiveness analysis based on a Dutch microsimulation model'

Inge M. C. M. de Kok[1], Joost van Rosmalen[1], Marjolein van Ballegooijen[1]

1) Erasmus MC, University Medical Center, Department of Public Health, Rotterdam, the Netherlands

Introduction

In this Web Appendix, we describe the model inputs of the MISCAN (microsimulation screening analysis) microsimulation model for cervical cancer.[1] This model can be used to assess the harms and benefits of different screening programs for cervical cancer, as well as human papillomavirus (HPV) vaccination. The model has been used previously for cost-effectiveness analysis of cervical cancer screening and HPV vaccination.[2-3]

The MISCAN model (Figure 1) consists of the following 4 parts: demography, natural history, screening, and cost-effectiveness. The assumptions used in each of these parts are described below.

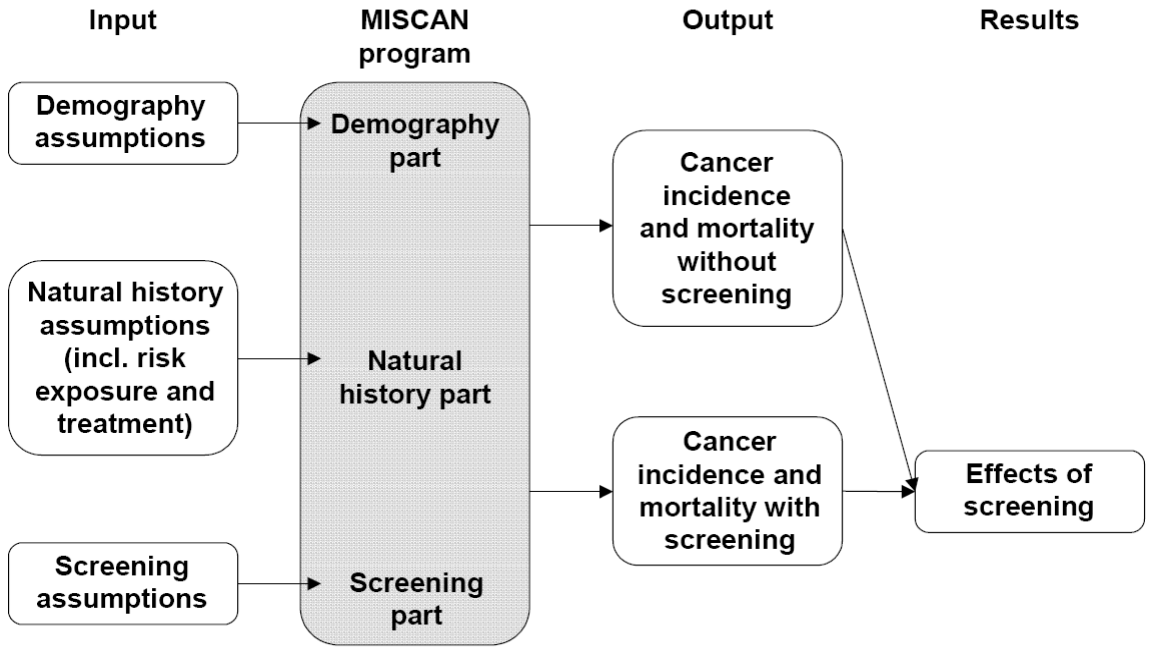

Figure 1: Structure of the MISCAN model

Demography

The MISCAN microsimulation model generates a simulated population of Dutch women born between 1939 and 1992. Women born after 1992 are eligible for HPV vaccination and are therefore not considered here. The relative sizes of the birth cohorts are based on the age distribution of women living in the Netherlands.

For each woman, a time of death from other causes (i.e. causes other than cervical cancer) is generated; this time of death is independent of the cervical cancer disease model. In the model, a woman's lifetime cannot exceed 100 years. The time of death from other causes is generated using a life table for women from Statistics Netherlands.[4] The assumed hysterectomy rates vary by age and by year of birth. These rates are based on data from Information Centre for Health Care[5-6] and are presented in Table 1.

Table 1: Model assumptions for the age-specific probability of having had a hysterectomy for reasons other than cervical cancer, for women with birth years 1939-1992. Linear interpolation is used to determine the probability of having had a hysterectomy at intermediate ages. Source: Information Centre for Health Care.[5-6]

Age	Birth year 1939-1949	Birth year 1949-1959	Birth year 1959-1992
20	0.000	0.000	0.000
25	0.002	0.004	0.004
30	0.012	0.018	0.018
35	0.057	0.049	0.049
40	0.122	0.098	0.098
45	0.170	0.146	0.146
50	0.199	0.176	0.176
55	0.214	0.191	0.191
60	0.230	0.206	0.206
65	0.246	0.222	0.222
70	0.262	0.239	0.239
75	0.275	0.252	0.252
80	0.284	0.259	0.259
85	0.287	0.263	0.263

Natural history

During her lifetime, each woman has an age-specific risk of acquiring high-risk HPV infections (i.e., an infection caused by an HPV type that can cause cancer and that can be detected by the HPV test) and HPV-negative CIN 1 lesions. Although most HPV infections clear or regress naturally, some HPV infections can progress to CIN 1, CIN 2, CIN 3, cervical cancer, and death from cervical cancer. A woman dies from cervical cancer only if death from cervical cancer occurs before the time of death from other causes.

To account for the fact that HPV-infections and CIN may clear or regress naturally, 6 disease pathways are distinguished in MISCAN. Each instance of these disease pathways represents an HPV-infection or a 'lesion' (i.e., CIN of a certain grade or a stage of cervical cancer). Each disease pathway starts as either an HPV infection or as an HPV-negative CIN lesion. The natural history (i.e. in the situation without screening) of these 6 disease pathways is shown in Figure 3 and can be described as follows.

A) HPV-infections that clear naturally without ever leading to CIN
B) HPV-infections that progress to CIN 1 and then regress
C) HPV-infections that progress to CIN 1 and CIN 2 and then regress
D) HPV-infections that progress to CIN 1, CIN 2, and CIN 3 and then regress
E) HPV-negative CIN 1 lesions that regress naturally or become HPV-negative CIN 2 and then regress naturally
F) HPV-infections that progress to CIN 1, CIN 2, CIN 3, preclinical FIGO 1A (micro-invasive) cervical cancer, and preclinical FIGO 1B cervical cancer. Preclinical FIGO 1B cervical cancer can either become clinically detected FIGO 1B cervical cancer or progress to preclinical FIGO 2+ cervical cancer and then to clinical FIGO 2+ cervical cancer. Clinically detected cervical cancer can progress to death from cervical cancer or remain in that state forever (if the woman is cured from cervical cancer).

A woman can acquire multiple lesions / HPV-infections during her lifetime, and multiple lesions/ HPV-infections may be present at the same time. In each simulated life history (i.e. between ages 0 and 100), the number of lesions of each type follows a Poisson distribution, and the starting age of each lesion / HPV-infection follows a piecewise uniform distribution.

The mean number of lesions of each type depends on a woman's birth year, based on the results of an age-period-cohort analysis; based on this analysis, we assumed a constant risk for woman born after 1949 and a risk that is 28% lower for women born from 1939 to 1949.[7] In addition, we assume that the expected number of lesions (i.e. the background risk) is 3 times higher for women who do not attend screening.[8] Any transitions or newly acquired HPV-infections that occur after the time of death are not counted in the model results. Figures 2A, 2B, and 2C present the annual background incidence of the 6 disease pathways for women who attend screening and are born after 1949.

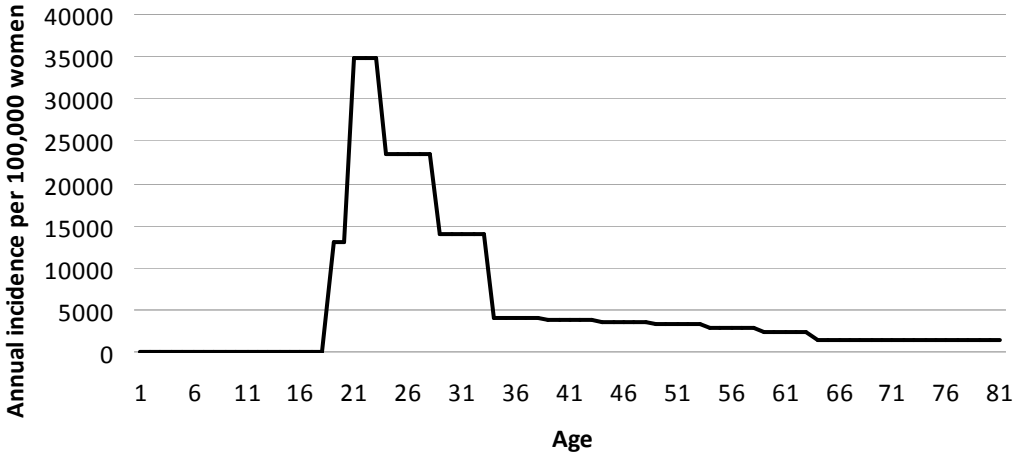

Figure 2A: Model assumptions for the age-specific probability of acquiring a HPV-infection that will not progress to CIN, disease pathway type A in Figure 1) for the potential screening attenders (90% of female population) born after 1949.

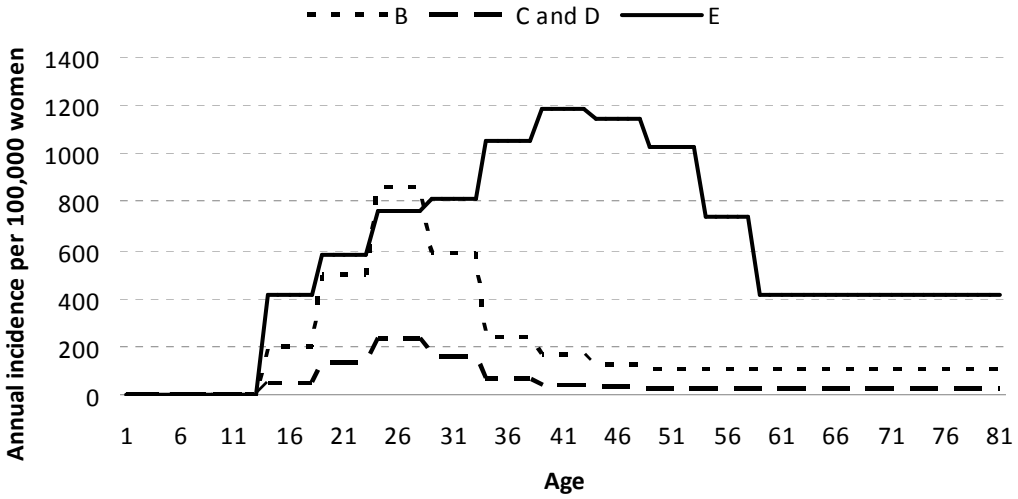

Figure 2B: Model assumptions for the age-specific probability of acquiring a HPV-infection / CIN lesion that will not progress to cervical cancer, disease pathway type B, C, D, and E in Figure 1) for the potential screening attenders (90% of female population) born after 1949.

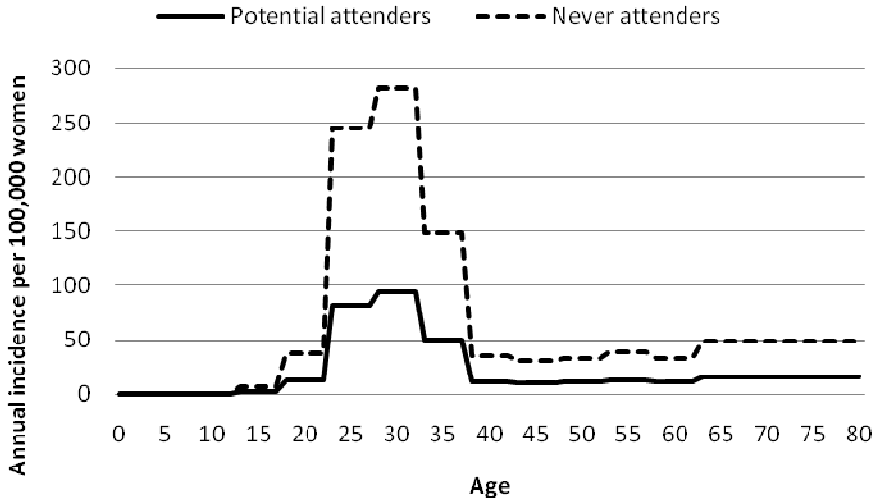

Figure 2C: Model assumptions for the age-specific probability of acquiring a progressive HPV-infection (i.e. HPV infections that can progress to cervical cancer, disease pathway type F in Figure 3) for women born after 1949.

In the model, 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 HPV-infections and CIN-lesions. Women with a hysterectomy will no longer acquire HPV-infections or CIN lesions and are also no longer invited for screening tests. The transitions and sojourn times of the HPV-infections/ lesions are simulated based on a continuous-time semi-Markov process. The sojourn times of transitions have an exponential, a Weibull or a piecewise uniform probability distribution.

The assumptions for the probability and the duration of survival after a clinically detected (i.e. detected because of symptoms) cervical cancer are based on data from selected parts of the Netherlands in the prescreening period 1970-1984.[7] The assumed probability of long-term survival depends on age and stage (FIGO 1B or FIGO 2+); in the model, FIGO 1A cervical

cancer cannot be clinically detected. The model assumptions for the long-term survival probabilities are shown in Table 2A and the assumed duration distributions are shown in Table 2B.

Table 2A: Model assumptions for the age-specific probability that clinical FIGO 1B and FIGO 2+ cervical cancer will lead to death from cervical cancer (i.e. 100% - probability of long-term survival), in the absence of other-cause mortality. Linear interpolation is used to determine the probabilities at intermediate ages. Source: observed age-specific and stage-specific survival for the prescreening period 1970-1984 in selected parts of the Netherlands.

Age	Clinical FIGO1B	Clinical FIGO 2+
0	0.14	0.37
30	0.14	0.37
35	0.09	0.24
60	0.28	0.76
80	0.32	0.86
100	0.32	0.86

Table 2B: Model assumptions for the duration of clinical FIGO 1A and FIGO 2+ cervical cancer, if the transition to death from cervical cancer occurs. The values in this table represent the percentages of cervical cancer deaths that occur within a given number of years after the moment of clinical diagnosis. Source: observed age-specific and stage-specific survival for the prescreening period 1970-1984 in selected parts of the Netherlands.

Years after detection	Clinical FIGO 1B	Clinical FIGO 2+
1	0.28	0.28
2	0.51	0.51
3	0.71	0.71
4	0.91	0.91
5	0.94	0.94
6	0.97	0.97
7	1.00	1.00
8	1.00	1.00
9	1.00	1.00
10	1.00	1.00

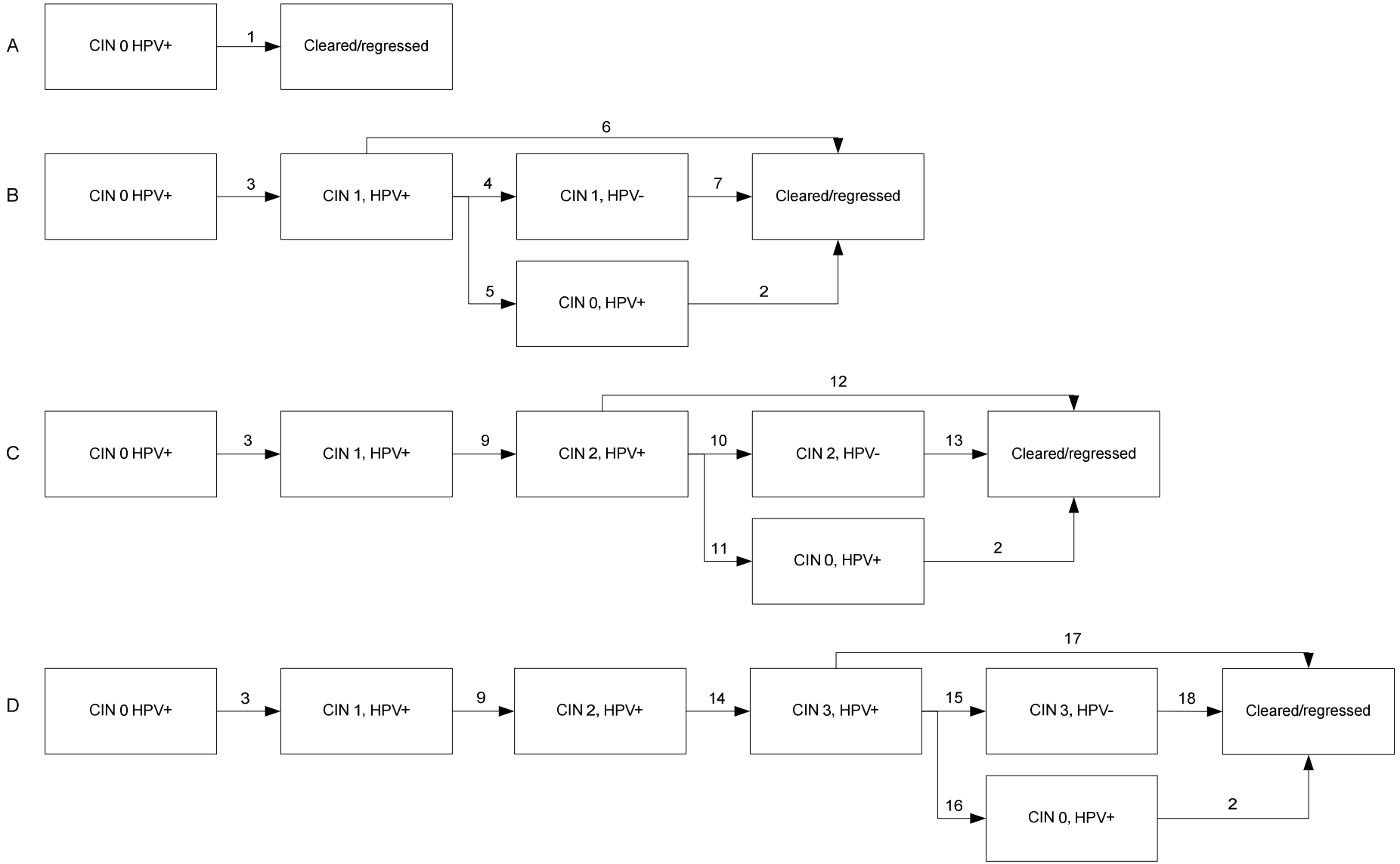

Figure 3: Schematic representation of the MISCAN model, with disease pathways A through F.

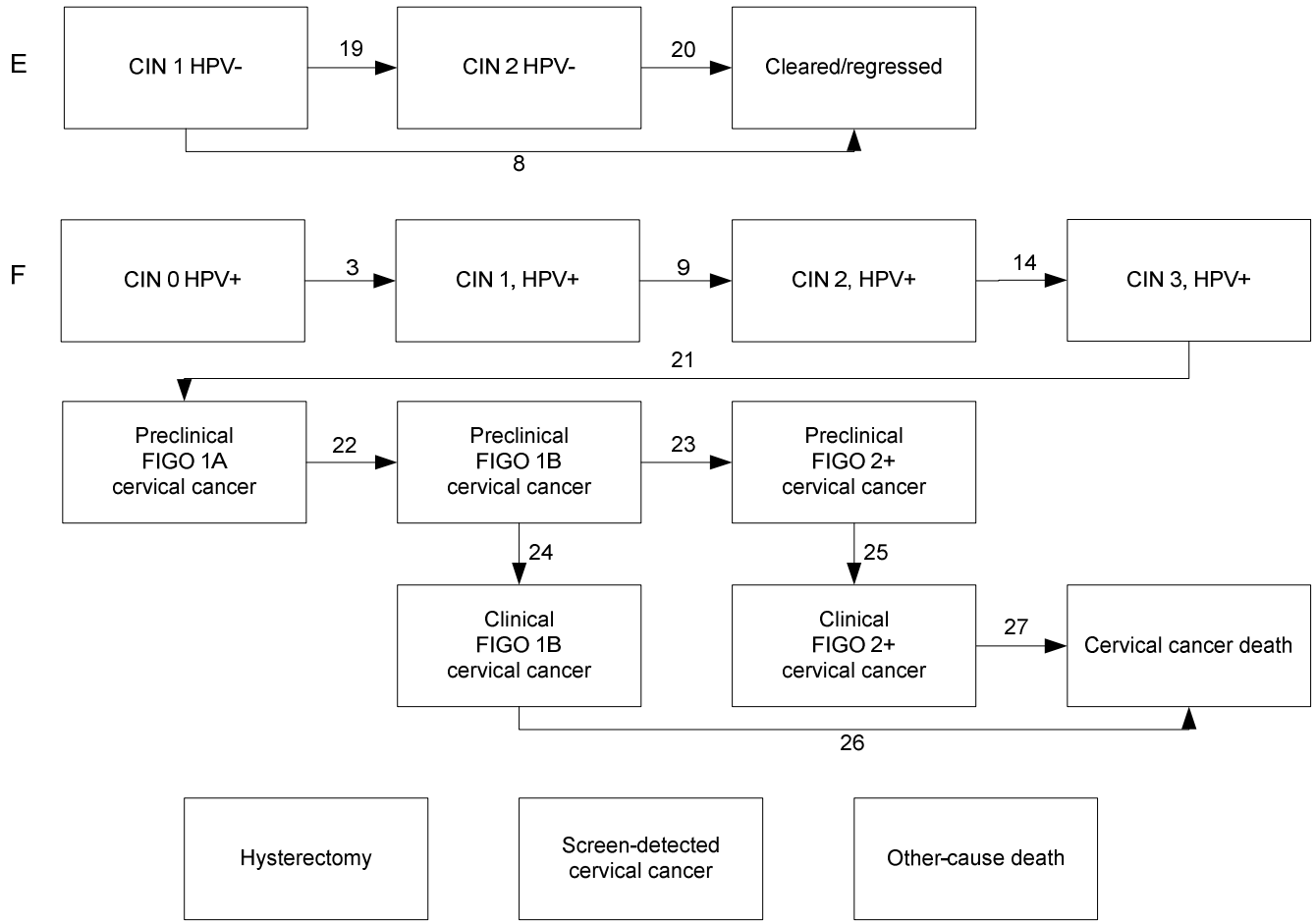

Figure 3 (continued): Schematic representation of the MISCAN-cervix model, with disease pathways A through F.

Notes: There are six disease pathways (types A through F) in MISCAN. All lesions start as either a HPV-infection without CIN (disease pathways A, B, C, D, and F) or CIN 1 without HPV-infection (disease pathway E). Cleared/regressed denotes the absence of CIN and HPV-infection; CIN 0 denotes the absence of CIN and cervical cancer. All cervical cancer states are HPV-positive. The arrows between the states show which types of transitions can occur. The numbers above the arrows refer to the duration distributions shown in Table 3. In every state before death, a transition to Other-cause death can occur, and in every state before cancer, a transition to Hysterectomy can occur (connecting arrows not shown); in these cases, the transition applies to all HPV-infections/ CIN lesions of that person simultaneously

Table 3: Transitions and duration distributions used in MISCAN

Transition number[1]	Disease pathway[1]	From state	To state	Probability of transition	Type of distribution	Mean duration (years)	Weibull shape parameter
1	A	CIN 0 HPV+	Cleared/ regressed	1	Exponential	1.1	1
2	B, C, D	CIN 0 HPV+	Cleared/ regressed	1	Exponential	0.8	1
3	B, C, D, F	CIN 0 HPV+	CIN 1 HPV+	1	Exponential	1	1
4	B	CIN 1 HPV+	CIN 1 HPV-	0.4	Exponential	0.3	1
5	B	CIN 1 HPV+	CIN 0 HPV+	0.3	Weibull	1	1.58
6	B	CIN 1 HPV+	Cleared/ regressed	0.3	Weibull	1	1.58
7	B	CIN 1 HPV-	Cleared/ regressed	1	Exponential	0.8	1
8	E	CIN 1 HPV-	Cleared/ regressed	0.97	Weibull	1	1.58
9	C, D, F	CIN 1 HPV+	CIN 2 HPV+	1	Weibull	1	1.58
10	C	CIN 2 HPV+	CIN 2 HPV-	0.4	Exponential	1.3	1
11	C	CIN 2 HPV+	CIN 0 HPV+	0.3	Weibull	2	1.58
12	C	CIN 2 HPV+	Cleared/ regressed	0.3	Weibull	2	1.58
13	C	CIN 2 HPV-	Cleared/ regressed	1	Exponential	0.8	1
14	D, F	CIN 2 HPV+	CIN 3 HPV+	1	Weibull	2	1.58
15	D	CIN 3 HPV+	CIN 3 HPV-	0.4	Weibull	11.1	1.58
16	D	CIN 3 HPV+	CIN 0 HPV+	0.3	Weibull	11.8	1.58
17	D	CIN 3 HPV+	Cleared/ regressed	0.3	Weibull	11.8	1.58
18	D	CIN 3 HPV-	Cleared/ regressed	1	Exponential	0.8	1
19	E	CIN 1 HPV-	CIN 2 HPV-	0.03	Weibull	1	1.58
20	E	CIN 2 HPV-	Cleared/ regressed	1	Weibull	2	1.58
21	F	CIN 3 HPV+	Preclinical FIGO 1A	1	Weibull	11.8	1.58
22	F	Preclinical FIGO 1A	Preclinical FIGO 1B	1	Weibull	2	1.9
23	F	Preclinical FIGO 1B	Preclinical FIGO 2+	Age-specific.[3]	Weibull	1.9	1.9
24	F	Preclinical FIGO 1B	Clinical FIGO 1B	Age-specific.[3]	Weibull	1	1.9
25	F	Preclinical FIGO 2+	Clinical FIGO 2+	1	Weibull	0.9	1.9
26	F	Clinical FIGO 1B	Cervical cancer death	Age-specific[4]	Piecewise uniform	Age-specific[4]	-
27	F	Clinical FIGO 2+	Cervical cancer death	Age-specific[4]	Piecewise uniform	Age-specific[4]	-

[1] See Figure 3

[3] Transition probability depends on age. In case a FIGO 1B cancer is present, the probability that it is clinically detected decreases linearly from 82% at age 0 to 2% at age 100.

[4] See Table 2A and 2B for the duration distribution of the clinically detected cancer states.

.

Screening

Screening can change the simulated life histories. In the model, each simulated life history is considered in both a situation without screening and a situation with screening. In each life history, a screening test (i.e. cytology or HPV test) can be applied at certain ages. If a screening test is applied, each HPV-infection/ lesion prevalent at the time of screening has a probability (i.e. the sensitivity) of producing a positive test. Based on the result of the test, a woman can be either advised to attend another test, or be referred to colposcopy and treatment. If a woman attends colposcopy (and the associated treatment), it is assumed that all prevalent CIN-lesions are removed and can thus no longer lead to cervical cancer. HPV-infections without CIN are not treated. For screen-detected cervical cancer, a stage-specific improvement (compared to the situation without screening) in the probability of cure is assumed.

Both cytology and the HPV-test are used in the model. The assumptions for the characteristics of these tests are shown in Table 1 in the printed version. Additional assumptions for screening are shown in Table 4. In the model, the group of potential screening attenders consists of 90% of the female population; the remaining 10% of the female population never attends screening.[8] The potential attenders are assumed to attend a primary screening test every screening round with attendance probability of 80%. As a result, the total attendance of the primary screenings is 72%. The screening attendance rate was based on observed rates form the Dutch Network and National Database for Pathology (PALGA).[9] We assume that triage tests and referrals to colposcopy are always attended.

Table 4: Model assumptions for screening attendance

Parameter	Value
Attendance of potential attenders (90% of population)	80%
Attendance of nonattenders (10% of population)	0%
Attendance at triage tests and colposcopy	100%
Relative background risk nonattenders compared to attenders	3

Notes: the assumptions for the test characteristics (sensitivity and specificity) of cytology and the HPV test are presented in Table 1 of the printed manuscript.

The effects of early detection on survival

In the model, detection of cervical cancer by screening can prevent cervical cancer mortality. However, if cervical cancer death is not prevented, the time of death from cervical cancer is not changed by screening. For screen-detected FIGO 1A cervical cancer, we set the reduction in the risk of dying from cervical cancer to 80%, so that the simulated survival probabilities of FIGO 1A cervical cancer fit the observed survival data. For FIGO 1B cervical cancer, we assume that the survival probability does not differ between screen-detected and clinically detected FIGO 1B cervical cancer. To ensure that this assumption is met, we set the reduction in the risk of dying for screen-detected FIGO 1B cervical cancer to 60%. Finally, a reduction in the risk of dying of 20% is assumed for screen-detected FIGO 2+ cervical cancer, based on an estimate of the effects of different observed stage distributions of clinically detected and screen-detected FIGO 2+ cervical cancers.[7]

Calculation of health effects and costs of screening

For each simulated woman whois alive, MISCAN can determine the state, which can be Normal, HPV-infected, CIN 1, CIN 2, CIN 3, FIGO 1A, FIGO 1B, and FIGO II+. The model produces the number of life years spent in each state as well as the numbers of certain events (e.g. screenings and cervical cancer diagnoses) in a lifetime. These outputs are used to determine the cost-effectiveness of screening, based on the number of quality-adjusted life years (QALYs) gained and the net costs. The state can be determined as the state of the most severe HPV-infection/ CIN-lesion/ cervical cancer, using the order HPV-infection, CIN 1, CIN 2, CIN 3, FIGO 1A cervical cancer, FIGO 1B cervical, and FIGO 2+ cervical cancer; if no HPV-infections or CIN-lesions are present, the woman's state is Normal.

The number of LYsG is calculated as the difference in total years lived by the population between the situation in which the screening programme is implemented in 2009 and the situation in which no screening occurs after 2008. To determine the number of QALYs gained (or lost) by screening, we computed the difference in total number of QALYs between both situations.
The woman's quality-adjusted life years (QALYs) are calculated as the weighted sum of the number of years spent in each of these states, using utility weights that can range from 0 to 1; for some events, a fixed utility (which can be negative) is added to this weighted sum. The total effectiveness of screening (QALYs gained and life years gained) is determined as the difference in the number of life years/ QALYs between the situation with screening and the situation without screening. A similar approach is used to determine the net costs of screening. The quality-of-life weights and costs associated with specific events and specific states are presented in Table 2 of the printed paper.

References

1. Habbema JD, van Oortmarssen GJ, Lubbe JT, van der Maas PJ. The MISCAN simulation program for the evaluation of screening for disease. *Comput Methods Programs Biomed* 1985;20(1):79-93.
2. de Kok IM, van Ballegooijen M, Habbema JD. Cost-effectiveness analysis of human papillomavirus vaccination in the Netherlands. *J Natl Cancer Inst* 2009;101(15):1083-92.
3. van den Akker-van Marle ME, van Ballegooijen M, van Oortmarssen GJ, Boer R, Habbema JD. Cost-effectiveness of cervical cancer screening: comparison of screening policies. *J Natl Cancer Inst* 2002;94(3):193-204.
4. CBS (netherlands Central Bureau of Statistics). Death by cause of death, age and sex 1950-1992. Voorburg, 1994.
5. SIG (Information Centre for Health Care). Hospital Diagnosis Statistics 1963-1985. Utrecht: SIG, 1985.
6. Statistics Netherlands (CBS). StatLine database, 2011.
7. van Ballegooijen M. Effects and costs of cervical cancer screening. Erasmus University, 1998.
8. van Oortmarssen GJ, Habbema JD. Epidemiological evidence for age-dependent regression of pre-invasive cervical cancer. *Br J Cancer* 1991;64(3):559-65.
9. van Ballegooijen M, Rebolj M, Essink-Bot ML, Meerding WJ, Berkers LM, Habbema JDF. De effecten en kosten van het bevolkingsonderzoek naar baarmoederhalskanker in Nederland na de herstructurering. Rotterdam: Erasmus MC, afdeling Maatschappelijke Gezondheidszorg, 2006.