MODEL PROFILE DOCUMENT
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ERASMUS MEDICAL CENTER

Important note: This document will remain archived as a technical appendix for publications. New versions will be added periodically as model refinements and updates are completed. The most current version is available at http://cisnet.cancer.gov/profiles. Note that unlike most PDF documents, the CISNET model profiles are not suitable for printing as they are not typically written or read in sequential fashion.

We recommend you let your interests guide you through this document, using the navigation tree as a general guide to the content available.

The intent of this document is to provide the interested reader with insight into ongoing research. Model parameters, structure, and results contained herein should be considered representative but preliminary in nature.

We encourage interested readers to contact the contributors for further information.

Go directly to the: Reader's Guide.

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READER'S GUIDE

Core Profile Documentation

These topics will provide an overview of the model without the burden of detail. Each can be read in about 5-10 minutes. Each contains links to more detailed information if required.

Model Purpose

This document describes the primary purpose of the model.

Model Overview

This document describes the primary aims and general purposes of this modeling effort.

Assumption Overview

An overview of the basic assumptions inherent in this model.

Parameter Overview

Describes the basic parameter set used to inform the model, more detailed information is available for each specific parameter.

Component Overview

A description of the basic computational building blocks (components) of the model.

Output Overview

Definitions and methodologies for the basic model outputs.

Results Overview

A guide to the results obtained from the model.

Natural History

MODEL PURPOSE

Despite successful cervical cancer screening in the United States (US), over 12,000 women develop and 4,000 women die from cervical cancer each year (1). New technologies, including screening tests and vaccines against human papillomavirus (HPV), a sexually-transmitted virus known to cause cervical cancer, are dramatically changing the landscape of cervical cancer control in the US and worldwide. MISCAN-CERVIX is originally developed to evaluate screening of disease. The model produces output on the effects of screening procedures, morbidity and mortality, which can be used to explain and predict trends in cervical cancer incidence and mortality, and to quantify the effects of primary and secondary prevention.

Three main aims of the MISCAN-CERVIX model are defined as follows:

to evaluate the harms, benefits and costs of cervical cancer prevention strategies, including HPV vaccination and screening.

to identify the most efficient and cost-effective cervical cancer control strategies, taking into consideration new and forthcoming technologies for the overall population and high-risk subgroups

to integrate findings of MISCAN-CERVIX and STDSIM (a stochastic microsimulation model for the transmission of HPV) in order to identify the most cost-effective cervical cancer control strategies in women.

MODEL OVERVIEW

SUMMARY

The MISCAN-Cervix model, first developed in 1985, is a micro-simulation model in which individuals are simulated successively and independently of each other (2-3). In MISCAN, a comparison is made between the situation with and without screening. The model consists of three main parts:

- demography
- natural history
- screening

Based on assumptions on trends in demography, natural history, treatment, screening dissemination and impact of screening MISCAN-Cervix projects cancer incidence and mortality by stage, age and calendar year.

PURPOSE

The MISCAN simulation program was developed at the Department of Public Health, Erasmus University Rotterdam, The Netherlands, and has been used to evaluate breast, cervix, colon, prostate, lungs and esophageal cancer screening programs (2-6). Using the MISCAN-CERVIX model, we can simulate how HPV infections / lesions develop in individuals, how they might lead to cervical cancer, up to the moment when an individual eventually dies: from cervical cancer or from another cause of death. The results derived from the model can be used to evaluate the long-term effectiveness and cost-effectiveness of various early detection and prevention strategies for cervical cancer.

BACKGROUND

MISCAN-CERVIX will reproduce the US female population and by using demographic and epidemiologic data obtained from SEER database. The model will be used for laying down assumptions regarding the disease process and the impact of screening strategies. It will provide opportunities to disseminate findings and improve transparency, understanding, and confidence in model-based analyses of cervical cancer control strategies.

MODEL DESCRIPTION

Figure 1 shows the structure of MISCAN-CERVIX. In the static MISCAN model, acquired HPV infection (we divide it into four categories: HPV16, HPV18, 5 HPV types included in the 9-valent vaccine types such as 31/33/45/52/58 and all other high-risk types excluding three last categories mentioned) can progress to pre-invasive cervical intraepithelial neoplasia (CIN). The progression of cervical disease is subdivided into six sequential stages: three pre-invasive stages (CIN grade 1, 2 and 3), and three invasive stages (FIGO stages IA, IB and II+). Cancer may be detected clinically (stages IB and II, III) or through screening (all stages). In the model, most HPV infections will clear without ever resulting in neoplasia, and lesions in pre-invasive stages can regress spontaneously (7). CIN grades 1 and 2 can also develop in the absence of a high-risk HPV infection; these lesions will never progress to cancer. CIN grade 3 and cancer can only develop if a high-risk HPV infection is present.

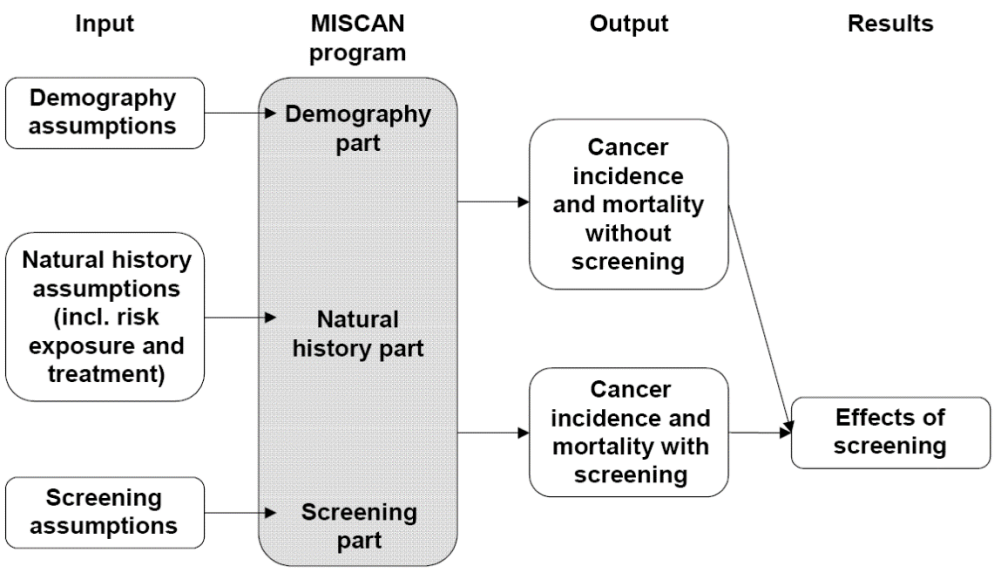

Figure 1: Basic structure of MISCAN-CERVIX

Figure 1 shows that the model consists of the following three parts:

- demography
- natural history
- screening

DEMOGRAPHY

MISCAN-Cervix model generates a simulated population, which corresponds with the 1963 US birth cohort. General characteristics of the simulated population (i.e. those not related to the disease) are based on demographic and hysterectomy data; mortality from other causes was estimated using the observed age-specific mortality in the United States.

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. 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 SEER US cohort 1995. The assumed hysterectomy rates vary by age. These rates are based on hysterectomy incidence data such as single year of age data available from to 1998-2009 (NHDS) and age grouped data available (NHDS & NIS).

Rates were scaled to adjust for outpatient procedures for 2000-2009 using literature (Doll and SASD).

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 CIN lesions without a (detectable) high-risk HPV infection. 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. Transitions from HPV infection to CIN and cancer are sequential.

The age-specific onsets of HPV infections that progress to cervical cancer were calibrated to the age-specific incidence of cervical cancer, which was obtained from the SEER database 2007-2009. The age-specific incidence of pre-invasive lesions that do not progress to cervical cancer was calibrated so that the simulated detection rates of CIN lesions fit the observed detection rates in the US (Rapp 1996-2000 and 2001-2002 data).

The incidence of high-risk HPV infections that do not progress to CIN was calibrated so that the simulated prevalence of all high-risk HPV infections fits the observed high-risk HPV prevalence (Jooste, CEBP 2015, NMHPVPR).

In MISCAN-Cervix different disease pathways are distinguished. 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 (HPV16, HPV18, 9-valent vaccine HPV types and other high-risk HPV) or as an HPV negative CIN 1 lesion.

SCREENING

In the third part of the program, screening for cervical cancer is simulated. The life histories of women will be adjusted for the effects of screening. The screening part is simultaneously run with the natural history part, making detection of CINs and cancers in different states possible. The aggregated changes in life history constitute the effectiveness of the screening.

When a screening test is applied, each infection or lesion prevalent at the time of screening has a probability of producing a positive test (i.e. the sensitivity). If a test result is positive, all prevalent CIN lesions or are diagnosed and can be successfully removed/treated. The difference between the situation with and without screening is the screen effect.

In the model, detection of cervical cancer by screening prevents death from cervical cancer in some but not all cases. However, if death from cervical cancer is not prevented, the time of death from cervical cancer is not changed by screening.

EFFECTIVENESS AS A COMPLEMENTARY / ADDITIONAL PART OF THE MODEL

For each simulated woman who is alive, MISCAN-Cervix can determine the state, which can be Normal, HPV infected, CIN 1, CIN 2, CIN 3, FIGO 1A, FIGO 1B, and FIGO 2+. A woman can have multiple HPV infections or CIN lesions at the same time. Her state is determined by the most severe disease stage present, 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 model produces the number of life years spent in each state as well as the number of certain events (e.g. screenings and cervical cancer diagnoses) in a lifetime. For each of these events, the amount of quality-adjusted time lost can be presented. To calculate the total disutility of a screening scenario, a sum can be taken over all the numbers of events multiplied by their associated quality-adjusted time lost.

REFERENCES:

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ASSUMPTION OVERVIEW

SUMMARY

Summarizes the assumptions used in the present version of the MISCAN-CERVIX model.

BACKGROUND

MISCAN-CERVIX uses three kinds of assumptions:

- assumptions on demography
- assumptions on natural history
- assumptions on screening

ASSUMPTION LISTING

1. Demography assumptions

Via the input file it is possible to specify demographic data from which it can be determined in which year an individual was born and in which year one will die. This is done by means of so-called birth tables and life tables.

The total population can be divided in different strata and cohorts. Currently, only one strata and 10 cohorts of 10 years are specified.

- A cohort is a group of the population that is specified by a number of birth years.
- The life table differs per birth cohort.

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COHORT NAMES
1 Coh1
2 Coh2
3 Coh3
…
10 Coh10
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- Death from cervical cancer and death from other causes are considered independent from each other.
- The age distribution of the cancer initiation rate is the same for all birth cohorts.
- It is possible that women have had their uterus removed earlier because of a reason other than cervical cancer. In such a case, it is no longer possible to contract an HPV infection / lesion or get cervical cancer. For these cases it has been made possible in the input file to indicate the chance of having the uterus removed for a certain age, for reasons other than cervical cancer. This is done by means of the so-called organ removal table. An organ removal table represents the age distribution of termination of the risk of getting the target disease because of organ removal. Currently, we use 10 different organ removal tables per each birth cohort as with time, the risk of having a hysterectomy has changed.
- It is possible to differentiate between localizations of the target disease when multiple diseases are modelled. Currently, only one localization is specified in this model: Cervix.

2. Natural history assumptions:

A. Human Papillomavirus

- Infection: During her lifetime, each woman has an age-specific risk of acquiring high-risk HPV infections –HPV16, HPV18, hi-5 HPV types and other high-risk HPV (i.e. an infection caused by an HPV type that can cause cancer and that can be detected by the HPV test)
- The annual probability of acquiring an HPV infection is age-dependent and depicted in regressive disease pathways progressive disease pathway.
- Contribution to CIN and cervical cancer: 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.

B. Cervical Intraepithelial Neoplasia (CIN)

- Usually CIN lesions will develop from an HPV infection
- The annual probability of acquiring a CIN lesion is age-dependent and depicted in regressive disease pathways progressive disease pathway.

C. Non-progressive CIN lesions

- Only CIN 1 and CIN 2 might develop in the absence of a high-risk HPV infection, but these lesions will never progress to cervical cancer.

D. Multiple infections and lesions

- A woman can acquire multiple HPV infections and CIN lesions during her lifetime, and these lesions and HPV infections may be present at the same time.

E. Cervical cancer development

- Cervical cancer always grows from a CIN lesion
- There is no cancer caused in the absence of HPV infection

F. Multiple disease

- MISCAN-Cervix is a multiple disease model.

G. Recurrent disease

- After detection of cervical cancer, the organ is removed. Therefore, there is no possibility to have a recurrent cervical cancer.
- In cases that women have had their uterus removed earlier because of a reason other than cervical cancer, it is no longer possible to contract an HPV infection/ lesion or get cervical cancer.

H. Progressive CIN lesions and cancer

- We distinguish five initial health states (Figure 2):
  - **Initial state 1** involves a normal state where no HPV infection or neoplasia is present
  - **Initial state 7** involves an HPV 16 infection that can either regress to normal state or progress to a CIN 1 HPV 16 state (state 12). The CIN1 HPV 16 state can sequentially progress to CIN 2 HPV 16 (state 17) -> CIN 3 HPV 16 (state 27) -> preclinical cancer stages FIGO 1A (state 28) -> preclinical cancer FIGO 1B (state 29). From each preclinical state (FIGO 1B, 2 or 3) there is a probability to transit to a clinical cancer state such as: -> from pre-clinical cancer FIGO 1B (state 29) -> clinical cancer FIGO 1B (state 34), from preclinical cancer FIGO 2 (state 30) -> clinical cancer FIGO 2 (state 35) and from preclinical cancer FIGO 3 (state 31) -> clinical cancer FIGO 3 (state 36). Progression can also be sequentially in the direction: FIGO 1B -> FIGO 2 -> FIGO 3 in both preclinical and clinical stages. All the clinical cancer states can lead to the final state that is cervical cancer death (state 54).

- **Initial state 6** involves an HPV 18 infection that can either regress to normal state or progress to a CIN 1 HPV 18 state (state 11). The other transition probabilities follow the same logic as in the case of HPV 16 (state 7).

- **Initial state 5** involves an HPV- type 31/33/45/52/58. All the transition probabilities follow the same logic as in the case of HPV 16 (state 7).

- **Initial state 4** involves a high – risk HPV type that excludes the HPV 16, 18 and 31/33/45/52/58. All the transition probabilities follow the same logic as in the case of HPV 16 (state 7).

With each transition in Figure 2, the input file indicates the probability of that transition, and after how long that transition takes place.

- As mentioned, 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).

I. Hysterectomy

- 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.

J. State duration

We assume the same duration for all HPV infections irrespective to the type and also within CIN 1, CIN 2 and CIN 3 lesions independent of the HPV type.
All transitions above have a certain probability that differs depending on each transition. All transitions above have a certain duration distribution. We assume a positive correlation between duration in successive states.

K. Survival rates

- 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 the SEER statistics for the year of diagnosis 1975 and after.

- We assumed that all cervical cancer mortality occurs in the first 10 years after diagnosis.

- 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.

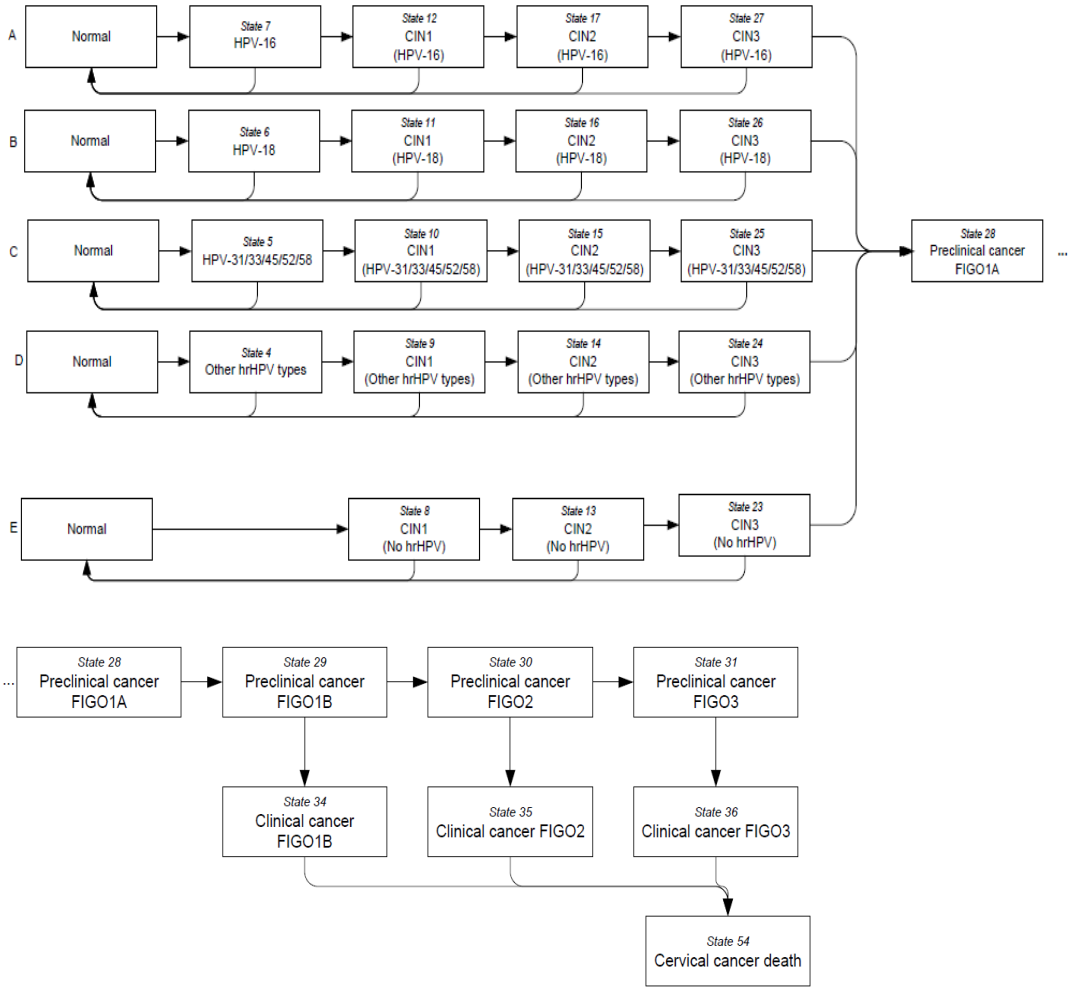

Fig. 2 Schematic representation of the MISCAN-cervix model, with disease pathways A through F

Notes: All lesions start as either an HPV infection without CIN or as a CIN 1 lesion without HPV infection. 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. 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 and CIN lesions of that person simultaneously.

3. Screening

A. Sensitivity of screening
The sensitivity for tests used (cytology and HPV test) depends on stage of the lesion.

B. Compliance to screening
The compliance to primary test, to triage testing and referrals to colposcopy depends on the screening scenario.

C. Tests and follow-up

- Cytology and HPV test are considered primary tests and these can be followed by triage or surveillance test. Primary and follow-up tests depend on the screening algorithm.

- If a woman is referred to colposcopy, all prevalent CIN lesions are assumed to be diagnosed and successfully removed.

- HPV infections without CIN are not directly treated, but women are followed up until the lesion regresses or progresses to CIN 2 and thereafter being removed.

D. Impact of early detection and treatment after screening
In case of detection and treatment of a CIN lesion, it is assumed that the CIN is prevented from growing into a cancer. In case of detection of a cancer, we assume the same stage specific survival for screen-detected as for clinically detected cancers. For each screen-detected lesion a new survival is generated.

E. Surveillance
In the MISCAN-Cervix model surveillance is not explicitly modelled, but it is included in calculation of costs and QALYs (average number of smears, biopsies per diagnose).

PARAMETER OVERVIEW

SUMMARY

Provides a complete overview of the parameters used to quantify the MISCAN-CERVIX model.

BACKGROUND

The MISCAN-CERVIX model uses four types of parameters: demography parameters, natural history parameters, screening parameters and output parameters.

PARAMETER LISTING OVERVIEW

I. demography parameters
   a) number of birth cohorts
   b) proportion of the population in each birth cohort
   c) for each birth cohort parameters of its birth table
   d) for each birth cohort the parameters of its life table

II. natural history parameters
   a) HPV16 onsets
   b) HPV18 onsets
   c) HPV hi-5 types onsets
   d) other high-risk HPV types onsets
   e) parameters for the transition probability of HPV infections
   f) parameters for the transition probability of CIN
   g) parameters for the transition probability of cancers
   h) parameters for the duration distribution of HPV infection
   i) parameters for the duration distribution of CIN
   j) parameters for the duration distribution of cancer
   k) parameters for the duration of progression of CIN
   l) correlation between duration in subsequent states
   m) parameters for survival after clinical diagnosis

III. screening test parameters
   a) parameters for the dissemination of screening
   b) sensitivity, specificity of different screening test
   c) parameters for survival after screen detected diagnosis
   d) surveillance after a positive test result

IV. output parameters
   a) HPV, CIN and cancer states required in the output

b) age groups required in the output
c) parameters for life years in treatment
d) number of persons to be simulated

CATEGORIES

The above parameters can be divided into three categories:

- parameters that are directly estimated from available data
- parameters for which no data (or only limited data) are available
- parameters that will be varied to fit reference data

Table 1 shows which parameters belong to each of these categories.

Parameters that are directly estimated from available data	**Parameters for which no data (or only limited data are available)**	**Parameters that will be varied to fit reference data (calibrated)**
Birth table parameters	Duration distribution in preclinical states	Onsets for HPV16, HPV18, HPV hi-5 and other high-risk HPV types
Life table parameters	Transition probabilities from preclinical to clinical states	Probability for an HPV infection to progress to CIN
Hysterectomy (organ removal) parameters	Duration distribution of regressive disease states	Probability for a CIN to progress to cancer
Survival data		Regression probabilities for HPV infection and CIN
		Prevalence HPV by age
		Incidence by age
		Stage division by age
		Detection rations CIN 1, 2, 3 and cancer by age and grade
		Detective cancer by age, grade, result cytology
		Prevalence HPV in CIN1, CIN2 and CIN3 (assumption was previously that CIN3 is always HPV +)
		Distribution of cancers over invasive stages
		Sensitivity, specificity of screening tests

Table 1: Classification of the parameters in the model

The parameters are based on literature, expert opinion and SEER data.

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COMPONENT OVERVIEW

SUMMARY

An overview of the major components in the MISCAN-CERVIX model.

OVERVIEW

These are the primary components in the MISCAN-CERVIX model:

1. population component which represents the simulated population
2. cohort component which represents a birth cohort in the population
3. person component representing a person
4. HPV infection component
5. CIN 1, CIN 2 and CIN 3 component
6. survival component representing survival after clinical diagnosis
7. screening dissemination component
8. screening test component which represents the screening tests used
9. impact of screening component
10. output component which produces the output tables for a simulation run

COMPONENT LISTING

1. The population component consists of the following:
   - a certain number of cohort components
   - screening dissemination component

   The population component uses the following parameters:
   - number of birth cohorts
   - parameters for the distribution of the population among the birth cohorts

2. A cohort component consists of the following parameters:
   - birth table
   - life table
   - organ removal table

3. A person component consists of the following:
   - date of birth
   - age at HPV infection acquisition
   - initiation of CIN

- cancer components
- screening ages
- date of death of other causes

4. The CIN component consists of the following:
   - the development of a CIN
   - probability to develop into another CIN stage
   - transition probabilities to cancer (although a person may die from other causes before the cancer actually has developed)
   - duration distribution for each transition

   It consists of the following subcomponents:
   - transition probabilities for the different states
   - duration for CIN stages transition

   The progressive CIN component uses the natural history parameters

5. A survival component simulates the survival for a clinical cancer
   - survival rate after detection of the cancer for each stage

   The survival component uses the survival rate parameters

6. The screening dissemination component consists of the following:
   - certain number of screening test components
   - function that produces screening ages for a person given the date of birth
   - It uses the following parameters:
   - parameters for the dissemination of screening

7. The screening test simulates whether an HPV infection or lesion is detected by screening.

   The screening test component uses the following parameters:
   - parameters for sensitivity and specificity of the screening tests

8. The impact of screening component simulates the effect of screening on the course of the disease.

   The impact of screening component uses the following parameters
   - parameters for survival after screen detected diagnosis
   - parameters for surveillance

9. The output component produces the output tables for a simulation run.
   It uses the output parameters.

OUTPUT OVERVIEW

SUMMARY

Describes the outputs generated by the MISCAN-CERVIX model.

OVERVIEW

The MISCAN-CERVIX model simulates among others the Base Case outputs. In case the screening part is activated MISCAN-CERVIX also provides output on screening effects. It is also possible to consider quality of life. This also generates extra output.

OUTPUT LISTING

The output component produces the final output of the model:

Base Case

1. Incidence counts by calendar year (1972-2071), stage and age in every year
2. Mortality counts by calendar year (1972-2071) and age in every year
3. Population on January 1 of each calendar year (1972-2071) by age in five-year age groups
4. HPV infection prevalence by calendar year (1972-2071) and age in every year
5. CIN 1, CIN 2 and CIN 3 prevalence by calendar year (1972-2071) and age in every year
6. Cervical cancer prevalence counts by calendar year (1972-2071), stage, location and age in five-year age groups

SCREENING

7. Number of invitations for screen-tests, of screen-tests, diagnostic tests surveillance and opportunistic screen tests for each year
8. Number of positive and negative HPV test results (primary screening and surveillance) per HPV type (divided in HPV16, HPV18, HPV hi-5, HPV other high-risk types) and per year
9. Number of positive and negative test results (primary screening and surveillance) per CIN state, HPV type and per year

10. Number of positive and negative test results (primary screening and surveillance) per preclinical state and per year (preclinical FIGO 1A, 1B, 2 and 3)
11. Number of positive and negative test results (primary screening and surveillance) per clinical state and per year (clinical FIGO 1A, 1B, 2 and 3)
12. Total number of life years, life years lost due to cancer, number of specific deaths and non-specific deaths
13. Number of tests per calendar year both in screening and surveillance
14. Number of life years gained due to screening by year of screening
15. Interval cancers

QUALITY OF LIFE

16. Total number of life years after screen-detected HPV infection for each type
17. Total number of life years after screen-detected CIN for each type
18. Total number of life years after screen-detected or clinical invasive cancer for each state
19. Total number of life years lost
20. Total number of life in screen and clinically detected cancer by stage

RESULTS OVERVIEW

SUMMARY

Describes the general results obtained from the MISCAN-CERVIX output.

BACKGROUND

The output from MISCAN-CERVIX opens a number of possibilities for policy recommendations.

OVERVIEW

The results of MISCAN-CERVIX provide solid policy recommendations based on cost-benefit evaluation of simulated effects.

RESULTS LISTING

MISCAN-CERVIX generates the following results:

NATURAL HISTORY

SUMMARY

Describes the natural history part of MISCAN-CERVIX.

OVERVIEW

MISCAN-CERVIX consists of two parts: the natural history part and the screening part. At the beginning of each run a population is simulated. Each person consists of a date of birth and date of death. At the generated ages HPV infection starts in the begin-state corresponding to the type of infection.

The development of the CIN lesion depends on the transition probabilities and the duration distribution. The duration is assumed to be exponentially distributed.

The assumptions of the natural history of cervical cancer are based on literature [1-8], expert opinion and SEER-data. The assumptions of the screening are based on literature [9-16]

DETAIL

I. States tracked by the model

MISCAN-CERVIX distinguishes the following states of the disease process:

1.	Normal	NO HPV AND NO CERVICAL NEOPLASIA
	PRECLINICAL	
2.	Cleared	CLEARED FROM HPV (WITHOUT EVER NEOPLASIA)
3.	Regressed	NORMAL, REGRESSED FROM NEOPLASIA (AND HPV)
4.	HPVOHR	HPV, NO NEOPLASIA, Other HrHPV types
5.	HPV9V	HPV, NO NEOPLASIA, Nonavalent vaccine type 31/33/45/52/58
6.	HPV18	HPV, NO NEOPLASIA, type 18
7.	HPV16	HPV, NO NEOPLASIA, type 16
8.	NoHPVC1	No hrHPV, CIN1
9.	HPVOHRC1	HPV, CIN1, Other HrHPV types
10.	HPV9VC1	HPV, CIN1, Nonavalent vaccine type 31/33/45/52/58
11.	HPV18C1	HPV, CIN1, type 18
12.	HPV16C1	HPV, CIN1, type 16
13.	NoHPVC2	No hrHPV, CIN2
14.	HPVOHRC2	HPV, CIN2, Other HrHPV types
15.	HPV9VC2	HPV, CIN2, Nonavalent vaccine type 31/33/45/52/58
16.	HPV18C2	HPV, CIN2, type 18
17.	HPV16C2	HPV, CIN2, type 16

18.	NoHPVAD	No hrHPV, Adeno in situ
19.	HPVOHRAD	HPV, Adeno in situ, Other HrHPV types
20.	HPV9VAD	HPV, Adeno in situ, Nonavalent vaccine type 31/33/45/52/58
21.	HPV18AD	HPV, Adeno in situ, type 18
22.	HPV16AD	HPV, Adeno in situ, type 16
23.	NoHPVC3	No hrHPV, CIN3
24.	HPVOHRC	HPV, CIN3, Other HrHPV types
25.	HPV9VC3	HPV, CIN3, Nonavalent vaccine type 31/33/45/52/58
26.	HPV18C3	HPV, CIN3, type 18
27.	HPV16C	HPV, CIN3, type 16

INVASIVE

28.	PC_F1A	PRECLINICAL MICRO-INVASIVE, FIGO 1A
29.	PC_F1B	PRECLINICAL INVASIVE, LOCALIZED, FIGO1B
30.	PC_F2	PRECLINICAL INVASIVE, NON-LOCALIZED FIGO 2
31.	PC_F3	PRECLINICAL INVASIVE, NON-LOCALIZED FIGO 3
32.	PC_F4	PRECLINICAL INVASIVE, NON-LOCALIZED FIGO 4

CLINICAL

33.	CL_F1A	CLINICAL MICRO-INVASIVE, FIGO 1A
34.	CL_F1B	CLINICAL INVASIVE, LOCALIZED, FIGO1B
35.	CL_F2	CLINICAL INVASIVE, NON-LOCALIZED FIGO 2
36.	CL_F3	CLINICAL INVASIVE, NON-LOCALIZED FIGO 3
37.	CL_F4	CLINICAL INVASIVE, NON-LOCALIZED FIGO 4

SCREENDETECTED

38.	SD_Normal	SCREEN DETECTED WITHOUT HPV AND CIN x (false positive)
39.	SD_HPV	SCREEN DETECTED HPV WITHOUT CIN x
40.	SD_NoHC1	SCREEN DETECTED CIN 1 WITHOUT HPV
41.	SD_HPVC1	SCREEN DETECTED CIN 1 WITH HPV
42.	SD_NoHC2	SCREEN DETECTED CIN 2 WITHOUT HPV
43.	SD_HPVC2	SCREEN DETECTED CIN 2 WITH HPV
44.	SD_NoHAD	SCREEN DETECTED Adeno in situ WITHOUT HPV
45.	SD_HPVAD	SCREEN DETECTED Adeno in situ WITH HPV
46.	SD_NoHC3	SCREEN DETECTED CIN 3 WITHOUT HPV
47.	SD_HPVC3	SCREEN DETECTED CIN 3 WITH HPV

INVASIVE

48.	SD_F1A	SCREEN DETECTED MICRO-INVASIVE, FIGO1A
49.	SD_F1B	SCREEN DETECTED PRECLINICAL INVASIVE, LOCAL, FIGO 1B
50.	SD_F2	SCREEN DETECTED PRECLINICAL INVASIVE, NONLO, FIGO 2
51.	SD_F3	SCREEN DETECTED PRECLINICAL INVASIVE, NONLO, FIGO 3
52.	SD_F4	SCREEN DETECTED PRECLINICAL INVASIVE, NONLO, FIGO 4

ORGAN REMOVAL

53.	Hysterec	HYSTERECTOMY
	END	
54.	DeathSP	DEATH FROM CERVICAL CANCER (SPECIFIC)
55.	DeathOC	DEATH FROM OTHER CAUSES

II. Temporal aspects

The possible transitions between the different states are explained in figures 2:

All states in the above figure have a certain transition probability and duration distribution. All cervical cancer states are HPV positive. The arrows between the states show which types of transitions can occur. 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 and CIN lesions of that person simultaneously. The transition probabilities through different preclinical states are given. The transition probabilities from the preclinical states to the clinical states are based on stage distribution in SEER data.

III. Key attributes

CIN and cervical cancer incidence and development depends on:

a. age
b. gender

IV. CIN and cancer localization is always cervix

V. Relevant assumptions

The most important assumptions on natural history concern:

- development of CIN from HPV infection
- development of cervical cancer from CIN
- multiplicity of CIN
- age dependent incidence for HPV, CIN and cancer
- transition probabilities and duration distribution per state

A more extensive description of the assumptions can be found in the assumption overview

VI. Relevant parameters

The parameters used to simulate natural history are:

a. HPV16 onsets
b. HPV18 onsets
c. HPV hi-5 types onsets
d. other high-risk HPV types onsets
e. parameters for the transition probability of HPV infections
f. parameters for the transition probability of CIN
g. parameters for the transition probability of cancers

h. parameters for the duration distribution of HPV infection
i. parameters for the duration distribution of CIN
j. parameters for the duration distribution of cancer
k. parameters for the duration of progression of CIN
l. correlation between duration in subsequent states
m. parameters for survival after clinical diagnosis

All input-parameters for MISCAN-CERVIX are described in the parameter overview.

VII. Dependent outputs

The outputs most dependent on natural history are:

- cancer incidence
- cancer stage distributions
- cancer mortality

VIII. Calibration, validation process and sources

Calibration

The assumptions of the natural history of cervical cancer are based on literature [1-8], expert opinion and SEER-data. Not all parameters can be obtained directly from data. These parameters must be calibrated to fit actual data. These parameters include for instance HPV progression to cancer. The progression probability will be varied until simulated HPV prevalence and cervical cancer incidence reflect actual data. We use in MISCAN a built-in optimization method, which is an adaptation of the Nelder - Mead Simplex Method [17] to optimize these and other parameters. A complete list of parameters to be calibrated depends on data available. Due to large number of parameters to be calibrated we used a **three-step approach.**

- Step 1: Calibrate the 'progressive parameters' by fixing all regression chances at 0 and only calculate GOF on cancer data. No differentiation is made between the different HPV-types yet.
- Step 2: Calibrate the 'regressive parameters' by fixing the 'progressive parameter' on the values found at step 1. Still no differentiation is done between different HPV-types.
- Step 3: Calibrate the 'HPV-type specific factors' by dividing onsets over 4 pathways while allowing differences in transition chances.

Validation

Different model specifications are simulated and the output of these different models is compared to actual data. The goodness of fit of model assumptions is evaluated by the deviance, which compares outcomes of the model with actual data. The outcomes that can be evaluated are for example the cancer incidence by

age, the stage distribution of clinical cancers and the prevalence of HPV infections. We intend to validate the MISCAN-CERVIX model on different data sources in the US and Europe.

IX. Key questions

The reduction in cancer incidence by screening is realized in MISCAN-CERVIX by assuming that treated HPV infections or CIN lesions will not develop into a cancer anymore. The survival rate for a detected invasive cancer is assumed to be equal to the survival rate for a clinical invasive cancer in the same stage.

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