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MIcrosimulation SCreening ANalysis Colorectal Cancer Model (MISCAN-Colon): Model Profile

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Version Table

Version	Date	Notes
1.0.00	2025-09-30	Major update
HI.001.03122015.70025	2015-12-03	Historical release

Other Publications

- Loeve F, Boer R, van Oortmarssen GJ, van Ballegooijen M, Habbema JD. The MISCAN-COLON simulation model for the evaluation of colorectal cancer screening. Comput Biomed Res. 1999;32(1):13-33. doi:10.1006/cbmr.1998.1498
- van Hees F, Habbema JDF, Meester RG, Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG. Should Colorectal Cancer Screening be considered In Elderly Persons without previous screening? A cost-effectiveness analysis. Ann Intern Med. 2014;160(11):750-759. doi:10.7326/M13-2263

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Readers Guide

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.

Key References

A list of references used in the development of the model.

Model Purpose

Summary

This document describes in broad terms, the purpose(s) for which the MISCAN-Colon model was developed.

Purpose

Trends in colorectal cancer incidence and mortality and the (potential) impact of interventions depend on many factors related to the biology of the adenoma-carcinoma sequence, the characteristics of the population, and the potential impact and usage of primary prevention, early detection and treatment. A simulation model is a helpful tool to estimate the effect of each of the listed factors on cancer incidence and mortality. MISCAN-Colon is developed to analyze trends in colorectal cancer due to changes in lifestyle, improvement of treatment and implementation of screening strategies.

The purpose of MISCAN-Colon can be described in three specific aims:

1. to simulate colorectal cancer incidence and mortality according to observed figures
2. to estimate the absolute and relative contribution of CRC cancer screening, risk factors and improved therapy on observed cancer incidence and mortality trends
3. to predict how changes in lifestyle, CRC screening and treatment practices will impact on future incidence and mortality

The development of colorectal cancer is based on the adenoma-carcinoma sequence of Morson [1] and Vogelstein [2] and is an important underlying assumption of the model.

References

1. Morson, B. The polyp-cancer sequence in the large bowel. Proc R Soc Med. 1974;67:451–7.
2. Vogelstein, B, Fearon, ER, Hamilton, SR, Kern, SE, Preisinger, AC, et al. Genetic alterations during colorectal-tumor development. N Engl J Med. 1988;319(9):525–32.

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Model Overview

Summary

MISCAN-Colon is designed to analyze trends in colorectal cancer. MISCAN-Colon is a microsimulation model, consisting of three parts:

- Demography part
- Natural history part
- Screening part

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

Purpose

MISCAN-Colon is developed to analyze trends in colorectal cancer due to changes in lifestyle, improvement of treatment and implementation of screening strategies. See Model Purpose for more details.

Background

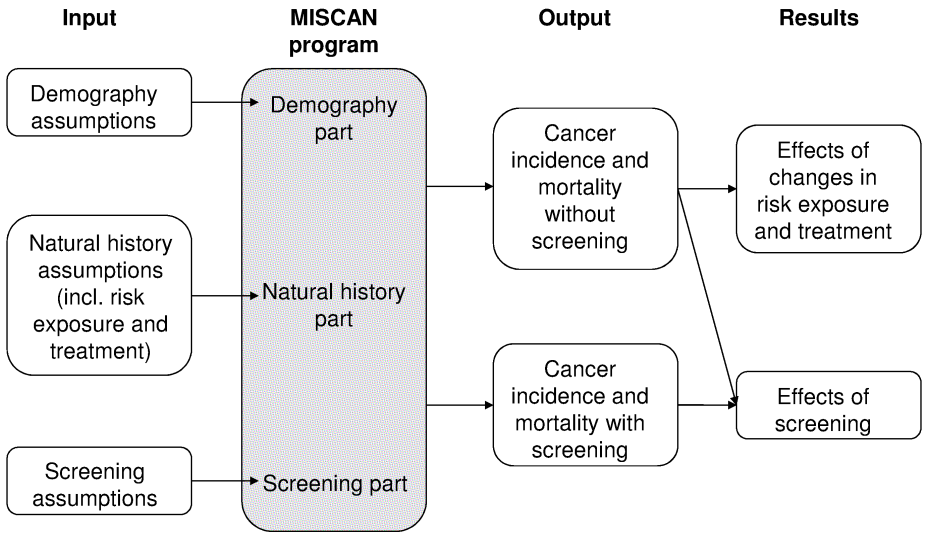
The MIcrosimulation SCreening ANalysis (MISCAN) computer program has been used for simulating cancers of the breast, cervix, colon, stomach, prostate, as well as for dementia [1-7]. MISCAN-Colon will simulate a population of persons in which colorectal cancer and its precursor lesion, the adenomatous polyp, develop, resulting in "clinical" diagnosis, treatment, and possible death from this disease. Different assumptions on risk exposure and treatment and their influence on cancer incidence and mortality can be simulated. The output of the program can be used among others to compare situations with and without screening, or different screening policies with each other.

By combining demographic and epidemiological information from the Surveillance, Epidemiology and End Results (SEER) program, information on lifestyle and risk factors and information on screening dissemination, we will gain insight into what extent the observed trends in incidence and mortality of colorectal cancer can be explained by screening. Also, the effects of other factors such as changes in treatment and lifestyle (risk exposure) will be studied. Using the knowledge gathered during the project, MISCAN-Colon will reproduce the total US population to predict effects of future cancer control strategies on a population level. The results may be used for public health policy making.

Model Description

The basic structure of MISCAN-Colon is illustrated in figure 1. It describes the way in which effects of risk exposure and improvement of treatment are modeled and how effects of different screening strategies are estimated. By running MISCAN-Colon on different assumptions on for example risk exposure, the effects of risk exposure on cancer incidence and mortality and optimal screening policy can be evaluated.

Figure 1: Structure of MISCAN-Colon



MISCAN-Colon is a microsimulation program, generating individual life histories. MISCAN uses the Monte Carlo method to simulate all events in the program. Possible events are birth and death of a person, adenoma incidence and transitions from one state of disease to another.

Figure 1 demonstrates that MISCAN-Colon consists of three parts:

- demography part
- natural history part
- screening part

These parts are not physically separated in the program, but it is useful to consider them separately.

MISCAN-Colon first generates a series of individual life histories in the demography part to form a population according to the Demography Parameters (e.g. the life table). Each person in the population consists of a date of birth and a date of death from other causes than colorectal cancer.

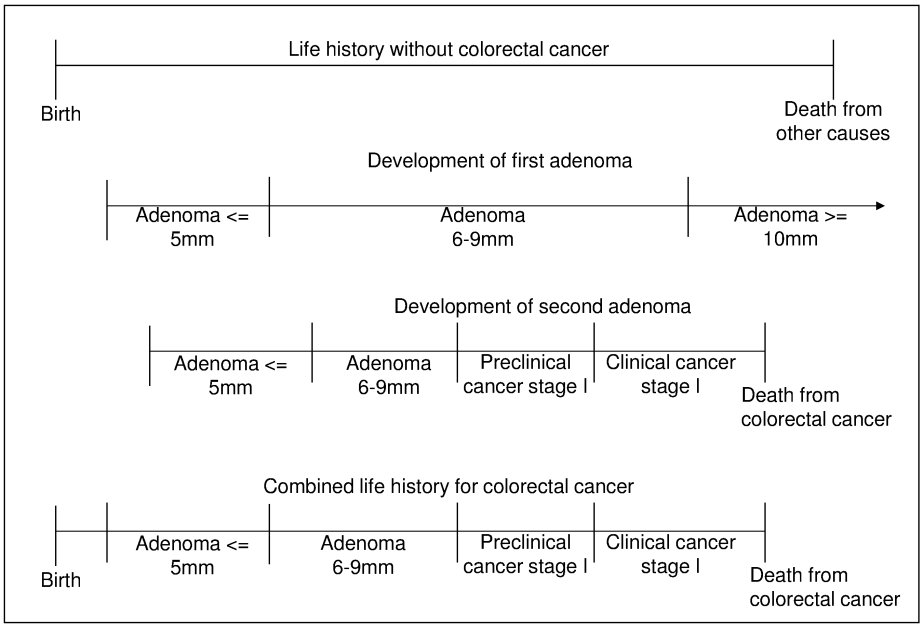
Subsequently the Natural History Component part of MISCAN-Colon simulates colorectal cancer histories (natural histories) for each individual life history separately. We based our natural history model on the adenoma-carcinoma sequence of Morson [8] and Vogelstein [9]. This means that adenomas are generated according to a personal risk index and an age specific incidence rate, resulting in no adenomas for most persons and 1 or more adenomas for others. Some of these adenomas develop into colorectal cancer, depending on the Natural History Parameters. The development from adenoma into cancer covers different stages. Each disease state represents a state in a Markov process. This is a generalized Markov process in the sense that:

- non-exponential distributions in each disease state are possible,
- distributions are age dependent
- distributions are calendar time dependent
- intervention by screening is possible

The survivorship of a person is generated according to the Survival Parameters, once an adenoma has developed into clinical colorectal cancer.

The life history of each person is altered according to the natural history that is simulated for that person. This means that the state a person is in is the same as the state of the most advanced adenoma or carcinoma they have. If they die from colorectal cancer before they die from other causes, their death age is adjusted accordingly. This procedure is explained in figure 2a. In this example the life history of a person is shown who develops two adenomas. One of these adenomas develops into a cancer and causes death before the age of death from other causes. The combination of life history without colorectal cancer and the development of adenomas is shown in the bottom line: combined life history for colorectal cancer.

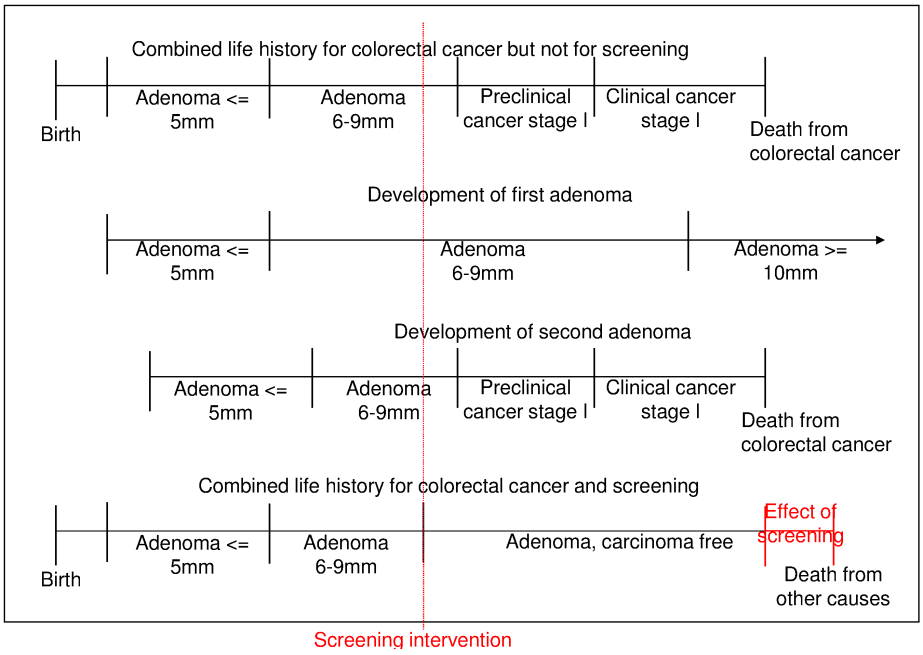
Figure 2a: Modeling natural history into life history



In the third part of the program, screening for colorectal cancer is simulated. After the life history of a person is adjusted for colorectal cancer, the history will now be adjusted for the effects of screening. The screening part is simultaneously run with the natural history part, making detection of adenomas and carcinomas in different states possible. The aggregated changes in life history constitute the effectiveness of the screening. The effect of screening on life history is explained in figure 2b.

The top line in this figure is the combined life history for colorectal cancer from figure 2a. The development of the separate adenomas is shown in the second and third line. In this picture there is one screening intervention. During the screening both prevalent adenomas are detected and removed. This results in a combined life history for colorectal cancer and screening (bottom line), where the person is adenoma-carcinoma free after the screening intervention. The effect of screening is now equal to the lifeyears gained by the screening intervention.

Figure 2b: Modeling screening into life history



The effects of different screening policies can be compared by applying them to identical natural histories. If one is solely interested in modeling the natural history of disease, the screening part is not necessary.

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Assumption Overview

Summary

Overview of the main assumptions used in the present version of the MISCAN-Colon model.

Background

A model is defined as a simplified representation of a complex process. Because of lack of data or to prevent the model from becoming too complicated, simplifying assumptions have to be made in all models.

In each of the three parts of the MISCAN-Colon program assumptions are made:

- Assumptions on demography
- Assumptions on natural history
- Assumptions on screening

Model validation is an important tool for testing the model assumptions. During validation we use MISCAN-Colon to simulate, for example, a trial situation and compare the observed trial outcomes with the model outputs. Discrepancies between the trial and simulated outcomes are further investigated. If external reasons are not sufficient to explain discrepancies, the model parameters are re-examined. If re-estimating the model parameters does not lead to a good fit of model output and observations, the assumptions are reconsidered.

Assumption Listing

Demography Assumptions

Demography Assumptions focus on the actuarial characteristics of the population. The following assumptions on demography are made:

- The life table differs per birth cohort
- Death from colorectal cancer and death from other causes are considered independent from each other

Natural History Assumptions

Natural History Assumptions focus on the initiation, progression and response to treatment of colorectal cancer in the model. Natural history includes assumptions on:

- Colorectal cancer development
- Adenoma incidence
- Multiplicity of adenomas
- Adenoma types
- Non-progressive adenomas
- Progressive adenomas and cancer
- Transition probabilities
- State durations
- Anatomical site of adenomas
- Survival rates

A more detailed description of the natural history assumptions can be found in Natural History Assumptions.

Screening Assumptions

Screening Assumptions focus on all aspects of screening, including compliance and operational characteristics of the screening process. Assumptions are listed in detail below:

- *Sensitivity of screening* - The sensitivity for all tests depends on location, state and size of the lesion. It is also possible to assume systematic error on screening results. There can be systematic errors for

certain persons or lesions.

- *Reach of screening* - It is possible to limit the reach of screening tests by indicating the probability for a test to reach a certain localization in the large bowel.
- *Impact of early detection and treatment after screening* - In case of detection and removal of an adenoma, it is assumed that the adenoma is prevented from growing into a cancer. In case of detection of a cancer, a screen-detected cancer can be detected in the same stage as it would have become clinical in the absence of screening, or it can be detected in an earlier stage. In the former case, we assume the same stage specific survival for screen-detected as for clinically detected cancers. In the latter case, we assume the stage specific survival of one stage earlier for screen-detected cancers. For each screen-detected lesion a new survival is generated.
- *Surveillance* - MISCAN-Colon enables the user to define a surveillance-scheme after detection of an adenoma during screening or surveillance. Surveillance will be modeled according to current guidelines [1]. A description of the parameters specifying these guidelines can be found in the Parameter Overview section.

References

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Parameter Overview

Summary

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

Background

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

Parameter Listing Overview

Demography Parameters

1. number of birth cohorts
2. proportion of the population in each birth cohort
3. for each birth cohort the parameters of its birth table
4. for each birth cohort the parameters of its life table

Natural History Parameters

1. adenoma-carcinoma sequence states
2. age-specific adenoma incidence rate by birth cohort
3. parameters for the distribution of the individual risk index
4. distribution of adenomas over the colorectal sites
5. probability for an adenoma to be progressive
6. parameters for the transition probability of non-progressive adenomas for each state
7. parameters for the duration distribution of non-progressive adenomas for each state
8. parameters for the transition probability of progressive lesions for each state
9. parameters for the duration distribution of progressive lesions for each state
10. correlation between duration in subsequent states
11. parameters for survival after clinical diagnosis by age at diagnosis, year of diagnosis, stage of disease and localization of the cancer

Screening Test Parameters

1. parameters for the dissemination of screening
2. reach, sensitivity, specificity of different screening tests
3. dependency of test outcomes on previous test outcomes of the same individual
4. parameters for survival after screen-detected diagnosis
5. surveillance after screen-detected adenomas

Output Parameters

1. age groups required in the output
2. year groups required in the output
3. number of persons to be simulated
4. overall seed for reproducibility or seeds for specific model parts

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)
Demography	Duration distribution in preclinical states	Probability for an adenoma to be progressive
Distribution of lesions over large bowel	Transition probabilities from preclinical non-invasive states	Individual risk index
Survival after clinical diagnosis	Correlation between durations in subsequent states	Incidence rate of adenomas
Sensitivity, specificity and reach of screening tests	Dependency of test outcomes	Transition probabilities from preclinical invasive states to clinical states
Distribution of cancers over invasive stages	Survival after screen-detected diagnosis	Screening dissemination
Relative risk associated with risk and protective factors	-	-
Prevalence of risk and protective factors	-	-
Treatment dissemination	-	-
Hazard ratios of treatment	-	-

The parameters are based on literature (see: References For Model Parameters), expert opinion and SEER data.

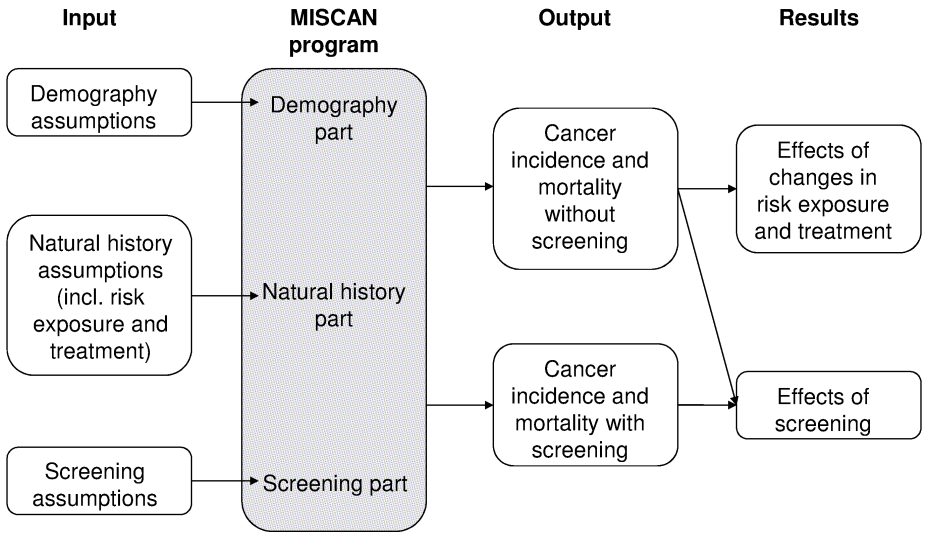
Component Overview

Summary

Overview of the major components in the MISCAN-Colon model.

Overview

As described in the Model Overview document, the MISCAN-Colon model contains three primary components: Demography, Natural History Component and Screening.



Component Listing

Demography Component

The demography component simulates a population of individual life histories, according to the demography parameters. The demography parameters are:

- birth table parameters (http://seer.cancer.gov/popdata)
- life table life table parameters (National Center for Health Statistics)
  Each individual in the population has a date of birth and age of death.

Natural History Component

Subsequently, the Natural History part of MISCAN-Colon simulates colorectal cancer histories (natural histories) for each individual separately. Adenomas are generated according to an individual risk index and age-specific incidence rate. The age-specific adenoma incidence rate depends on exposure to risk factors and therefore varies by birth cohort. Some of these adenomas develop into colorectal cancer, depending on the natural history parameters (see Parameter Overview). The development from adenoma into cancer covers different stages. The survivorship of a person once an adenoma has developed into clinical colorectal cancer, depends on year of diagnosis, age at diagnosis, localization of the cancer and stage of disease. The life history of each person is altered according to the natural history that is simulated for that person. If they die from colorectal cancer before they die from other causes, their death age is adjusted accordingly.

Screening Component

The Screening Component is simultaneously run with the Natural History Component, making detection of adenomas and carcinomas in different states possible. Screening in the model potentially affects all preclinical

disease stages, resulting either in removal of an adenoma and preventing CRC or early detection of a preclinical carcinoma, possibly in an earlier stage resulting in a favorable stage shift and thus improved prognosis. The effectiveness of screening depends on the screening parameters (see Parameter Overview).

Output Overview

Summary

Overview of the outputs generated by the MISCAN-Colon model.

Overview

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

Output Listing

The following outputs can be calculated based on the final output of the model:

Base Case

1. Incidence counts by calendar year, location, stage and age
2. Mortality counts by calendar year and age
3. Population counts by each calendar year by age
4. Adenoma prevalence by calendar year, location, size, sex and agegroups
5. CRC prevalence by calendar year, stage, location and age

Screening

6. Number of invitations for screen tests, diagnostic tests, surveillance tests and number of opportunistic screen tests for each year
7. Number of positive and negative test results per preclinical state and per year
8. Total number of life years, life years lost due to cancer, number of specific deaths and non-specific deaths
9. Number of screenings that prevented cancer by year of screening
10. Number of screenings that detected cancer early by year of screening
11. Number of surveillance tests that prevented cancer by year of surveillance
12. Number of surveillance tests that detected cancer early by year of surveillance
13. Number of life years gained due to screening by year of screening

Quality of life

14. Total number of life years in surveillance
15. Total number of life years with initial therapy after screen-detected or clinical invasive cancer for each state
16. Total number of life years with terminal care before death from other causes
17. Total number of life years with terminal care before death from colorectal cancer

Results Overview

Summary

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

Overview

One of the strengths of the MISCAN-Colon model is that it has been validated against several large screening trials, and we will continue to update the model when new data becomes available. This document shortly describes the main validation studies that were performed with the model to date. Subsequently, a list is provided of all studies that were published with the validated model.

Results List

Validation of the MISCAN-Colon model

The Kaiser validation study [1]

CoCaP is a large program of sigmoidoscopy screening conducted by Kaiser Permanente of Northern California (KPNC), a large non-profit Health Maintenance Organization. We compared the model predicted and observed cancer incidence after screening to assess the assumptions for the sensitivity of sigmoidoscopy to detect adenomas and CRC. Many combinations of sensitivity and duration of adenomas were consistent with the observed findings. These assessments will be modeled subsequently when data on repeat screenings are available.

National Polyp Study data: evidence for regression of adenomas [2]

The data of the National Polyp Study, a large longitudinal study on surveillance of adenoma patients, is used for testing assumptions on the adenoma-carcinoma sequence. The observed adenoma and colorectal cancer incidence in the National Polyp Study were compared with the simulated outcomes of the MISCAN-Colon model for the U.S. population. Variants of this model were explored in order to identify assumptions on the adenoma-carcinoma sequence that are consistent with the study observations.
The high observed adenoma detection rates at surveillance and low observed colorectal cancer incidence in the National Polyp Study could only be explained by assuming a high incidence rate of adenomas accompanied by regression of adenomas. The National Polyp Study data suggest that adenoma prevalence results from a dynamic process of both formation as well as regression of adenomas. This lowers the expectations for the effects of colorectal cancer screening strategies that focus on adenoma detection.

Metasynthesis validation study of 3 randomized FOBT trials [3]

Data of the Minnesota, Funen, and Nottingham FOBT trials were used to compare expected model outcomes and observed data on screen-detected cancers and adenomas, interval cancers and mortality. All three trials are randomized controlled trials of FOBT screening where participants were offered annual screening (Minnesota only), biennial screening or usual care. All three trials have shown a significant mortality reduction ranging from 15% to 33%. Adjusting the model for differences in design and background incidence between trials, we tried to find one disease model that simultaneously fit all three studies. Parameters varied were FOBT sensitivity and dwelling time of preclinical cancer stages. Assuming a fixed sensitivity of FOBT for all cancer stages would imply short dwelling times for the local stages, and long dwelling times for the advanced stages. Despite the short estimated dwelling time, too many Dukes A cancers were still found in consecutive screening rounds. Varying sensitivity of FOBT by stage gave better results for Dukes A cancers detected, but still resulted in too many Dukes A cancers found in consecutive screening rounds. We therefore proposed a novel hypothesis that sensitivity is higher for the stage in which the cancer would have been diagnosed in the absence of screening than for earlier stages. This hypothesis, with a high sensitivity shortly before diagnosis when the cancer is likely to bleed, gave the best fit to results of the randomized controlled trials of Minnesota, Nottingham and Funen.

Healthy People 2010 [4,5]
The Healthy People consortium acknowledged the burden of colorectal cancer and formulated the target of reducing colorectal cancer mortality from 21.2 per 100,000 in 1998 with 34% by 2010. We used the MISCAN-Colon microsimulation model to examine the possibilities of reaching the Healthy People 2010 colorectal cancer mortality goal when assuming various trends in risk factor prevalence, screening participation and improvements in CRC treatment.

For this project the model was calibrated to reproduce the 1975 to 1979 age-specific CRC incidence rates, which were representative of the U.S. population prior to the introduction of screening. Subsequently, by adding the observed trends in risk-factor prevalence, screening and treatment use from 1975 to 2000, a population was generated with the characteristics of the 2000 U.S. population. The model predictions for CRC incidence and mortality from 1975 until 2000 all were within 6% of the observed incidence and mortality in the U.S.

United Kingdom Flexible Sigmoidoscopy Study [6]
We validated the MISCAN-Colon model, as well as two other CISNET CRC microsimulation models, against outcomes from the United Kingdom Flexible Sigmoidoscopy Study (UKFSS), a randomized controlled trial that examined the effectiveness of one-time flexible sigmoidoscopy screening to reduce CRC mortality.[7] All three models accurately predicted the relative effect of one-time flexible sigmoidoscopy on CRC mortality ten years after screening. However, the models predicted absolute mortality and the effect of screening on disease incidence with varying degrees of success. One major difference between the models is ‘dwell time’, the average time from adenoma initiation to presentation with clinical CRC, simulated as 25.8 years for CRC-SPIN, 25.2 years for SimCRC, and 10.6 years for MISCAN. MISCAN predicted too many screen-detected cancers and higher 10-year CRC incidence rates than estimated, especially in the control group, but 10-year CRC mortality rates that were slightly lower than estimated. The shorter dwell time specified by the MISCAN model resulted in predicted CRC incidence in the intervention group that ‘caught up’ too quickly to incidence rates the control group. When the MISCAN model was updated to incorporate a longer transition time and then recalibrated, the updated model predicted hazard rates for both 10-year CRC incidence and mortality that were within the study error bounds.

Applications of the MISCAN-Colon Model

The MISCAN-Colon model has been applied to a wide range of research and policy questions, supporting decision-making in colorectal cancer (CRC) screening at national, state, and international levels. These applications fall into three main areas: directly informing policy, indirectly informing policy, and advancing model methodology and validation.

Applications that Directly Inform Policy

MISCAN-Colon has been used to inform CRC screening policy in the United States and internationally. The model has directly informed national guidelines, such as those issued by the US Preventive Services Task Force [8,9], and contributed to policy decisions regarding the implementation and optimization of screening programs at both state and international levels [10-13]. For example, the model was used to identify optimal screening scenarios for underserved rural areas of South Carolina [14], and to estimate how differences in risk factors, screening, and treatment explain CRC mortality differences in New Jersey and Louisiana (manuscript in preparation). Internationally, MISCAN-Colon has supported projects in Canada and Australia, and has been used to inform the Dutch national FIT screening program. The model has also evaluated the impact of policy changes, such as the introduction of new screening modalities, adjustments to screening intervals, and responses to public health emergencies like the COVID-19 pandemic [15-20].

Applications that Indirectly Inform Policy

Many MISCAN-Colon applications have examined policy-relevant issues by evaluating and optimizing CRC screening strategies, as well as assessing cost-effectiveness. Studies have assessed the effectiveness of different screening intervals, starting and stopping ages [21-23], and the use of risk factors such as comorbidity and family history to personalize screening recommendations [24-28]. The model has compared the benefits of various screening modalities (e.g., FIT, colonoscopy, sigmoidoscopy) [29-32], and explored the impact of adherence, demographic differences, and emerging technologies [33,34].

The model has also been used extensively to assess the cost-effectiveness of CRC screening strategies, including the introduction of new tests, risk-stratified approaches, and programmatic changes [35-44]. These analyses have informed reimbursement decisions, guided the adoption of innovative technologies, and provided evidence for the efficient allocation of healthcare resources. By quantifying both the costs and health outcomes associated with different screening options, MISCAN-Colon has helped ensure that policy decisions are grounded in value-based care.

Model Assumptions, Methodology, and Validation

Applications that provide insight into model performance and relationships between assumptions and model output are critical to thoughtful model application. MISCAN-Colon has undergone rigorous validation and methodological development. Studies in this area have focused on external and predictive validation, comparative modeling, and the refinement of key model assumptions [6,45,46,47,48,49,50,51,52,53,54,55,56,57,58]. This body of work underpins the model's use in high-stakes policy settings and supports its ongoing evolution in response to new scientific evidence and analytic challenges.

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Natural History Component

Summary

This document describes the Natural History Component of the model and discusses aspects of the patient's progression from a disease free state to diagnosis.

Overview

MISCAN-Colon consists of three parts: the demography part, the natural history part and the screening part. At the beginning of each run a population is simulated. Each person has a date of birth and date of death. For each person a personal risk index is generated. Based on this risk index and the age specific incidence rate the ages at which lesions develop are generated. At the generated ages lesions start in the begin-state corresponding to the type of lesion.

The development of the lesion depends on the type of lesion (non-progressive / progressive), the transition probabilities and the duration distribution. The duration is assumed to be exponentially distributed.

The assumptions of the natural history of colorectal cancer are based on literature (see ReferencesForModelParameters), expert opinion and SEER-data.

Detail

States tracked by the model
MISCAN-Colon distinguishes the following states of the disease process:

Disease free state

- no lesion

Non-progressive states

- non-progressive adenoma <=5mm
- non-progressive adenoma 6-9mm
- non-progressive adenoma >=10mm

Preclinical non-invasive states

- progressive adenoma <=5mm
- progressive adenoma 6-9mm
- progressive adenoma >=10mm

Preclinical invasive states

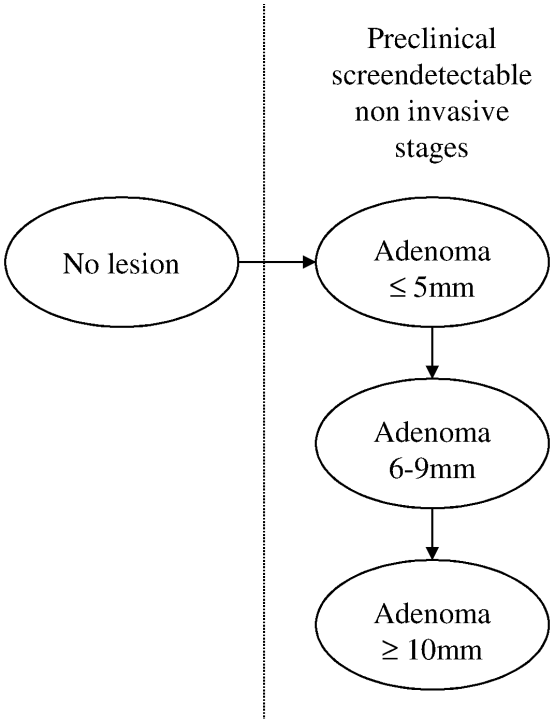
- preclinical colorectal cancer, stage I
- preclinical colorectal cancer, stage II
- preclinical colorectal cancer, stage III
- preclinical colorectal cancer, stage IV

Clinical invasive states

- clinical colorectal cancer, stage I
- clinical colorectal cancer, stage II
- clinical colorectal cancer, stage III
- clinical colorectal cancer, stage IV

Temporal aspects
The possible transitions between the different states are explained in Figures 1 below and Figure 1 of the Natural History Assumptions section.

Figure 1: Non-progressive adenoma sequence



All states in the above figure have a certain transition probability and duration distribution. 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.

The duration distribution is assumed to be dependent on the age of a person and location of the lesion. All durations are assumed to be exponentially distributed. We assume a positive correlation between duration in successive states.

Key attributes
Adenoma incidence and development depend on:

a. age
b. gender
c. race
d. location
e. personal risk index
f. risk factor exposure

Adenoma localization options
Adenomas and cancers are modeled to be continuously distributed over the bowel. In the output they are categorized according to the part of the bowel they are in. MISCAN-Colon distinguishes the following parts of the large bowel:

1. Rectum
2. Rectosigmoid
3. Sigmoid
4. Descending Colon
5. Transverse Colon
6. Ascending Colon

7. Cecum

Relevant Assumptions

The most important assumptions on natural history concern:

- development of colorectal cancer
- multiplicity of adenomas
- age-dependent adenoma incidence
- existence of non-progressive and progressive adenomas
- transition probabilities and duration distribution per state
  A more extensive description of the assumptions can be found in Natural History Assumptions.

The reduction in cancer mortality due to screening in MISCAN-Colon is realized in two ways. First of all it is assumed that a removed adenoma will not develop into a cancer anymore. On top of that a cancer can be detected at an earlier stage (stage-shift) with potentially better survival.

Relevant Parameters

The parameters used to simulate natural history are:

- adenoma states
- age-specific adenoma incidence rate
- parameters for the individual risk index
- distribution of adenomas over the colon and rectum
- probability for an adenoma to be progressive
- parameters for the transition probability of non-progressive adenomas for each state
- parameters for the duration distribution of non-progressive adenomas for each transition
- parameters for the transition probability of progressive lesions for each state
- parameters for the duration distribution of progressive lesions for each transition
- correlation between duration in subsequent states
  All input-parameters for MISCAN-Colon are described in the Parameter Overview.

Calibration
The assumptions of the natural history of colorectal cancer are based on literature (see References For Model Parameters), 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 age-specific adenoma incidence. The adenoma incidence will be varied until simulated adenoma prevalence and colorectal cancer incidence reflect actual data. In MISCAN, we use an adaptation of the Nelder and Mead Simplex Method [1,2]or genetic algorithms to optimize these and other parameters. A complete list of parameters to be calibrated depends on data available and will be determined during the process.

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 adenomas. The MISCAN-Colon model has been validated on different data sources in the US and Europe (see Results Overview).

Dependent Outputs

The outputs most dependent on natural history are:

- cancer incidence
- cancer stage distributions
- cancer mortality

Relevant Results

The results of MISCAN-Colon provide solid policy recommendations based on evaluation of simulated effects of risk factors, improved therapy and screening interventions.

References

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Natural History Assumptions

Summary

This document describes the assumptions inherent in the modeling of disease initiation and progression.

Overview

Much of the natural history of disease is unobserved and parameters cannot be measured directly. To be able to model natural history of colorectal cancer, assumptions have to be made. The model assumptions are based on expert opinion by consensus of a group of clinical experts in the field of colorectal cancer.

See also Assumption Overview, Natural History Component

Detail

The Natural History Component assumptions are listed in detail below.

Colorectal cancer development
Colorectal cancer always grows from an adenoma.

Adenoma incidence
It is possible for individuals to develop multiple adenomas. In the whole population risk differences are present: some people will never develop an adenoma while others have more than one. This risk difference is modeled by the introduction of a risk index for each individual. A high-risk index indicates a high probability to develop adenomas. The risk index is randomly drawn from a gamma distribution.

Adenoma incidence also varies with age. The age-specific adenoma incidence rate can differ by birth cohort to reflect differences in relative risk between birth cohorts.

Multiple adenomas
Development of a new adenoma in a person is assumed to be independent of the number of adenomas already present. The development of this adenoma is also independent of the development of other adenomas.

Adenoma types
MISCAN-COLON distinguishes two types of adenomas[1]: non-progressive and progressive adenomas. The probability for an adenoma to be progressive is age-dependent.

[1]Note:

- Hyperplastic polyps are not modeled because we assume that hyperplastic polyps never grow into a cancer. Since their removal has no influence on incidence and mortality they are not included in MISCAN-COLON. In cost-effectiveness analyses the costs of removal of hyperplastic polyps will be accounted for.
- Flat adenomas are implicitly modeled as progressive adenomas that have short duration before developing into invasive states.

Non-progressive adenomas
Non-progressive adenomas never develop into an invasive state. These lesions can only transit through the states: adenoma <=5mm, adenoma 6-9mm and adenoma >=10mm. Some of the non-progressive adenomas never develop into an adenoma >=10mm.

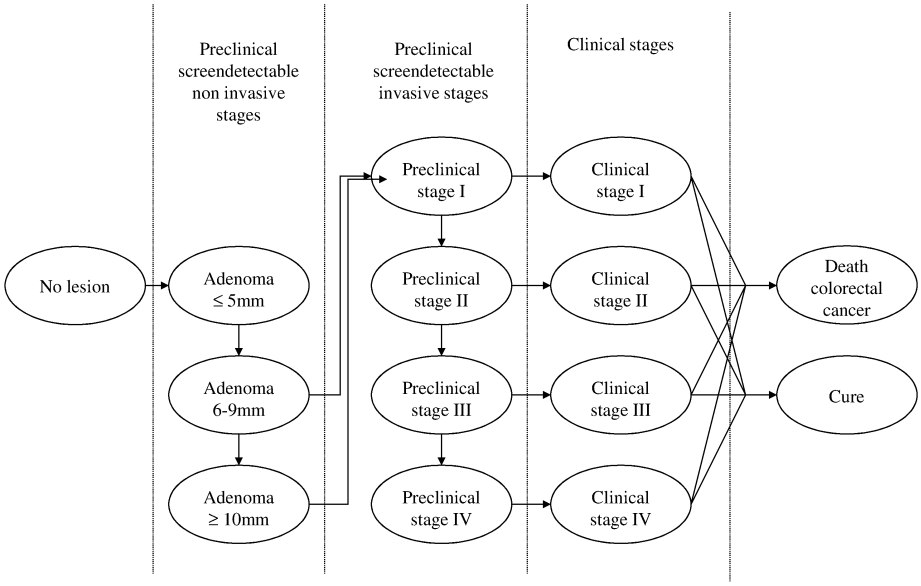
Progressive adenomas and cancer

Progressive adenomas are assumed to eventually develop into colorectal cancer (although a person may die from other causes before the cancer actually has developed). In this development the following states are possible:

1. progressive adenoma <= 5mm
2. progressive adenoma 6-9mm
3. progressive adenoma >= 10mm
4. preclinical colorectal cancer, stage I
5. preclinical colorectal cancer, stage II
6. preclinical colorectal cancer, stage III
7. preclinical colorectal cancer, stage IV
8. clinical colorectal cancer, stage I
9. clinical colorectal cancer, stage II
10. clinical colorectal cancer, stage III
11. clinical colorectal cancer, stage IV

Possible transitions between the different states are explained in figure 1:

Figure 1: Adenoma-carcinoma sequence for progressive adenomas



Transition probabilities

Each transition in figure 1 has a certain probability to occur. The transition probabilities can depend on age of the patient and localization of the adenoma. Transition probabilities are independent of risk exposure.

State duration

All transitions above have a certain duration distribution. This distribution can be assumed dependent of age and location of the lesion. We assume all durations to be exponentially distributed. We assume a positive correlation between duration in successive states. Durations are independent of risk exposure.

Anatomical site of adenomas

For every adenoma an anatomical site is determined. The anatomical site of a new polyp is independent of the anatomical site of previous polyps. We distinguish the following sites of the large bowel:

1. Rectum
2. Rectosigmoid
3. Sigmoid
4. Descending Colon
5. Transverse Colon
6. Ascending Colon
7. Cecum

Cancer incidence for which localization is not otherwise specified is proportionally distributed over the possible localizations. The site distribution for progressive and non-progressive adenomas is assumed to be equal.

Survival rates

After clinical diagnosis of one cancer, all adenomas and cancers in a person are assumed to be clinical. The model generates a stage-specific survival for the most advanced clinically diagnosed cancer. The patient dies from colorectal cancer at the moment this colorectal cancer reaches death. Survival depends on year of diagnosis, age at diagnosis, localization of the cancer and stage of disease.

Planned Model Extensions

Future updates to the model will incorporate additional lesion states, such as adenomas with high-grade dysplasia, tubular, tubulovillous, and villous adenomas. A distinct pathway for sessile serrated lesions, including hyperplastic polyps, is also under development.

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