ERASMUS MC (BREAST)

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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.

READERS 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.

Further Reading

These topics will provide a intermediate level view of the model. Consider these documents if you are interested gaining in a working knowledge of the model, its inputs and outputs.

JNCIMonograph Outline

This topic provides links to profile content organized according to the JNCI Monograph Outline for Model Description Chapters. Use this outline for comparisons focused on the CISNET Base Case simulations.

Advanced Reading

These topics denote more detailed documentation about specific and important aspects of the model structure

MODEL PURPOSE

SUMMARY

This page summarizes the model's purpose.

PURPOSE

The MISCAN computer simulation program[2] has been developed for building models for cancer screening in a dynamic population, and for subsequently applying these models to analyze and explain results of cancer screening trials, to predict and compare the (cost-) effectiveness of different screening policies, and to monitor the results of population screening programs. MISCAN models have been made and applied for cancer of the cervix, breast, colon, and prostate[6]. In these standard MISCAN models, the natural history is described by defining discrete tumor stages, transition probabilities between these stages, and dwelling times in each stage. A problem of such a discrete disease stage model is that no clear distinction is made between local parameters that are specific to a situation in an area, and "biological" parameters that can be assumed to be equal in different areas. It also appeared to be difficult to explore assumptions about the natural history or other explanations for the differences between model results and observations, for example regarding the stage distribution of screen-detected cancer, interval cancers, and cancers diagnosed in case of no screening.

Therefore we decided to develop a more biologically oriented continuous tumor growth component as an alternative for the standard discrete stage natural history and screening component in MISCAN. In this alternative MISCAN breast cancer model, which is described here, a new component is used for the Natural History Component of invasive breast cancer and the effect of treatment and screening on survival. This 'Fadia' component simulates histories of tumors based on continuous tumor growth and the concept of a fatal diameter: each tumor has a size (the fatal diameter, which differs between tumors) at which diagnosis and treatment will no longer result in cure (reflecting the available treatment options), at this point the tumor enters the stage of fatal disease., i.e. one or more micro metastases exist for which treatment will not be

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effective and will cause death from breast cancer for this woman. If the tumor is diagnosed (either on the basis of symptoms or by screening) and treated before the tumor reaches the fatal diameter the woman will be cured. In Fadia a distinction is made between tumor biology (tumor growth rate distribution) and model variables that may vary between areas and over time and / or age (diameter at clinical diagnosis, screening threshold diameter and fatal disease diameter, and survival). In the remainder "MISCAN-Fadia" will refer to the MISCAN version that includes this Fadia component, as described here; "standard MISCAN" will refer to the standard MISCAN model that can be used for simulating cancer screening as described by Loeve et al[2], and the "standard MISCAN breast cancer model" refers to the existing model for breast cancer with discrete tumor stages[4].

We also developed a cohort version of the MISCAN-Fadia population model and used it to estimate the parameters of the Fadia component using data from the Two County trial for breast cancer screening in Sweden[9]. See also Model Calibration Procedures

For the CISNET-Breast Base Case, the MISCAN-Fadia model was used to perform a series of model simulations for the years 1975-2000, including a background run assuming no screening and adjuvant treatment and runs with the assumed use of screening and / or adjuvant treatment during this period.

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MODEL OVERVIEW

SUMMARY

This document provides an overview of the modeling effort, and describes the model itself in general terms.

PURPOSE

In the MISCAN-Fadia model knowledge on natural history, screening and adjuvant treatment practice and breast cancer risk derived from randomized controlled trials and observational studies will be integrated. In this way MISCAN-Fadia can be helpful in analyzing and explaining results of cancer screening trials, predicting the (cost-) effectiveness of different screening policies, and predicting the potential of present and new interventions on future national trends. See also Model Purpose.

BACKGROUND

The MISCAN computer program has been used for building screening models for cancers of breast, cervix, colon en prostate [1,2,3,4,5]. In the standard MISCAN breast cancer model, the natural history is described as a semi Markov model. A problem of such a discrete disease stage model is that no clear distinction is made between local parameters that are specific to a situation in an area, and "biological" parameters that can be assumed to be equal in different areas. The Fadia natural history model is an alternative for the standard MISCAN breast cancer natural history model. It is based on continuous tumor growth instead of discrete tumor stages and on the concept of fatal diameter (a woman will die from breast cancer unless the tumor is detected before the tumor has reached the fatal diameter). In Fadia a distinction is made between tumor biology (tumor growth rate distribution) and model variables that may vary between areas and over time and / or age (diameter at clinical diagnosis, screening threshold diameter and fatal disease diameter, and survival).

MODEL DESCRIPTION

The MISCAN models use microsimulation: using the model inputs, independent life histories are generated including a possible cancer history and the effects of treatment and early detection by screening. Major differences between MISCAN-Fadia the standard MISCAN breast cancer model are: The MISCAN-Fadia model uses a continuous tumor growth model for the natural history of a tumor instead of a discrete stage natural history model;

- In the standard MISCAN models the screening test result depends on a stage-specific test sensitivity. In the MISCAN-Fadia model each tumor has a threshold diameter, which differs between tumors. If a tumor's diameter at the moment of screening is larger than this threshold the test result will be positive;

- In the standard MISCAN breast cancer model, the favorable effect of screening is relative to a woman's disease history without screening: a stage-specific proportion of screen-detected cancers will be cured. The MISCAN-Fadia model uses the fatal disease concept for modeling the survival of both clinically diagnosed and screen-detected cancers, and the diameter at which disease becomes fatal depends on the treatment given;

- The MISCAN-Fadia model allows for alternative adjuvant treatments that differ in the associated survival, and in their usage over time;

- In the standard MISCAN model it is possible to allow for multiple disease histories in a person, in the MISCAN-Fadia model each woman can only have one disease history;

- The MISCAN-Fadia model uses an external program for dissemination of screening.

Also see: Model Verification Procedures, Model Calibration Procedures, Model Validation Procedures

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ASSUMPTION OVERVIEW

SUMMARY

Summarizes the assumptions used in the MISCAN-Fadia model.

BACKGROUND

The MISCAN-Fadia model can be used to simulate breast cancer screening and treatment policies in a dynamic population (see Model Purpose), based on assumptions on demography, natural history of breast cancer, screening and treatment. Compared to the other major model components (see Component Overview), the natural history component uses the most assumptions, as the natural history is modeled very detailedly.

ASSUMPTION LISTING

The MISCAN-Fadia model uses the following assumptions:

1. Demography Assumptions
2. Natural History Assumptions
3. Screening Assumptions
4. Treatment Assumptions

Limitations

The present version of the MISCAN-Fadia model has the following limitations:

1. only one tumor per woman
2. only one screening test
3. test result is completely determined by tumor size and the threshold for a screening test (no random variation in performance of the test or in reading the test result)
4. No ER status modeled

PARAMETER OVERVIEW

SUMMARY

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

BACKGROUND

The MISCAN-Fadia model consists of four basic components (see Component Overview): the Population Component, the Natural History Component, the Screening Component and the Treatment Component.

PARAMETER LISTING OVERVIEW

1. Demography Parameters (See also Population Component)

2. Natural History Parameters (See also Natural History Component)

3. Screening Parameters (See also Screening Component)

4. Treatment Parameters (See also Treatment Component)

COMPONENT OVERVIEW

SUMMARY

This document describes the major components of the model, their function and relative arrangement.

OVERVIEW

The MISCAN-Fadia model consists of four major components (see figure 1). The population component simulates the demography of the population, the natural history component simulates the natural history of a breast cancer tumor, the screening component simulates dissemination of mammography screening and its effects, and the adjuvant treatment component simulates dissemination of adjuvant treatment and its effects on survival and on breast cancer mortality

Figure 1 also shows the data used by the Cohort Model for estimation of the parameters of the Fadia natural history component, and data used by MISCAN-Fadia for producing the Base Case results.
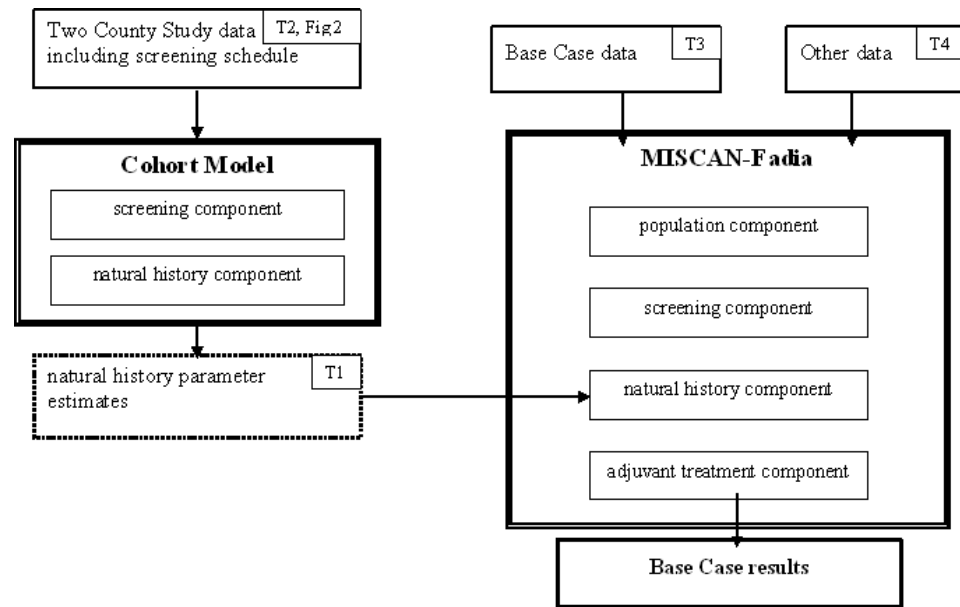

FIGURE 1: The two simulation models used for producing the Base Case results. The Cohort Model is used to estimate the parameters of the Fadia natural history of breast cancer, using the data from the Two County trial for breast cancer screening, by simulating the screening schedule of this trial. These natural history estimates are used in the MISCAN-Fadia population model, in combination with the Base Case data and other data, to run the simulations that produce the Base Case results for the US breast cancer incidence and mortality in the period 1975-2000. The labels T1...T4 refer to the tables that give an overview of the data used by the two models, Fig 2 refers to the survival data in Figure 2 (see Two County Study Result).

COMPONENT LISTING

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

- Natural History Component which simulates the natural history of a breast cancer tumor. In MISCAN-Fadia cancer incidence (see Cancer Incidence Component) and survival/mortality (Survival And Mortality Component) are a part of the Natural History Component.

- Population Component which simulates the demography of the simulated population

- Screening Component which simulates dissemination of mammography screening and its effect on the simulated population

- Treatment Component which simulates dissemination of adjuvant treatment and its effect on the simulated population

OUTPUT OVERVIEW

SUMMARY

Describes the outputs generated by the MISCAN-Fadia model.

OVERVIEW

The MISCAN-Fadia model simulates the Base Case outputs.

OUTPUT LISTING

The output component produces the final output of the model:

(1) Incidence counts by calendar year (1975-2000), stage and age in five year age groups (30-84)

(2) Mortality counts by calendar year (1975-1999) and age in five year age groups (30-84)

(3) Population on July 1 of each calendar year (1975-1999) by age in five year age groups (30-84)

(4) Mean lead time by age (30-84, 30-39, 40-49, 50-59, 60-69, 70-84). Lead time is defined as the time from screen detection to the time a person would have been clinically detected in the absence of screening. Persons are excluded if they die of other causes during their lead time.

(5) Overdiagnosis percent by age (30-84, 30-39, 40-49, 50-59, 60-69, 70-84). Overdiagnosis percent is defined as the # of women who are screen detected who never would have been clinically detected / # of women who are screen detected .

(6) Overdiagnosis count by five year age group and calendar year

(7) Detection rate at first screen by age (30-84, 30-39, 40-49, 50-59. 60-69, 70-84). Detection rate is defined as cancers detected / # of women screened

(8) Detection sate at second and later screen by age (30-84, 30-39, 40-49, 50-59. 60-69, 70-84). Detection rate is defined as cancers detected / # of women screened

(9) Program sensitivity* by age at screening using one year interval (ages 30-84, 30-39, 40-49, 50-59, 60-69, 70-84).

(10) Program sensitivity* by age at screening using two year interval (ages 30-84, 30-39, 40-49, 50-59, 60-69, 70-84).

- Each case diagnosed within an age range can be classified as screen detected, clinically detected with a negative screening exam within the defined interval before detection (interval case), or clinically detected with no screening exam within the defined interval before detection (not included in the calculation). Program sensitivity = (# screen detected)/(#screen detected + # interval cases)

RESULTS OVERVIEW

SUMMARY

This document lists various results generated by the model.

OVERVIEW

The main results from the MISCAN-Fadia model are the results for the breast Base Case analysis. Another important analysis using the Fadia natural history component was the Two County Study analysis (see Model Calibration Procedures). This analysis led to two important results. First, it gave us estimates for the parameters of the Fadia natural history component (see Natural History Component) that were used in order to produce the Base Case results. Second, the Two County Study analysis gave us more insight in the (dis)advantages of using a biogically grounded natural history component.

RESULTS LIST

- Two County Study Results
- Base Case Results

NATURAL HISTORY COMPONENT

SUMMARY

This document describes the Natural History generation portion of the microsimulation.

OVERVIEW

We will first describe the Fadia natural history component. Then we will describe how we estimated its parameters based on data from the Two County study using the Cohort Model and describe the results. Next, we will describe how the Fadia natural history component was adapted for the Base Case analysis.

The continuous tumor growth natural history model

The Fadia natural history component simulates invasive tumors, as well as ductal carcinoma in situ (dcis). In the sub-component for dcis, as in the standard MISCAN breast cancer model, three different types of dcis are assumed: regressive dcis, dcis that will be diagnosed clinically and dcis that will progress to invasive disease.

In Fadia, invasive breast tumors are initiated and are assumed to have a constant growth rate, which differs between tumors. Tumors also differ in the size (the fatal diameter) at which diagnosis and treatment will no longer result in cure (reflecting the available treatment options). At this point the tumor enters the stage of fatal disease. Clinical diagnosis of the tumor is triggered by two competing risks: by signs or symptoms resulting from the primary tumor, or by symptoms related to distant metastases. The probability of primary tumor related signs or symptoms is assumed to depend on the diameter of the primary tumor. The probability of distant metastases related signs or symptoms is assumed to depend on time since the disease became fatal. If the disease is already fatal at the moment of diagnosis of the tumor, the time of death from breast cancer is described by a probability distribution for the survival time since the start of fatal disease. This time between start of fatal disease and death from breast cancer applies both to the case in which the breast cancer is diagnosed clinically and to the case where this cancer is detected by screening.

DETAIL

The life course of a tumor is described by the following five variables, which are governed by probability distribution functions with two parameters each (scale and shape), and a sixth variable with one parameter:

1. Growth rate of the tumor (lognormal distribution with parameters μ_1 and σ_1);

2. Fatal diameter of the tumor (weibull distribution with a scale and a shape parameter);

3. Survival time after reaching the fatal diameter (lognormal distribution with parameters μ_3 and σ_3);

4. Threshold diameter of a tumor for a screening test, i.e. the tumor diameter at which a tumor becomes screen detectable (Weibull distribution with a scale and a shape parameter);

5. Tumor diameter at clinical diagnosis because of the primary tumor (lognormal distribution with parameters μ_2 and σ_2);

6. Moment at which distant metastases lead to clinical diagnosis of the tumor, modeled as a constant fraction of the survival time after reaching the fatal diameter (with this fraction as parameter).

In order to obtain a reasonable fit of the Two County Study screening trial data, we had to assume that three of the model variables—the tumor growth rate, the tumor diameter at clinical diagnosis, and the survival after inception of fatal disease—are correlated. This adds three more parameters to the model: the correlation ρ_1 between tumor growth rate and the survival time after reaching the fatal diameter, the correlation ρ_2 between tumor growth rate and the tumor diameter at clinical diagnosis because of the primary tumor, and the correlation ρ_3 between the tumor diameter at clinical diagnosis because of the primary tumor and the survival time after reaching the fatal diameter.

The tumor history model is thus characterized by the values of these 14 parameters (five pairs, one fraction, and three correlations). In MISCAN-Fadia, changes in the survival over time or as a result of improved treatment are modeled as a shift in the fatal diameter (parameter μ_3), and changes in the screening test sensitivity are modeled as a time dependent scale parameter of the threshold diameter distribution.

When a breast tumor is initiated in a simulated woman, values of the six tumor variables are generated. For each simulated tumor, the clinical diagnosis diameter is determined by the minimum of the diameter at clinical diagnosis because of the primary tumor and the diameter at clinical diagnosis because of metastases. The growth rate of the tumor then determines the times since its initiation at which it reaches the fatal diameter, the clinical diagnosis diameter, and the threshold diameter for a screening test. If the clinical diagnosis diameter is larger than the fatal diameter, then the sum of the time at which the fatal diameter is reached and the survival time after reaching the fatal diameter will give the time at which a woman will die of breast cancer. The woman will be cured if the cancer is detected, either clinically or by a screening test, before the fatal diameter is reached. For a woman with a tumor, the result of a screening test is completely determined by the tumor diameter and the threshold diameter for this test for this tumor, i.e. no allowance is made for random variation in performance of the test or in reading the test result.

RELEVANT ASSUMPTIONS
See Natural History Assumptions

RELEVANT PARAMETERS
See Natural History Parameters

RELEVANT COMPONENTS

- Cancer Incidence is described in the Cancer Incidence Component
- survival mortality is decribed in the Survival And Mortality Component

MODEL CALIBRATION PROCEDURES

Overview

The main calibration procedures of the model are the one in which the parameters of the Cohort Model have been estimated from the Two County screening trial and the one in which th MISCAN-Fadia model is calibrated for the Base Case analyses. Other calibration procedures have been described in the Cancer Incidence Component.

Estimation of natural history model parameters using results from the Swedish Two County breast cancer screening trial

For estimation of the parameters of Fadia component, we used a simplified cohort version that allows for efficient estimation of model parameters using data from screening trials. This Cohort Model focuses on the natural history of invasive breast cancer tumors and the effect of screening in a cohort of women that participate in a screening trial; it does not include age (and thus neglects age-dependencies), it only includes tumor size as tumor attribute (e.g. neglecting distant metastases and lymph node status) and also neglects death from other causes, dcis, time trends in breast cancer incidence or survival, and the impact of adjuvant treatment. The Cohort Model also uses microsimulation, but it simulates screening in a cohort instead of in a full dynamic population. Moreover, it simulates tumor histories instead of life histories of women. The Cohort Model was used to estimate model parameters from the results reported by the Swedish Two County breast cancer screening trial (TCS)[3]. The tumor histories simulated by the Cohort Model are used to generate output on detection rates at successive screening rounds, interval cancer rates, tumor diameter distribution of screen detected cancers, of interval cancers and of cancers diagnosed in the control group, on survival by time since diagnosis for screen detected cancers, interval cancers and cancers diagnosed in the control group, and on survival by tumor diameter and by time since diagnosis.

The TCS started in October 1977 in Kopparberg and in May 1978 in Östergötland[1]. Women aged 40-74 were randomized to either the study group, consisting of 77,080 women, or control group, consisting of 55,985 women. Women in the study group were invited to mammography screening; women aged 40-49 were invited every 24 months and women aged 50-74 every 33 months. In our analysis, we used data from women aged 50-69 at entry ([1],[2], personal communication). The follow-up period after the last screening round ended on average 8 years after start of the study. At that moment women in the control group were invited for a screening examination too. Data on cancers detected at this screening are not included in the estimation of the model parameters.

Tumors are assumed to initiate with a diameter of 0.1 mm with constant onset rate of 2.2 per 1000 women years, which is the observed incidence rate in the control group[1]. Predicted detection and interval rates are corrected for the aging of the women during the trial, to adjust for the fact that age is not incorporated in the Cohort Model whereas breast cancer incidence increases by age. For given values of the model parameters, a single micro-simulation run will produce expected values (rates or proportions) for each of the results of the TCS study. Maximum likelihood estimates of the model parameters are derived by repeated evaluation of the simulated histories using the Score Function (SF) method in combination with a quasi-Newton optimization

procedure[5]. With respect to the likelihood of the model, the screening data considered are either very small proportions of breast cancer cases, e.g. detection rates at screening and interval cancer rates, or distributions of breast cancer cases over sub categories, e.g. tumor stage distribution of screen detected cancers and interval cancers. The observed numbers of cases were assumed to be governed by a Poisson and a multinomial distribution, respectively.

The goodness of fit of the model is calculated using the deviance, which is defined as minus two times the difference in log likelihood between the expected model and the saturated model (i.e. the best possible model which takes the observed numbers as expected values for the Poisson and multinomial distributions).

Initially, we fitted the Cohort Model to the TCS data assuming Weibull probability distribution functions for all variables. However, when it became apparent that correlation had to be assumed between some of the variables, a switch was made to lognormal distributions that are more convenient in this respect. Thus, lognormal distributions were used for correlated variables: the tumor growth rate, the tumor diameter at clinical detection and survival time after reaching the fatal diameter. See also Two County Study Result.

Quantification of the MISCAN-Fadia model for the Base Case analyses

The Cohort Model quantification as based on the Two County Study data was used as starting point for the quantification of the natural history model parameters of MISCAN-Fadia. In order to quantify MISCAN-Fadia for the Base Case, we calibrated some of these natural history model parameters to Base Case data (see Table 3), described in *Calibration of natural history model parameters* below, and we made some extensions to the model, described in *Extensions of the MISCAN-Fadia natural history component* below. Table 4 gives an overview of how Base Case data were used for the quantification of MISCAN-Fadia.

TABLE 3. Overview of MISCAN-Fadia parameters that are based on other data than the Base Case data.

MISCAN-Fadia parameter	Method	Data used	value
tumor growth rate	Estimated with Cohort Model	TCS	Table 1
survival duration	Estimated with Cohort Model	TCS	Table 1
screening threshold	Estimated with Cohort Model + estimation of trend 1975-2000	TCS, HIP	Tables 1 and 6
Correlations between growth rate, diameter at clinical diagnosis because of primary tumor, and survival	Estimated with Cohort Model	TCS	Table 1
dcis duration and progression		Dutch	Table 8
dcis survival			100%

TABLE 4. Base Case Data Usage. U = Used as provided by Cisnet; P = Uses a processed version of the Base Case data; C = Model is calibrated to the Base Case data by varying a parameter of the continuous tumor growth model; O = is determined by other Base Case data used in the model

Base Case Data	Usage	Notes
Treatment Dissemination	U	Used as direct input
Mammography Dissemination	U	Base Case Dissemination model was directly used as external program
Other Cause Mortality	U	Used to calculate size of birth cohorts in the US population, see Table 11 in Population Component
SEER incidence	C	1975 size specific incidence was used to calibrate parameters for tumor diameter at diagnosis because of primary tumor, see Table 5.
1975 Breast Cancer Prevalence	O	Results from cohort risks, age specific distribution of incidence and calibration of fatal diameter to 1975 survival and time trend in fatal diameter prior to 1975
1975 Cause Specific Survival	C	Used to estimate 1975 fatal diameter parameters, see Table 5.
Historical Survival	C	Used to estimate time trend in fatal diameter prior to 1975, see Table 5
1975 Stage Distribution	C	Used to estimate AJCC stage distribution parameters, see Table 7
1975 Breast Cancer Mortality	O	Results from cohort risks, age specific distribution of incidence and calibration of fatal diameter to 1975 survival and time trend in fatal diameter prior to 1975
Breast Cancer APC Incidence	P	Converted to Age-Cohort model with cumulative incidences as cohort risks and one fixed age specific distribution of incidence of pre-clinical screen-detectable disease for all cohorts, see Tables 9 and 10.
Treatment Effect	C	Calibrated by a shift in fatal diameter, see Table 13 in Treatment Component
SEER 9 Mortality	O	Results from cohort risks, age specific distribution of incidence, calibration of fatal diameter to 1975 survival, and time trend in fatal diameter prior to 1975, dissemination of mammography and adjuvant treatment

TABLE 5. MISCAN-Fadia. Parameters of the distributions for the fatal diameter and for the diameter at clinical diagnosis because of the primary tumor.

Variable	distribution	year	par1	par2	mean	st.dev.
fatal diameter (cm)	Weibull (scale, shape)	1915	0.82	0.95	0.84	0.88
		1975	4.02		4.11	4.33
clinical diagnosis because of the primary tumor (diameter, cm)	Lognormal (ρ, σ)	(all)	0.97	0.63	3.22	2.25

Calibration of natural history model parameters

The diameter at clinical diagnosis because of the primary tumor was calibrated to the 1975 stage distribution as provided by the Base Case SEER incidence data, and the fatal

diameter was calibrated to 1975 Cause Specific Survival Base Case data. These model parameters were calibrated simultaneously since they both influence the stage distribution as well as the survival, see Table 5.

Extensions of the MISCAN-Fadia natural history component

The quantification obtained by the Cohort Model was extended by including a calendar time dependency of the fatal diameter, and an age and calendar time dependency of the screening threshold diameter. The tumor diameter distribution was extended to an AJCC stage distribution, and the effect of adjuvant treatment was included as a change in the scale parameter of the fatal diameter distribution. The quantification of the dcis part is equal to that used in the standard MISCAN breast cancer model. The Base Case APC incidence data was simplified to an age-cohort model, and then used to calculate age-specific onset of pre-clinical screen-detectable disease.

The quantification of the fatal diameter has been extended in the MISCAN-Fadia model: the scale parameter of the Weibull distribution for the fatal diameter has been made dependent on the year of diagnosis, accounting for the improvement of treatment. Assuming no improvements in treatment other than adjuvant treatment after 1975, we only modeled a time dependency prior to 1975. The quantification of this time dependency was based on the hazard ratio between 1940-1949 and 1970-1974 20 years survival, using the *Historical Survival Base Case* data, which in turn is based on Connecticut data.

In the MISCAN-Fadia model, a hazard ratio cannot be applied directly because survival is described by lognormal survival distribution for women (proportion: $1 - c_{1975}$) in whom the diameter at diagnosis exceeds the fatal diameter, and cure for the proportion $1 - c_{1975}$ of women in whom the diameter at diagnosis is smaller than the fatal diameter. So we translated the hazard ratio r between 1940-1949 and 1970-1974 into a shift in fatal diameter between 1975 and 1945. This shift in fatal diameter from 1975 to 1945 leads, in combination with the distribution of the clinical diagnosis diameter—which is modeled constant over time—to a new cure proportion c_{1945}. We approximated the 1945 cure proportion c_{1945}, using the hazard ratio r between 1940-1949 and 1970-1974, the 1975 cure proportion c_{1975} and the probability distribution function *F(t)* for the survival time since the moment at which the tumor reached its fatal diameter:

$$c_{1945} = \frac{\{1 - (1 - c_{1975}F(t)\}^{1/r} + F(t) - 1}{F(t)}$$

Based on the 1945 cure proportion c1945 and the distribution of the clinical diagnosis diameter, we calculated the value of the scale parameter of the fatal disease diameter for 1945 that corresponds to the 1945 cure proportion. Linear interpolation is applied from 1975 to 1945 and this time trend is extrapolated backwards to 1915, which is the first possible year of onset for the oldest women. The quantification of the threshold diameter for screen detection as estimated from the Two County trial data using the Cohort Model has been extended in the MISCAN-Fadia model: the scale parameter of the Weibull distribution for the threshold for screen detection has been made dependent on the year and the age of the woman at the moment of screening, using four age groups The stage distribution of invasive tumors was extended to AJCC stages by adding three more variables to the model and then calibrated to the Base Case 1975 stage distribution data (see also Table 7):

- the tumor diameter at which a N1 lymph node disease becomes detectable by modern techniques
- the difference in tumor diameters at which a N1 and a N2 lymph node disease become detectable by modern techniques
- The time at which distant metastases become detectable by modern techniques, modeled as a fraction of the time between the moment at which the tumor reaches the fatal diameter and the death from the breast cancer

Note that in MISCAN-Fadia, detectable distant metastases are assumed to be fatal. MISCAN-Fadia does not model the moment of initiation of distant metastases; it only models the moment at which distant metastases become detectable by modern techniques and the moment at which distant metastases lead to diagnosis of the primary tumor—the first event always preceding the latter.

The MISCAN-Fadia model includes a discrete disease state for dcis. The submodel for dcis was taken from the standard MISCAN breast cancer model[7], which was based on data from the screening trials in Utrecht and Nijmegen (The Netherlands). In this submodel, there are three different types of dcis: regressive dcis, dcis that will be diagnosed clinically and dcis that will progress to invasive disease. All types of dcis have a mean duration of 5.22 years. The distribution among the different types of dcis depends on age; the durations do not depend on age. (see Table 8).

In the MISCAN-Fadia model, the onset of invasive disease is defined as the minimal value of the threshold diameter over ages and time, i.e. the value at age 80 and in the year 2000. The minimal value of the threshold diameter thus has a Weibull distribution with scale parameter 0.65 (Table 6; age 80, year 2000) and shape parameter 2.95 (see Table 1 in Component Overview). We assumed the duration of dcis not to change over time for regressive dcis and for dcis that will be diagnosed clinically. For the duration of dcis that progresses to invasive disease—which is equal to the duration from onset of dcis to the moment the tumor reaches the minimal threshold size—we assumed the MISCAN quantification to hold for 1975. To this end, we adapted the mean duration of dcis that progresses to invasive disease in order for the sum of the mean duration of dcis that progresses to invasive disease and the mean duration between the minimal value of the threshold diameter and 1975 threshold diameter to match the quantification of the standard MISCAN breast cancer model (5.22 years, see Table 8).

For screening of dcis, the MISCAN-Fadia model also uses the same mechanisms as the standard MISCAN breast cancer model. The probability of screen detection of dcis is modeled through a test sensitivity parameter. The standard MISCAN quantification for the sensitivity of dcis (0.4) is used for 1975, which is 0.4, and has been made time dependent, increasing linearly to 0.8 in 2000. Screen detected dcis is, just like clinically detected dcis, assumed to have a 100% survival.

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MODEL VERIFICATION PROCEDURES

The standard MISCAN model has been rigorously tested during its development. A large number of test were designed , carried out, documented and evaluated to check all components of the MISCAN program. The results of these test have been evaluated in a group of primary users. Similar tests have been applied to later versions of the model, in particular when the MISCAN-Fadia version was created.

The Cohort Model was initially programmed in Pascal. The code was checked when it was reprogrammed in C++ (by another person) by comparing results of both versions.

The MISCAN extensions for the CISNET project involve implementation of the continuous tumor growth model in MISCAN, and creating additional model output. The continuous tumor growth model component in MISCAN was checked by inspecting individual histories (using Matlab for comparison), including checks of output. New output was also checked against existing MISCAN output with partially overlapping sub-classifications. Diagnostic runs with extreme assumptions were performed (0% and 100% adjuvant treatment effect, screening threshold diameter > clinical diagnosis diameter, etc.) and gave expected outcomes.

MODEL VALIDATION PROCEDURES

Independent validation

No independent validation has been performed yet. Earlier versions of the continuous tumor growth model that did not include correlation between growth rate, tumor diameter at clinical diagnosis, and survival since the moment at which fatal diameter was reached, were fitted both to the TCS and HIP screening trials, but did not give acceptable results. We will again include the HIP trial in further analyses, by checking the TCS estimates on the HIP data, and fit the HIP data with the current structure of the model including the correlation.

DEMOGRAPHY ASSUMPTIONS

Assumptions in the MISCAN-Fadia model regarding demography: (See also Population Component)

a. The age distribution of the tumor initiation rate is the same for all birth cohorts

b. the life time breast cancer risk is the same for all women in a certain birth cohort

c. the life table is the same for all women in a certain birth cohort

d. death from breast cancer and death from other causes are independent

NATURAL HISTORY ASSUMPTIONS

The MISCAN-Fadia model uses the following assumptions on natural history: (See also Natural History Component)

a.tumor initiation

In the MISCAN-Fadia model DCIS and invasive tumors are assumed to initiate with the same age specific initiation rate.

b.dCIS

dCIS is a preclinical discrete stage with a certain duration that precedes a proportion of the invasive tumors. There are three possible transitions from pre clinical dCIS:

1. regression
2. progression to an invasive tumor
3. clinical detection of dCIS

If a dCIS progresses to an invasive tumor, the invasive tumor starts growing from the smallest detectable stage. As soon as the dCIS has progressed to an invasive tumor, the invasive tumor will determine the stage of the tumor.

c.invasive breast cancer

Invasive tumors are assumed to grow exponentially, i.e. with constant growth rate. The natural history of an invasive breast cancer is characterized by the following variables.

1. tumor growth rate (governed by a lognormal distribution)
2. fatal diameter of the tumor (governed by a weibull distribution)
3. survival duration after reaching the fatal diameter (governed by a lognormal distribution)
4. tumor diameter at clinical diagnosis because of the primary tumor (governed by a lognormal distribution)
5. moment at which distant metastases lead to clinical diagnosis of the tumor, modeled as a constant fraction of the survival duration after reaching the fatal diameter (deterministic)
6. tumor diameter at inception of lymph node metastases N1 occur (governed by a weibull distribution)
7. difference between the tumor diameters at which N1 and N2 lymph node involvement occur (deterministic)
8. moment at which distant metastases occur, modeled as a constant fraction of the survival duration after reaching the fatal diameter (deterministic)

We assume that the tumor growth rate, the survival duration after reaching the fatal diameter and the tumor diameter at clinical diagnosis because of the primary tumor are correlated.

If the tumor is not detected before the tumor has reached the fatal diameter, the woman will die from breast cancer if the woman does not die from other causes before. If the tumor is detected before inception of detectable lymph node metastases, the stage of the detected tumor is node negative; otherwise it is node positive. If the tumor is detected before inception of detectable distant metastases, the stage of the detected tumor is distant metastases negative; otherwise it is distant metastases positive.

SCREENING ASSUMPTIONS

The MISCAN-Fadia model uses the following assumptions regarding mammography screening: (See also Screening Component)

a. effect of screening

1. dCIS: A preclinical dCIS may be detected by screening, depending on the sensitivity of the screening test for dCIS.

2. invasive tumor: The screen detectability of an invasive tumor is completely determined by its threshold size for screen detection. If a woman is screened before the threshold size is reached, the screening test will not detect the tumor; after the threshold size is reached a test will always detect the tumor. Each tumor has its own threshold size, which is governed by a weibull distribution with two parameters, mean and shape. The threshold size for screen detection is assumed to depend on age and year of diagnosis.

b. dissemination of screening

In the MISCAN-Fadia model there are two screening dissemination routines:

1. MISCAN screening dissemination routine, that simulates a regular invitation based screening schedule based on specified screening period, screening ages and attendance rates.

2. CISNET screening dissemination routine, that simulates the actual dissemination of mammography in the US during the period 1975-2000, given a woman's date of birth

TREATMENT ASSUMPTIONS

The MISCAN-Fadia model uses the following assumptions regarding treatment: (See also Treatment Component)

a. **Effect of adjuvant treatment**: A woman diagnosed with cancer may be given adjuvant treatment. There may be different kinds of adjuvant treatment. Each kind of adjuvant treatment has a certain probability to cure the woman, i.e. to eliminate the fatal metastasis if the tumor is diagnosed after inception of fatal metastasis.

b. **dissemination of adjuvant treatment**: In the MISCAN-Fadia model the dissemination of adjuvant treatment is simulated using the CISNET adjuvant treatment dissemination routine that simulates the actual dissemination of adjuvant treatment in the US during the period 1975-2000, given a woman's age at diagnosis, the tumor stage at diagnosis and the year of diagnosis.

POPULATION COMPONENT

SUMMARY
Describes the population component of the MISCAN-Fadia model.

OVERVIEW
The Population component simulates the demography of the simulated population.

DETAIL
The US population is simulated by 5-year birth cohorts starting from 1895-99 up to 1965-1969 and 1970 (the latter being a 1 year cohort which is necessary for simulating the year 2000), and all persons in the cohort are simulated from birth to death. Each cohort has its own lifetable (using 1 year age steps) for deaths from other causes which was derived directly from the Base Case data for other cause mortality, for the mid-year of each cohort (thus, 1892,1897,…). Death from other causes before age 30 is neglected in these lifetables because relevant model output is only produced for ages 30-79. The maximum lifetable age in the MISCAN is 100, at which all persons have died.

The relative size of each birth cohort (at birth) is calculated from the Base Case data for the size of the population in 1975, correcting for the probability of dying before 1975 (only for women who reached age 30 before 1975). The relative sizes of the cohorts are then translated into a proportion of the simulated population for each of the cohorts, see Table 11.

TABLE 11. MISCAN-Fadia. Proportion of the simulated population in each birth cohort

Birth cohort	Proportion
1895-99	4.1%
1900-04	4.6%
1905-09	5.2%
1910-14	5.3%
1915-19	5.6%
1920-24	6.0%
1925-29	5.7%
1930-34	5.2%
1935-39	5.4%
1940-44	6.5%
1945-49	7.1%
1950-54	8.5%
1955-59	9.5%
1960-64	10.1%
1965-69	9.4%
1970-71	1.8%

RELEVANT ASSUMPTIONS

See Demography Assumptions

RELEVANT PARAMETERS

See Demography Parameters

SCREENING COMPONENT

SUMMARY

Describes the Screening component of the MISCAN-Fadia model.

OVERVIEW

The screening component simulates the dissemination and the effect of screening.

DETAIL

Screening usage

The common Cisnet screening dissemination model was used as an external program, and the MISCAN simulation procedure was adapted accordingly for runs that include screening. First, MISCAN-Fadia generates dates of birth for all simulated women and these are written to a file. Next, the dissemination model is run, using the dates of birth from this file to generate a second file with screening ages for all women. Then, MISCAN-Fadia is run again (using common random numbers and the same seed values for the random number generator), and for each woman the screening ages are read from the second file, and a complete life history is generated.

Characteristics of screen-detected and interval tumors.

The tumor diameter distribution of cancers is determined by the continuous tumor growth model. For cancers diagnosed in never screened women it is influenced by the (positive) correlation between the variables growth rate and diameter at clinical diagnosis because of the primary tumor (Table 1b). For screen-detected and interval cancers it is also determined by these two variables, and in addition by the variable threshold diameter for screen-detection. The probability to detect a dcis depends on the sensitivity of dcis.

RELEVANT ASSUMPTIONS

See Screening Assumptions

RELEVANT PARAMETERS

See Screening Parameters

TREATMENT COMPONENT

SUMMARY

Describes the treatment component of the MISCAN-Fadia model.

OVERVIEW

The Treatment component is used to simulate the dissemination and the effect of adjuvant treatment.

DETAIL

Treatment dissemination is included in the MISCAN-Fadia model as a probability of being treated with a certain type of adjuvant treatment, i.e. chemotherapy or tamoxifen or both for two years, tamoxifen for 5 years, chemotherapy and tamoxifen for 5 years, or none. These probabilities depend on year, age, and stage, and are adopted from the common Base Case data.

The benefit of adjuvant treatment was modeled according to the results of the Cochrane meta-analyses[2], which reported proportional reductions in all cause mortality hazard for the different adjuvant treatment regimes (Base Case Treatment effect data). For chemotherapy, we used the age specific proportional reductions as reported in the meta-analysis directly. For tamoxifen, we calculated the age specific proportional reductions by multiplying the proportional reductions for women with ER+ tumors as reported in the meta-analysis with the proportion of ER+ tumors by age group as reported in the SEER for the period 1988-1993. Furthermore, the effects of chemotherapy and tamoxifen are assumed to be independent.

In MISCAN, a hazard reduction as reported in the meta-analysis cannot be applied directly because survival in absence of adjuvant treatment is described by lognormal survival distribution for women in whom the diameter at diagnosis exceeds the fatal diameter, and cure for the of women in whom the diameter at diagnosis is smaller than the fatal diameter. The effect of adjuvant treatment is modeled as a shift in the fatal disease diameter depending on the adjuvant treatment given, analogous to the way the time dependency of treatment prior to 1975 is modeled, with an extra correction for death from other causes - this correction was done in order to model the effect on breast cancer mortality, since hazard ratios were reported for all cause mortality[2-]. We approximated the new cure proportions for each adjuvant treatment cadjth, using the hazard ratio r as reported by Peto, the 1975 cure proportion c_{1975}, the probability distribution function $F(t)$ for the survival time since the moment at which the tumor reached its fatal diameter and the probability of dying from other causes $F_{oc}(t)$.

$$c_{adjth} = \frac{\{[1 - F_{oc}(t)]^{r-1}[1 - (1 - c_{1975})]F(t)\}^r + F(t) - 1}{F(t)}$$

We used $t=10$ years, corresponding to the average follow-up in Peto's meta-analysis[2]. The probability of dying from other causes was approximated using Base Case data. For each adjuvant treatment, the new cure proportion c_{adjth} was then translated into a shift in fatal diameter.

For each type of treatment and age group, a value of the scale parameter of the fatal diameter that corresponds to adjuvant treatment was calculated, see Table 12. This approach will lead to under-estimation of the short-term effect of adjuvant treatment and to over-estimation of the long-term effect. The shift in the fatal diameter leads to an additional delay in the moment of death from breast cancer because the moment of death from breast cancer is described by a distribution that starts at the moment at which the fatal diameter is reached. This will lead to an additional beneficial effect of adjuvant treatment.

TABLE 12. MISCAN-Fadia. Median value of fatal diameter corresponding to adjuvant treatment, by age and by type of treatment. Note that the mode is 0 for all adjuvant treatments and all ages, since the fatal diameter is governed by a Weibull distribution with shape parameter

TYPE AND DURATION	AGE		
	50-59	60-69	70+
Chemotherapy 2yr	4.34	3.60	3.23	3.73
Tamoxifen 2yr	3.23	3.60	3.88	5.11
Tamoxifen 5yr	3.60	4.18	4.70	8.64
Both 2yr	5.11	4.51	4.70	7.75
Both 5yr	5.56	5.32	5.81	14.73

TABLE 13. MISCAN-Fadia. Comparison of simulated and observed results for 1975: (rates per 100000)

CLINICAL INCIDENCE				MORTALITY(1973-1975)			PREVALENCE OF BREAST CANCER PATIENTS		
Age	MISCAN	APC	pct diff	MISCAN	BaseCase	pct diff	MISCAN	BaseCase	pct diff
30-34	28	28	-1%	6	6	10%	84	75	12%
35-39	61	62	-2%	14	13	6%	235	268	-12%
40-44	114	116	-2%	28	24	16%	507	636	-20%
45-49	176	180	-2%	49	43	12%	1023	1096	-7%
50-54	200	201	-1%	64	59	8%	1611	1527	6%
55-59	224	224	0%	74	74	0%	2097	1993	5%
60-64	259	264	-2%	87	84	3%	2643	2289	15%
65-69	293	294	0%	100	93	8%	3241	2556	27%
70-74	322	322	0%	117	104	12%	3856	2904	33%
75-79	329	331	-1%	119	118	1%	4363	3058	43%

RELEVANT ASSUMPTIONS

See Treatment Component

RELEVANT PARAMETERS

See Treatment Parameters

REFERENCES:

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[2] EBCTCG "Tamoxifen for early breast cancer: an overview of the randomised trials" 1998; 351: : 1451-67

DEMOGRAPHY PARAMETERS

Parameters for the MISCAN-Fadia Population Component :

a. number of birth cohorts

b. parameters for the distribution of the population among the birth cohorts

c. for each birth cohort parameters for its birth table.. Each birth cohort is defined by its first and last date of birth. A birth table gives the distribution of dates of birth within the birth cohort.

d. for each birth cohort the parameters of its life table

e. for each birth cohort the life time breast cancer risk

NATURAL HISTORY PARAMETERS

Parameters for the MISCAN-Fadia Natural History Component :

a. parameters for the age specific distribution of onset of the first screen detectable disease stage (dCIS or invasive)

b. parameters for the duration, regression and progression of dCIS

c. parameters for the distribution of the tumor growth rate

d. parameters for the distribution of the fatal diameter, scale parameter depends on year of diagnosis

e. parameters for the distribution of the survival duration after reaching the fatal diameter

f. parameters for distribution of tumor diameter at clinical diagnosis because of the primary tumor

g. parameter for the moment at which distant metastases lead to clinical diagnosis of the tumor, modeled as a constant fraction of the survival duration after reaching the fatal diameter

h. parameters for the distribution of the tumor diameter at inception of detectable lymph node metastases N1

i. difference between the tumor diameters at which N1 and N2 lymph node involvement occur

j. parameter for the moment at which distant metastases occur, modeled as a constant fraction of the survival duration after reaching the fatal diameter

k. correlation between tumor growth rate and survival duration after reaching the fatal diameter

l. correlation between tumor growth rate and tumor diameter at clinical diagnosis because of the primary tumor

m. correlation between survival duration after reaching the fatal diameter and tumor diameter at clinical diagnosis because of the primary tumor

SCREENING PARAMETERS

Parameters of the MISCAN-Fadia Screening Component :

a. parameters for the dissemination of mammography screening

b. parameters for distribution of threshold diameter for screen detection, scale parameter by age and year of diagnosis

c. sensitivity of the screening test for dCIS

TREATMENT PARAMETERS

Parameters for the Treatment Component

a. parameters for the dissemination of adjuvant treatment by age at diagnosis, year of diagnosis and treatment

b. for each specified adjuvant treatment the corresponding effects by age group, modeled as treatment dependent fatal diameter

TWO COUNTY STUDY RESULT

Overview

The analysis of fitting the Fadia Natural History Component to Two County Study data, as described in Model Calibration Procedures, resulted in parameter estimates presented in Table 1. The observed and simulated detection rates, interval cancer rates and stage distribution of screen-detected cancers, interval cancers, and cancers diagnosed in the control group (before screening started in this group) are presented in Table 2. The Fadia Natural History Component gives a reasonably good fit of TCS data. Note that the model predicts too few small tumors for the control group and too few the screen-detected cancers during the first round, and too many in interval cancers and cancers found at repeat screening. This corresponds with the finding that the observed stage distribution of breast cancers detected at a first screening round is often not more favorable than the distribution at repeat screenings[1]. Figure 2 shows the comparison between observed and simulated survival by tumor diameter.

The difference in mortality between study and control group was simulated including a screening in the control group at the end of the study period. The simulated mortality reduction after 11 years was 27% which is somewhat lower than the observed 30% reduction.[2]

The biological model structure makes quantification of MISCAN-Fadia less straightforward than we expected. For example, survival time is measured from the moment of reaching the fatal diameter, which means that survival parameters have to be estimated or calibrated, with the complication that survival since diagnosis depends on several model variables: tumor growth rate, clinical diagnosis diameter, survival time since moment of reaching the fatal diameter.

Details

Readers Guide
Model Overview
Assumption Overview
Parameter Overview
Component Overview
Output Overview
Results Overview
Key References

TABLE 1. Maximum likelihood estimates for the parameters of the natural history module based on the data from the Two County Study. "Survival" refers to survival time since the moment of reaching the fatal diameter.

A. PARAMETERS OF THE DISTRIBUTION FUNCTIONS

Variable	Distribution	par1	par2	mean	St.dev.
growth rate (1/year)	Lognormal (μ, σ)	0.062	0.87	1.55	1.65
fatal diameter (cm)	Weibull (scale, shape)	2.93	1.42	2.66	1.90
survival (duration, years)	Lognormal (μ, σ)	2.43	1.13	21.5	34.6
clinical diagnosis (diameter, cm)	Lognormal (μ, σ)	0.84	0.59	2.76	1.78
screening threshold (diameter, cm)	Weibull (scale, shape)	1.02	2.95	0.91	0.34

B. CORRELATION BETWEEN VARIABLES

Variables	ρ
growth rate - survival (ρ_1)	-0.90
growth rate - clinical diagnosis diameter (ρ_2)	+0.41
clinical diagnosis diameter - survival (ρ_3)	-0.43

C. TIME SINCE START OF FATAL DISEASE AT WHICH METASTASES LEAD TO CLINICAL DIAGNOSIS OF THE TUMOR
(fraction of the total survival time after reaching the fatal diameter):

0.9

TABLE 2. Comparison of the Two County Study data with the number of cancers as predicted by the Cohort model

A. SCREEN DETECTED CANCERS BY ROUND (STUDY GROUP)

	Observed	Simulated
1	286	286
2+3	303	265

B. INTERVAL CANCERS, BY ROUND (STUDY GROUP)

	Observed	Simulated
1	76	77
2+3	107	124

C. SIZE DISTRIBUTION FOR SCREEN DETECTED CANCERS, FIRST ROUND (STUDY GROUP)

Tumor diameter	Observed	Simulated
	9%	8%
6-10 mm	32%	27%
11-20 mm	39%	44%
>20 mm	20%	21%

D. SIZE DISTRIBUTION FOR SCREEN DETECTED CANCERS, SUBSEQUENT ROUNDS (STUDY GROUP)

Tumor diameter	Observed	Simulated
	8%	10%
6-10 mm	31%	34%
11-20 mm	49%	44%
>20 mm	13%	12%

E. SIZE DISTRIBUTION FOR INTERVAL CANCERS (STUDY GROUP)

Tumor diameter	Observed	Simulated
	1%	4%
6-10 mm	17%	22%
11-20 mm	41%	40%
>20 mm	41%	34%

F. SIZE DISTRIBUTION FOR CLINICALLY DIAGNOSED CANCERS (CONTROL GROUP)

Tumor diameter	Observed	Simulated
	3%	1%
6-10 mm	11%	10%
11-20 mm	36%	34%
>20 mm	50%	56%

breast cancer survival, TCS trial

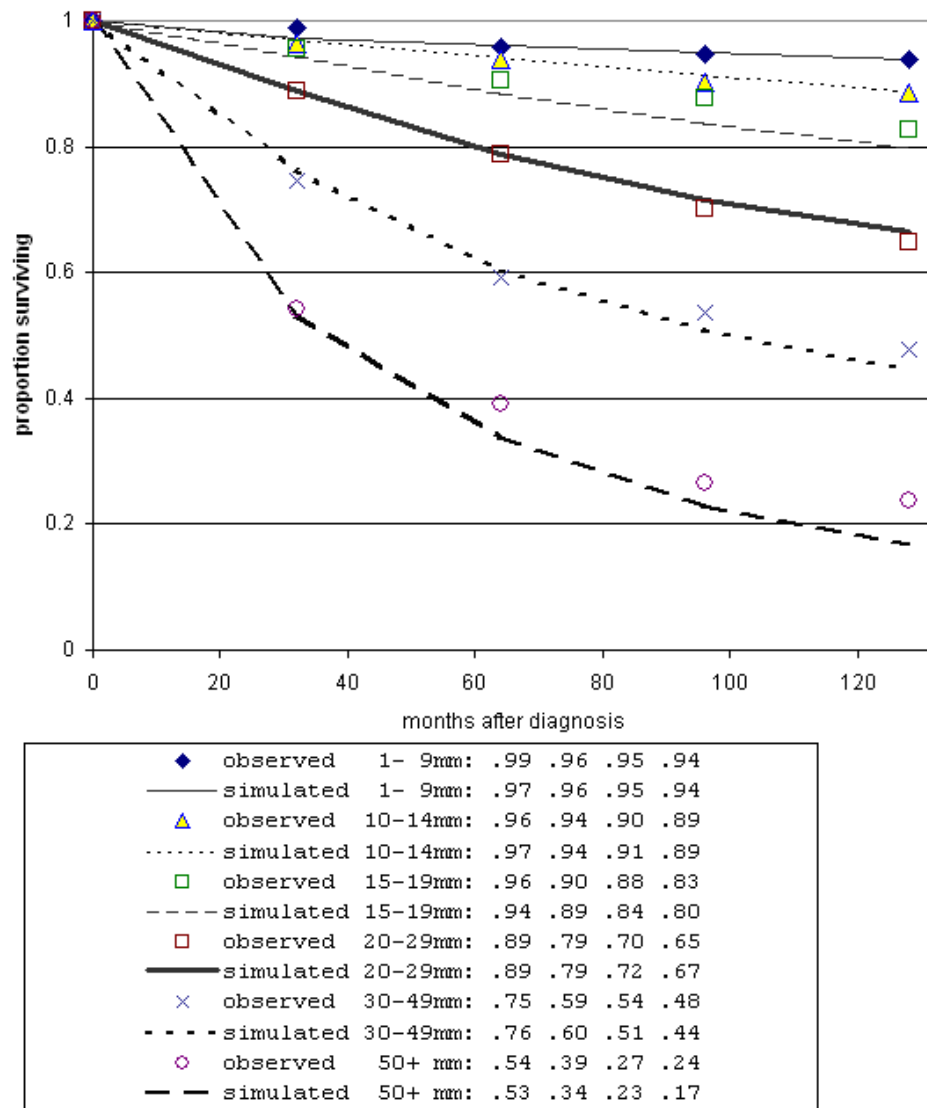|					
◆	observed	1- 9mm:	.99 .96 .95 .94		
—	simulated	1- 9mm:	.97 .96 .95 .94		
△	observed	10-14mm:	.96 .94 .90 .89		
······	simulated	10-14mm:	.97 .94 .91 .89		
□	observed	15-19mm:	.96 .90 .88 .83		
– – –	simulated	15-19mm:	.94 .89 .84 .80		
□	observed	20-29mm:	.89 .79 .70 .65		
━━	simulated	20-29mm:	.89 .79 .72 .67		
×	observed	30-49mm:	.75 .59 .54 .48		
·–·–	simulated	30-49mm:	.76 .60 .51 .44		
○	observed	50+ mm:	.54 .39 .27 .24		
— —	simulated	50+ mm:	.53 .34 .23 .17		

FIGURE 2: Cohort model. Comparison of simulated and observed survival by tumor diameter, Two County study. The legend displays observed and expected survival at 32, 64, 96 and 126 months since diagnosis.

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CANCER INCIDENCE COMPONENT

SUMMARY

This document describes how cancer incidence is generated in the model.

OVERVIEW

In the MISCAN-Fadia model, incidence is modeled as a probability distribution for the onset of pre-clinical disease by age, which refers to the first possible preclinical disease state in the model: preclinical dcis. In the model, many women will not have a detectable dcis prior to the invasive cancer which is modeled as a zero dwelling time in this stage and will thus start with preclinical cancer. Only one cancer per woman can occur in the model.

DETAIL

The model input on the incidence of the onset is specified in two steps: the cumulative probability at age 85 which differs between birth cohorts, and the age distribution of the onset given that the woman will develop breast cancer before age 85 which is equal for all birth cohorts (Age-Cohort model). The cumulative onset of preclinical disease is calculated from the cumulative incidence of clinical breast cancer (up to age 84) (Base Case APC Incidence) by applying correction factors for the proportion of non-progressive preclinical dcis. The cumulative incidences are converted into cumulative probabilities.

Calculation of the age-distribution of the incidence of the onset of preclinical disease starts from the age specific clinical incidence rates for 1975 (Base Case APC Incidence). For each single-year age group from age 20-84, this clinical incidence is first adjusted for differences in the cumulative incidence between the birth cohorts and for differences in proportion of regressive dcis between ages. Next, the age-specific cumulative hazards are converted into age-specific cumulative probabilities. From these cumulative probabilities of being diagnosed with cancer for ages 20-84, the conditional probabilities for ages 20-84 were calculated of being diagnosed with cancer, given she will be diagnosed between age 20 and 84. These conditional probabilities were then averaged into 5 years age groups. Using the probability distribution of the duration of the preclinical stage (time between onset of dcis and clinical diagnosis), the proportion of onset cases that would become diagnosed in the same or in each of the subsequent five-year age categories was calculated. In a calibration procedure, these proportions were used to derive (non decreasing) onset rates (by five-year age groups) of dcis that yield the adjusted 1975 age-specific clinical incidence of breast cancer. The resulting onset distributions by birth cohort and by age are presented in Tables 9 and 10.

TABLE 9. MISCAN-Fadia. Cumulative probability (up to age 85) of the onset of preclinical breast cancer by birth cohort

Birth cohort	Cumulative incidence
1895-99	0.112
1900-04	0.122
1905-09	0.132
1910-14	0.141
1915-19	0.154
1920-24	0.169
1925-29	0.176
1930-34	0.182
1935-39	0.200
1940-44	0.220
1945-49	0.223
1950-54	0.204
1955-59	0.198
1960-64	0.193
1965-69	0.189
1970-71	0.187

TABLE 10. MISCAN-Fadia. Age-distribution of the incidence of the onset of pre-clinical breast cancer (incl. dcis).

Age	Cumulative probability
20	0.000
25	0.002
30	0.005
35	0.021
40	0.046
45	0.105
50	0.169
55	0.233
60	0.328
65	0.436
70	0.563
75	0.707
80	0.852
85	1.000

SURVIVAL AND MORTALITY COMPONENT

OVERVIEW

The survival and mortality benefits of early detection

The survival and mortality benefits of early detection follow from the fatal disease concept (which is a special case of the "cure" type of screening model): for each woman there is a moment at which the disease can not be cured anymore, i.e. the moment at which the fatal tumor diameter is reached - this moment depends on the (adjuvant) treatment given at the moment of diagnosis. The screening benefit (cure) only occurs if the tumor is detected by screening before it has become fatal and would otherwise have been diagnosed after it had become fatal.

BASE CASE RESULTS

Simulation results and Base Case data for 1975 are compared in Table 13 (see Treatment Component). Simulated clinical incidence matches APC incidence quite well. Simulated mortality is too high, compared to Base Case data (1973-1975 SEER mortality). Simulated prevalence is too low at younger ages and increasingly too high at older ages, compared to Base Case prevalence data.

The cancer incidence between 1975 and 2000 as simulated by the MISCAN-Fadia model for the situation without screening or adjuvant treatment is very close to the age-adjusted incidence as provided in the Base Case data. When the Base Case screening dissemination and treatment dissemination data are used, MISCAN simulates a too high age adjusted incidence of invasive cancers for almost all years in the actual screening run, compared to SEER data, especially for tumors Without screening and adjuvant treatment the age-adjusted mortality rate was predicted to increase from 52.4 to 67.5 per 10^5 women; with actual screening and adjuvant treatment the rate decreases to 46.6 in the year 2000 (see figure 5). For the actual screening and adjuvant treatment run, the simulated age adjusted mortality rates are higher than SEER data, and the difference increases over time to a constant difference of around 12% for the period 1979-1997 and a 25% difference in 1999-2000 (see figure 4). According to the MISCAN-Fadia model, actual screening and treatment (according to the Base Case dissemination data for screening and adjuvant treatment) have similar effects on mortality; screening leads to a 15% mortality reduction and adjuvant treatment to a 21% mortality reduction, see table 14. Annual screening of all women between 1975 and 2000 would have resulted in 36% reduction in mortality.
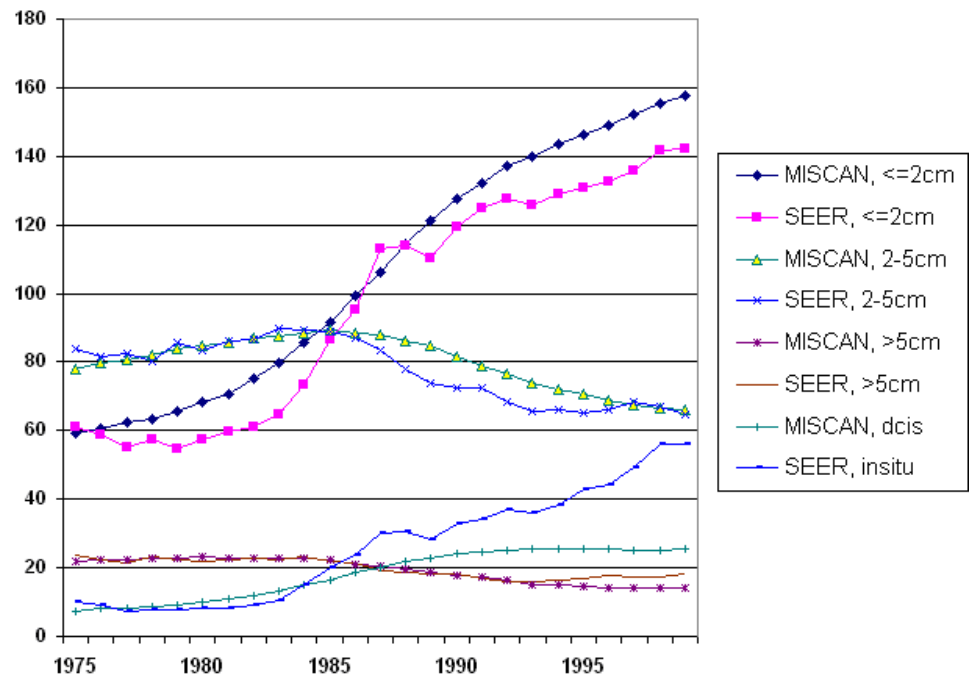

FIGURE 3: MISCAN-Fadia model. Simulated age adjusted incidence rates by tumor size (per 100,000) compared to SEER data (age adjusted to US 2000 standard population age 30-79)
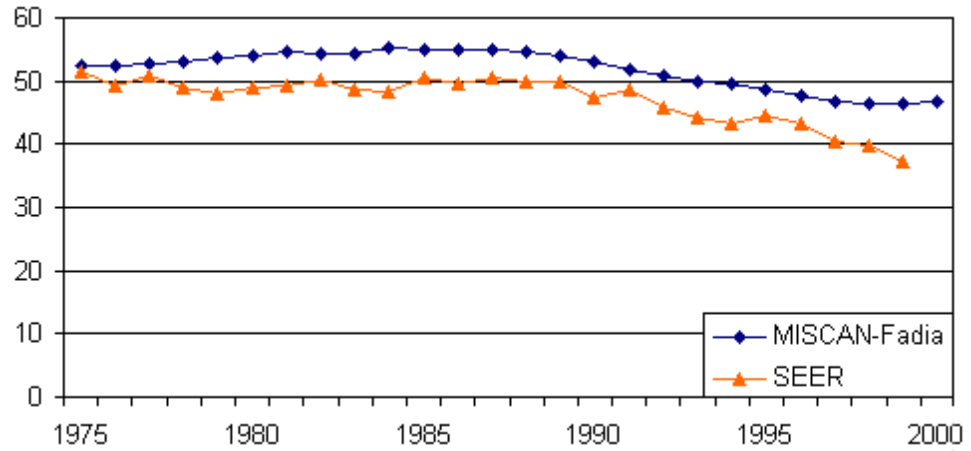
FIGURE 4: MISCAN-Fadia model. Simulated age adjusted mortality rates (per 100,000) compared to SEER data (age adjusted to US 2000 standard population age 30-79)
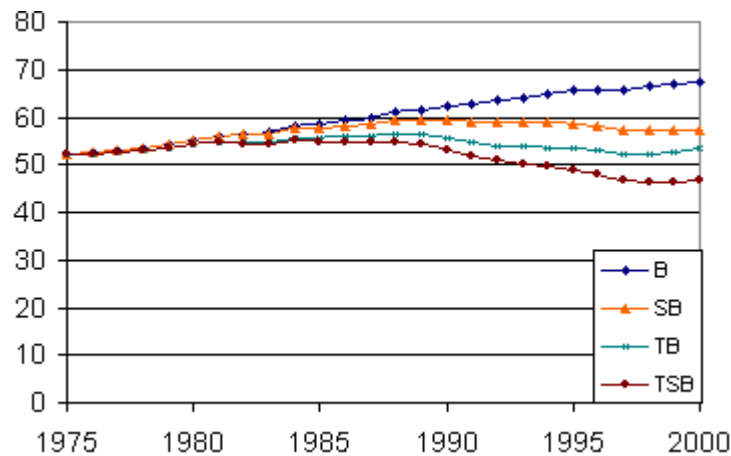

FIGURE 5: MISCAN-Fadia model. Simulated age adjusted mortality rates (per 100,000) for Base Case runs (age adjusted to US 2000 standard population age 30-79): B = Background risk only, SB = Mammography screening and background risk, TB = Adjuvant treatment and background risk, TSB = Adjuvant treatment, mammography screening and background risk

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