

Chapter 9:

The MISCAN-Fadia Continuous Tumor Growth Model for Breast Cancer

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The MISCAN-Fadia model was used to analyze the impact of screening and adjuvant treatment on U.S. breast cancer mortality between 1975 and 2000. MISCAN-Fadia uses the concept of “fatal diameter” to model survival and screening benefit and is based on continuous tumor growth. It consists of four major components: population, natural history, screening, and treatment. Population parameters were quantified using U.S. population data. Most natural history and screening parameters were fitted to the Swedish Two County screening trial data; some were based on Surveillance, Epidemiology, and End Results data. Adjuvant treatment parameters were quantified using data from the Early Breast Cancer Trialists’ Collaborative Group’s meta-analysis. The simulated trend in incidence matches the observed trend reasonably well; the simulated mortality is equal to the observed in 1975 but becomes increasingly too high in 2000. We estimate that screening leads to a 15% and adjuvant treatment to a 21% mortality reduction in the year 2000. [J Natl Cancer Inst Monogr 2006;36:56–65]

The Cancer Intervention and Surveillance Modeling Network (CISNET) is a consortium of National Cancer Institute–sponsored investigators whose focus is to use modeling to improve our understanding of the impact of cancer control interventions (e.g., primary prevention, screening, treatment) on population trends in incidence and mortality (1). The MISCAN-continuous tumor growth model is one of the seven breast cancer models that participated in a comparative modeling effort of the CISNET consortium to analyze the impact of screening and adjuvant treatment on U.S. breast cancer mortality between 1975 and 2000. Each of the models was requested to produce results in a standard format for a defined set of base case simulation runs for which a set of common input parameter values was provided.

Questions the Model is Designed To Answer

The MISCAN computer simulation program (2,3) 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 (4–7). In these models, the natural history is described by discrete tumor stages, transition probabilities between these stages, and dwelling times in each stage. For the CISNET project we developed an alternative natural history component based on a continuously growing tumor, called “Fadia” because of the use of the

concept of a fatal diameter. Each tumor has a size—which differs between tumors—at which the cancer becomes fatal; i.e., metastases are present for which the available treatment options are not effective. The woman will be cured only if the tumor is treated before it reaches the fatal diameter. The MISCAN program using the Fadia natural history component is called the “MISCAN-Fadia.” Henceforth “standard MISCAN” will refer to the stage-based approach described by Loeve et al. (3), and the “standard MISCAN breast cancer model” refers to the existing model for breast cancer screening with discrete tumor stages (7,8).

The rationale of developing this Fadia component was twofold. First, the Fadia component describes biological mechanisms, which allows for hypothesis testing, whereas the standard MISCAN model describes transitions between states and does not describe biological mechanisms underlying these transitions. Second, it appeared to be difficult to translate the standard MISCAN model to a new situation, because biological processes, which are assumed to be universal, could not be separated from processes related to human interventions—which are assumed to differ from situation to situation. Therefore, in Fadia, a distinction is made between tumor biology (tumor growth function) and model variables that may vary between areas and over time (e.g., diameter at clinical diagnosis, threshold size for screen detection). Furthermore, we consider tumor size (diameter) to be an attractive biological entry to modeling because both clinical diagnosis and screening are associated with tumor size and tumor size is easily measurable. And tumor staging systems like the American Joint Committee on Cancer involve tumor size.

We also developed a cohort version of the MISCAN-Fadia model and used it to estimate model parameters using data from the Two County Study of Sweden (TCS) for breast cancer screening [(9,10); personal communication].

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

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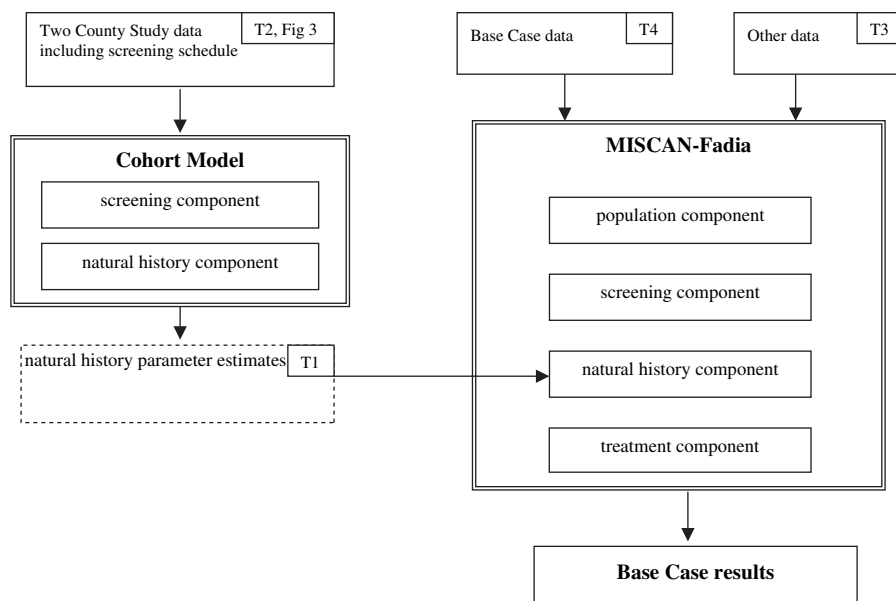
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Fig. 1. The two MISCAN-Fadia simulation models used for producing the base case results. The cohort model is used to estimate the parameters of the natural history of breast cancer, using the data from the Two County trial for breast cancer screening, by simulating the screening schedule of this trial. These natural history estimates are used in the population model, in combination with the base case data and other data, to run the simulations that produce the base case results for the U.S. breast cancer incidence and mortality in the period 1975–2000. **T1** ... **T4** are the tables that give an overview of the data used by the two models, and **Fig. 3** refers to the survival data in Fig. 3.



Modeling Approach

MISCAN-Fadia uses discrete-event microsimulation: Using the model inputs, independent individual life-histories are generated, possibly including a cancer history and the effects of treatment and of screening. A life-history is driven by events like birth, initiation of a breast cancer tumor, clinical diagnosis of the tumor, death from breast cancer, and death from other causes.

Major Components of the Model and How They Fit Together

The MISCAN-Fadia model consists of four major components (see Fig. 1). The population component simulates the demography and breast cancer incidence in 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. Fig. 1 also indicates the data used by the Cohort Model for parameter estimation, as well as the data used by MISCAN-Fadia for producing the base case results.

MODEL DETAILS

We will first describe the MISCAN-Fadia natural history. Then we will describe how we estimated its parameters using data from the Two County study. Later we describe how MISCAN-Fadia natural history, population dynamics and incidence, screening and treatment, were modeled for the Base Case analysis.

Continuous Tumor Growth-based Natural History Model

The Fadia natural history component simulates invasive breast tumors and ductal carcinoma in situ (DCIS). Invasive tumors start at a size of 0.1 mm and have a constant growth rate, which differs between tumors. Tumors also differ in the size

(the fatal diameter) at which available treatment options will no longer result in cure. Clinical diagnosis of the tumor is triggered by two competing mechanisms: signs or symptoms from the primary tumor or 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 fatal at the moment of diagnosis, the time of death from breast cancer is described by a survival distribution from the moment that the disease became fatal; i.e., the tumor reached its fatal diameter.

The course of a breast cancer from its initiation as a 0.1-mm tumor onward is determined by the parameters of the five variables each governed by a probability distribution function with two parameters, by a constant, and by three correlations:

1. μ and σ parameters for the growth rate of the tumor (lognormal distribution);
2. shape and scale parameters for the fatal diameter of the tumor (Weibull distribution);
3. μ and σ parameters for the survival time after reaching the fatal diameter (lognormal distribution);
4. shape and scale parameters for the threshold diameter of a tumor for a screening test, i.e., the tumor diameter at which a tumor becomes screen detectable (Weibull distribution);
5. μ and σ parameters for the tumor diameter at clinical diagnosis because of the primary tumor (lognormal distribution);
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); and
7. correlations between the tumor growth rate, the tumor diameter at clinical diagnosis, and the survival after inception of fatal disease. This assumption was needed for fitting the Two County Study screening trial data.

The tumor history model is thus characterized by the values of these 14 parameters (five pairs, one fraction, and three

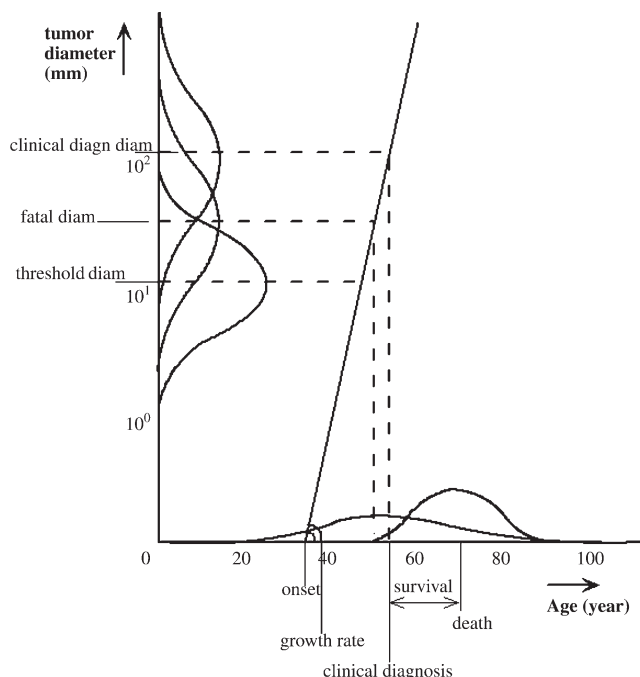


Fig. 2. The Fadia natural history model. The model is illustrated by a woman who is diagnosed with incurable breast cancer and for whom screening could have been beneficial. The natural history of breast cancer is simulated through the random selection of six variables from probability distributions, denoted by the various curves: **onset** = age at tumor onset, **growth rate** = tumor growth rate, **survival duration** = duration between the moment at which the tumor reaches the fatal diameter and the moment of death from breast cancer (not shown), **clinical diagn diam** = tumor diameter at which the tumor will be diagnosed clinically because of the primary tumor, **fatal diam** = tumor diameter at which available treatment options will no longer result in cure, **threshold diam** = tumor diameter at which the tumor becomes screen detectable. The figure shows clinical diagnosis because of the primary tumor; diagnosis because of distant metastases is omitted. After onset the tumor starts growing exponentially according to the tumor growth rate. The diagnosis results from the clinical diagnosis diameter combined with the tumor growth rate. If the tumor is diagnosed after it has reached the fatal diameter, the woman will die from breast cancer. Survival is modeled since fatal diameter. For observed survival (shown), the time between clinical diagnosis and the moment the tumor has reached its fatal diameter has to be subtracted. Screening can change this natural history: After the tumor has reached the threshold diameter, the tumor can be screen detected. If the tumor has not reached the fatal diameter yet at the moment of screen detection, the woman will be cured. Otherwise, screening will not affect the woman's age of death.

correlations). In MISCAN-Fadia, changes in the survival over time as a result of improved treatment are modeled as an increase in the fatal diameter, and changes in the screening test sensitivity are modeled as a shift in the threshold diameter.

When a breast tumor is initiated in a simulated woman, values of the tumor variables are generated. The growth rate of the tumor determines the time since its initiation at which it reaches the fatal diameter, the clinical diagnosis diameter, and the threshold diameter for a screening test. Unpredictability of the screening test result is governed entirely by the variability in the threshold diameter for screening, i.e., no explicit allowance is made for random variation in performance of the test or in reading the test result (see Fig. 2).

Estimation of Natural History Parameters Using Results From the Swedish Two County Study

For estimation of the natural history parameters, we used a simplified cohort model that focuses on the natural history of

invasive breast cancer tumors and the effect of screening in a cohort of women participating in a screening trial. Tumor size is the only tumor attribute. Death from other causes, DCIS, time trends in breast cancer incidence or survival, age dependencies, and the impact of adjuvant treatment are not modeled. Results of the TCS were used to estimate the parameters [(9,10); personal communication]. The tumor histories simulated by the Cohort Model yield predictions on the following TCS results: 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; survival by mode of detection and time since diagnosis; and survival by tumor diameter and time since diagnosis.

The TCS started in October 1977 in Kopparberg and in May 1978 in Östergötland (9). Women aged 40–74 years were randomized to either the study group, consisting of 77 080 women, or the 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 [(9,10); personal communication]. The follow-up period after the last screening round ended on average 8 years after start of the study. At that time women in the control group were invited for a screening examination too. Data on this screening are not used in the estimation process.

We assumed an incidence of 2.2 per 1000 women-years, the observed rate in the TCS control group (9,10). Simulated detection rates and interval rates are corrected for the aging of the women during the trial (11). For given values of the model parameters, one microsimulation 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 method in combination with a quasi-Newton optimization procedure (12,13). With respect to the likelihood of the model, the probability distributions are assumed to be Poisson for detection rates at screening and interval cancer rates, multinomial for tumor size distributions, and binomial for lethality rates per interval.

Initially, we assumed Weibull distributions for all variables. However, when it became apparent that correlations had to be assumed, the more convenient multivariate lognormal distribution was used for three correlated variables. The fit procedure resulted in the parameter estimates as presented in Table 1. We have used different starting values in the optimization procedure in view of the risk of local optima, but resulting parameter estimates and model outcomes were similar. For comparison of simulated data see Table 2 and Fig. 3. The fit is adequate, except that the predicted tumor size distribution is somewhat too unfavorable for the control group and somewhat too favorable for the interval cancers. The simulated mortality reduction after 11 years was 27%, as compared to an observed 30% reduction (9).

Base Case Natural History

Parameter estimates of the TCS analysis for tumor growth rate, survival since fatal diameter, threshold diameter for screen detection, clinical diagnosis because of distant metastases, and correlations (Table 1) were directly used in the base case simulation (see Table 3). The parameters for diameter at clinical

Table 1. Maximum likelihood estimates for MISCAN-Fadia natural history parameters based on the data from the Two County Study

A. For each variable: the distribution, the parameter estimates, mean and standard deviation, and 10%, 50%, and 90% percentiles of the distribution*						
Variable	Distribution	Mean	SD	10%	50%	90%
Growth rate (1/y)	Lognormal (0.062, 0.87)	1.6	1.6	0.3	1.1	3.2
Fatal diameter (cm)	Weibull (2.9, 1.4)	2.7	1.9	6.1	2.3	5.3
Survival duration since fatal diameter (y)	Lognormal (2.4, 1.1)	21	35	3	11	48
Diameter at clinical diagnosis because of primary tumor (cm)	Lognormal (0.8, 0.6)	2.8	1.8	1.1	2.3	4.9
Screening threshold diameters (cm)	Weibull (1.0, 3.0)	0.9	0.3	0.5	0.9	1.4
B. Correlation between variables						
Variable	ρ					
Growth rate—survival	−0.90					
Growth rate—clinical diagnosis diameter because of the primary tumor	+0.41					
Clinical diagnosis diameter because of the primary tumor—survival	−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.						

* See “Model Details” for description of parameters. SD = standard deviation.

diagnosis because of the primary tumor and the fatal diameter parameters were calibrated to U.S. data concerning 1975 stage distribution (14) and 1975 survival (14) (see Table 4). For the resulting estimates, see Table 5.

To have not only a tumor diameter distribution of invasive tumors but also a complete staging, we linked American Joint Committee on Cancer (AJCC) stages to tumor diameter by calibrating three more variables to the base case 1975 stage distribution data (between brackets are the calibrated values): the tumor diameter at which N1 lymph node disease becomes detectable by modern techniques (Weibull with scale parameter 4.3 and shape parameter 1.4); the difference in tumor diameters at which N1 and N2 lymph node disease become detectable by modern techniques (3.8 cm); and the time at which distant metastases become detectable by modern diagnostic 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 (0.68).

MISCAN-Fadia models both the moment at which distant metastases become detectable by modern diagnostic techniques and the moment at which distant metastases lead to diagnosis of the primary tumor because of symptoms—the first event always preceding the latter.

MISCAN-Fadia includes a DCIS sub model, taken without modification from the standard MISCAN breast cancer model (7,8) and based on data from the screening trials in Utrecht and Nijmegen (The Netherlands). In this submodel, there are three different types of preclinical DCIS: regressive DCIS, DCIS that will be diagnosed clinically, and DCIS that will progress to invasive disease. All have a mean duration of 5.22 years. The distribution between the three types depends on age (see Table 6). For screening of preclinical DCIS, the standard MISCAN value of 0.4 for the sensitivity of DCIS is used for 1975 and is assumed to increase linearly to 0.8 in 2000. Both screen-detected DCIS and clinically detected DCIS are assumed to have a 100% survival.

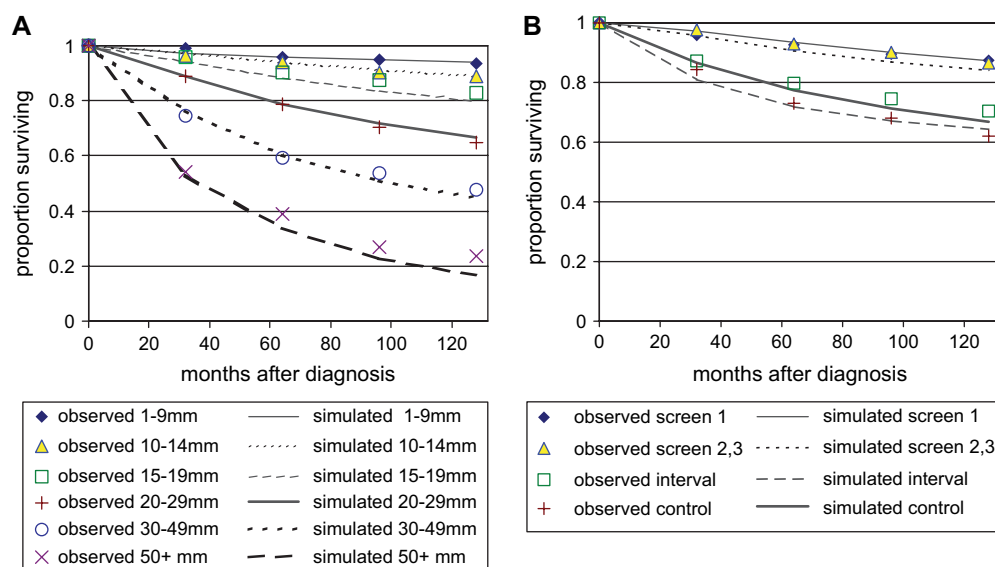
Base Case Population Dynamics and Breast Cancer Incidence

The U.S. population is simulated by 5-year birth cohorts starting from 1895–1899 up to 1965–1969 and 1970 (the last being a 1-year cohort that is necessary for simulating the year 2000).

Table 2. Comparison of the Two County Study data with the predictions by the cohort model (personal communication)

A. Screen-detected cancers by round (study group)		
Round	Observed	Simulated
1	286	286
2 + 3	303	265
B. Interval cancers by round (study group)		
Round	Observed	Simulated
1	76	77
2 + 3	107	124
C. Size distribution for screen detected cancers, first round (study group) (N = 254)		
Tumor diameter (mm)	Observed (%)	Simulated (%)
≤5	9	8
6–10	32	27
11–20	39	44
>20	20	21
D. Tumor size distribution for screen-detected cancers, second and third rounds (study group) (N = 301)		
Tumor diameter (mm)	Observed (%)	Simulated (%)
≤5	8	10
6–10	31	34
11–20	49	44
>20	13	12
E. Tumor size distribution for interval cancers (study) (N = 178)		
Tumor diameter (mm)	Observed (%)	Simulated (%)
≤5	1	4
6–10	17	22
11–20	41	40
>20	41	34
F. Tumor size distribution for control group cancers (N = 485)		
Tumor diameter (mm)	Observed (%)	Simulated (%)
≤5	3	1
6–10	11	10
11–20	36	34
>20	50	56

Fig. 3. Cohort model. Comparison of simulated and observed survival, Two County Study of Sweden (TCS). The legend displays observed (9) and expected survival at 32, 64, 96 and 126 months since diagnosis by tumor diameter (A) and mode of detection (B).



All persons in the cohort are simulated from birth to death. The life-table for death from other causes was derived directly from the base case data for each cohort (using 1-year age steps) (15), for the midyear of each cohort (thus: 1892, 1897, ...). Death before age 30 is not considered, because model output is produced only for ages 30–79. 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. The relative size of a cohort is then translated into a proportion of the simulated population; see Table 7.

Incidence is specified in two steps: the cumulative probability at age 85, which differs between birth cohorts, and on the age distribution of the onset, 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) (16), with an upward correction factor to account for nonprogressive DCIS (Table 8). Only one cancer per woman can occur. The age distribution for onset uses age-specific clinical incidence rates for 1975 (14), with a shift toward younger ages because of the time between onset of preclinical disease and clinical diagnosis (Table 9).

Base Case Screening

The threshold diameter for screen detection has been made dependent on the year and the age of the woman, using the age groups younger than 50, 50–59, 60–69, and 70 years or older; see

Table 10. The shape parameter of the Weibull distribution is kept at the TCS value of 3.0. The scale parameter as estimated from the TCS data was used for age 60, since TCS concerned women aged 50–69 years. Values for other age groups were based on the age-specific ratio between detection rate of cancers at first screening and incidence rate of clinically diagnosed cancers in the control group of the TCS, compared with the ratio for age 60. Because TCS screening is considered of high quality, these values from the 80s were used for the average U.S. situation in the year 2000. For 1975, the age-specific scale parameters have been derived similarly, using the results from the Health Insurance Plan of Greater New York (HIP) trial (17). Linear interpolation was used between 1975 and 2000. The common CISNET screening dissemination model (14,18) was used as an external program, to generate screening ages for all women for simulation runs that include the actual U.S. screening dissemination.

The tumor is screen detected if at the time of screening its diameter exceeds the threshold, and the tumor is not yet clinically diagnosed. Detection of DCIS is driven by the test sensitivity. Screening benefit occurs if the tumor is detected by screening before it has reached the fatal diameter and if without screening the tumor would have been diagnosed after it had become fatal.

Base Case Treatment Component

To account for improvement in treatment, a time dependency of the fatal diameter was modeled prior to 1975, using the

Table 3. MISCAN-Fadia parameters based on data other than the base case data*

Parameter	Method	Data used	Value
Tumor growth rate	Estimated with cohort model	TCS	Table 1
Survival duration since fatal diameter	Estimated with cohort model	TCS	Table 1
Screening threshold	Estimated with cohort model + estimation of trend 1975-2000	TCS, HIP	Tables 1 and 6
Moment at which distant metastases lead to clinical diagnosis of the tumor		TCS	Table 1
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%

*TCS = Two County Study of Sweden; HIP = Health Insurance Plan of Greater New York; DCIS = ductal carcinoma in situ.

Table 4. Base case data usage*

Data (ref)	Usage	Notes
Treatment dissemination (19)	U	Used as direct input
Mammography dissemination (14,18)	U	Base case dissemination model was directly used as external program
Other cause mortality (15)	U	Used to calculate size of birth cohorts in the U.S. population; see Table 11
SEER incidence (14)	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 (14)	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 (14)	C	Used to estimate 1975 fatal diameter parameters; see Table 5
Historical survival (14)	C	Used to estimate time trend in fatal diameter prior to 1975; see Table 5
1975 Stage distribution (14)	C	Used to estimate AJCC stage distribution parameters; see Table 7
1975 Breast cancer mortality (14)	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 (16)	P	Converted to age-cohort model with cumulative incidences as cohort risks and one fixed-age specific distribution of incidence of preclinical screen-detectable disease for all cohorts; see Tables 9 and 10
Treatment effect (19)	C	Calibrated by a shift in fatal diameter; see Table 13
SEER 9 mortality (14)	O	Results from cohort risks, age-specific incidence distribution, calibration of fatal diameter to 1975 survival, and time trend in fatal diameter prior to 1975, dissemination of mammography and adjuvant treatment

*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 = base case data not used in the model, model simulations for these data result from other base case data; SEER = Surveillance, Epidemiology, and End Results; AJCC = American Joint Committee on Cancer; APC = age-period-cohort.

Connecticut historical survival data (14). The difference in 20-year survival between 1940–1949 and 1970–1974 was translated into a shift in fatal diameter between 1975 and 1945, assuming that 20-year survival approximates cure (see Table 5). Linear interpolation is applied between 1945 and 1975. The trend is extrapolated backward to 1915, which is the first possible year for onset of breast cancer for the oldest women.

Dissemination of adjuvant treatment from 1975 onward is modeled in the MISCAN-Fadia model as the probability of being treated with a certain type of adjuvant treatment, i.e., chemotherapy, tamoxifen (for 2 years or for 5 years), or the combination of chemotherapy and tamoxifen. These probabilities depend on year, age, and stage and are adopted from the common base case data (19).

The benefit of adjuvant treatment was modeled according to the results of the Early Breast Cancer Trialists' Collaborative Group's (EBCTCG) meta-analyses (20,21), which reported proportional reductions in all-cause mortality hazard for the different adjuvant treatment regimens (19). 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 estrogen receptor-positive tumors as reported in the meta-analysis with the proportion of estrogen receptor-positive tumors by age group as reported in the Surveillance, Epidemiology, and End Results (SEER) for 1988–1993. Furthermore, the effects of chemotherapy and tamoxifen are assumed to be independent. Age-specific proportional reductions are shown in Table 11.

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 to model the effect on breast cancer mortality, since hazard ratios were reported for all-cause mortality (20,21). We approximated the new cure proportions for each adjuvant treatment c_{adjth} , using the hazard ratio r as reported by the EBCTCG, 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 the EBCTCG meta-analysis (20,21). The probability of dying from other causes was approximated using base case data (15). For each adjuvant treatment, the new cure proportion c_{adjth} was then translated into the corresponding fatal diameter. The resulting median values for the fatal diameter are given in Table 11.

RESULTS

Simulation results and base case data for 1975 are compared in Table 12. Simulated clinical incidence matches age-period cohort incidence in the situation without screening (16) closely.

Table 5. MISCAN-Fadia*

Variable	Distribution	Mean	SD	10%	50%	90%
Fatal diameter (cm)						
1945	Weibull (2.4, 0.95)	2.5	2.6	0.2	1.7	5.8
1975	Weibull (4.0, 0.95)	4.1	4.3	0.4	2.8	9.7
Diameter at clinical diagnosis because of the primary tumor (cm)	Lognormal (1.0, 0.6)	3.2	2.2	1.2	2.6	5.9

*Parameters of the distributions for the fatal diameter and for the diameter at clinical diagnosis because of the primary tumor. SD = standard deviation.

Table 6. MISCAN*

Type of DCIS history	Percent of ages 0–34	Percent of ages 80–100
Onset as invasive cancer (no DCIS)	76	92
Onset as DCIS	24	8
Preclinical DCIS is clinically diagnosed (as DCIS)	6	2
Transition from preclinical DCIS to invasive cancer	15	5
Preclinical DCIS is regressive	3	1
Total	100	100

*Age-dependent percentages of the onset that have the four possible trajectories with or without ductal carcinoma in situ (DCIS). For ages 35–79 years, linear interpolation is applied.

Simulated mortality is somewhat higher than the observed SEER mortality (14). Simulated prevalence is too low at younger ages and increasingly too high at older ages, compared with SEER prevalence (14). The cancer incidence between 1975 and 2000 as simulated by the MISCAN-Fadia model for the situation without screening or adjuvant treatment is close to the age-adjusted age-period cohort incidence (16). When the base case screening dissemination and treatment dissemination data are used, MISCAN simulates an about 3% too high age-adjusted incidence of invasive cancers for almost all years in the actual screening run, compared with SEER data, which is caused mainly by tumors less than 2 cm; see Fig. 4. Simulated incidence rates of DCIS are increasingly too low from 1985 onward.

Without screening and adjuvant treatment, the age-adjusted mortality rate was predicted to increase from 52 to 68 per 10⁵ women; with actual screening and adjuvant treatment, the rate is predicted to decrease to 47 in the year 2000. For the actual screening and adjuvant treatment run, the simulated age adjusted mortality rates are higher than those in 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 Fig. 5). 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

Table 7. MISCAN-Fadia*

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

*Proportion of the simulated population in each birth cohort.

Table 8. MISCAN-Fadia*

Birth cohort	Cumulative incidence
1895–99	.112
1900–04	.122
1905–09	.132
1910–14	.141
1915–19	.154
1920–24	.169
1925–29	.176
1930–34	.182
1935–39	.200
1940–44	.220
1945–49	.223
1950–54	.204
1955–59	.198
1960–64	.193
1965–69	.189
1970	.187

*Cumulative probability (up to age 85) of the onset of preclinical breast cancer by birth cohort.

adjuvant treatment to a 21% mortality reduction; see Table 13 and Fig. 6. The hypothetical scenario of annual screening of all women between 1975 and 2000 would result in a 36% mortality reduction.

MODEL VERIFICATION

The standard MISCAN model has undergone rigorous verification during its development. Tests were designed, carried out, documented, and evaluated to check all components of the MISCAN program. The results of these tests have been evaluated in a core group of primary users.

Programming the MISCAN-Fadia model as used for the base case analyses mainly involved implementation of the Fadia continuous tumor growth model and creating additional model output. The Fadia continuous tumor growth model was checked by inspecting individual histories (using Matlab for comparison), including output checks. Output was also checked against comparable output of standard MISCAN. Diagnostic runs with extreme assumptions were performed and gave expected outcomes.

Table 9. MISCAN-Fadia*

Age (y)	Cumulative probability
20	.000
25	.002
30	.005
35	.021
40	.046
45	.105
50	.169
55	.233
60	.328
65	.436
70	.563
75	.707
80	.852
85	1.000

*Age distribution of the incidence of the onset of preclinical breast cancer (including ductal carcinoma in situ).

Table 10. MISCAN-Fadia*

Year	Parameter value for age (y):			
	30–49	50–59	60–69	70–79
1975	2.2	1.7	1.3	1.0
2000	1.5	1.1	0.9	0.6

*Scale parameters for the Weibull distribution of the threshold diameter for screen detection. Values are constant within age groups and will be interpolated for years between 1975 and 2000. The scale parameter is constant at the value of 3.0.

DISCUSSION

We have developed and used a simulation model in which continuous tumor growth is pivotal. Screen detection, clinical diagnosis, and (in-)curability are defined in terms of tumor diameter. Changes over time in quality of the screening test, clinical stage distribution, and treatment effectiveness are modeled by changes in tumor diameter for which screen detection–clinical diagnosis and cure are possible. Moreover, variation between patients and their tumors is modeled by probability distributions of tumor growth, threshold diameter for screen detection, clinical diagnosis diameters, and fatal disease diameter.

Is this mechanistic link to tumor size too much of a straitjacket? Should a clinical biological model not explicitly model lymph node spread and distant metastatic spread? Are the parameters of the model always identifiable? Is an approach using discrete stages, stage transitions, and stage-specific survival not simpler, closer to observed data, always identifiable, and easier to interpret? These questions have to be addressed. A well-designed and detailed comparison between a discrete-stage approach and a tumor diameter approach would not aim at showing complete superiority of

one of the approaches, but may identify strengths, weaknesses, and may be circumstances or research questions for which one approach is to be preferred over the other.

We will now turn to the results—first the mortality predictions. The simulated breast cancer mortality is about equal to the observed mortality in 1975, which is not surprising because we calibrated to the 1975 situation. But simulated mortality becomes increasingly too high during the period until 2000. We did not calibrate to the 1975–2000 trend: In our model, the decrease in mortality is not fully explained by screening and adjuvant therapy. The difference in mortality can be explained only very partly by our too high prevalence of breast cancer cases in 1975, because mortality in 2000 will be only slightly affected by prevalence in 1975. Also, we did not extrapolate the general treatment improvement between 1945 and 1975 to more recent years but instead used the 1975 values up to 2000. A simple linear extrapolation, which is reasonable, would bring simulated and observed mortality much closer together. Exploring this possibility ranks high on our agenda for future activities.

The predictions for DCIS were good until 1985, subsequently somewhat too low until 1993 and increasingly a lot too low from 1994 to 2000. These results are consistent with the predictions in The Netherlands up to 1993 (22), although the differences were larger for the U.S. predictions. We have no recent DCIS data for The Netherlands. The steep increase in DCIS in the United States between 1995 and 1999 cannot be explained by screening dissemination. Our model would lead to improved DCIS predictions if we were to assume that more invasive cancers are preceded by DCIS, combined with a sudden increase in sensitivity of mammography for DCIS during 1995–1999. We are not sure, however, if this is a reasonable assumption.

According to our base case results, screening and adjuvant treatment contribute to a similar extent to the mortality reduction

Table 11. MISCAN-Fadia: proportional reductions and corresponding median values of fatal diameter corresponding to adjuvant treatment, by age and by type of treatment

Type and duration, age (y)	Proportional reduction				Median value fatal diameter			
	<50	50–59	60–69	≥70	<50	50–59	60–69	≥70
Chemotherapy, 2	0.27	0.14	0.08	0.08	4.3	3.6	3.2	3.7
Tamoxifen, 2	0.11	0.14	0.14	0.15	3.2	3.6	3.9	5.1
Tamoxifen, 5	0.18	0.22	0.22	0.24	3.6	4.2	4.7	8.6
Both, 2	0.35	0.26	0.21	0.22	5.1	4.5	4.7	7.7
Both, 5	0.40	0.33	0.28	0.30	5.6	5.3	5.8	14.7

Table 12. MISCAN-Fadia: comparison of simulated and observed results for 1975 (rates per 100 000)*

Age (y)	Incidence			Mortality (1973–1975)			Prevalence		
	MISCAN	APC (16)	% Diff	MISCAN	SEER (14)	% Diff	MISCAN	SEER (14)	% 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

*APC = age–period–cohort; SEER = Surveillance, Epidemiology, and End Results; Diff = difference.

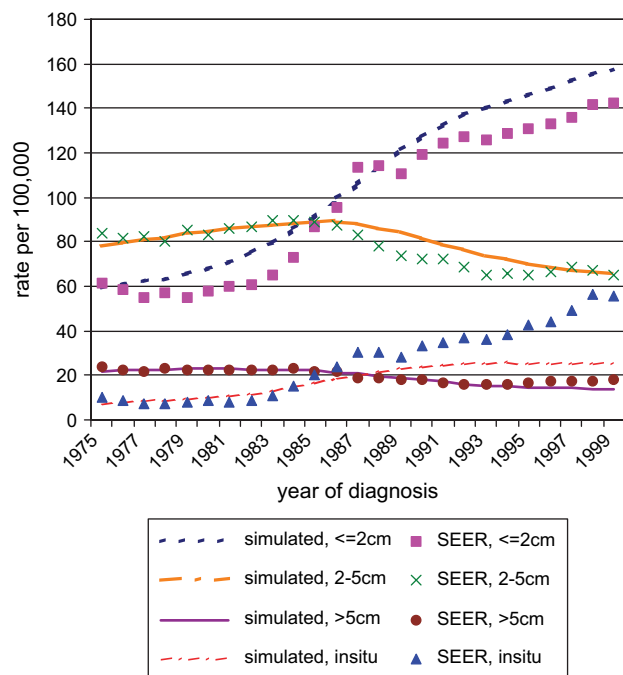


Fig. 4. MISCAN-Fadia model. Simulated age adjusted incidence rates by tumor size (per 100 000) compared to Surveillance, Epidemiology, and End Results (SEER) data (age adjusted to U.S. 2000 standard population aged 30–79 years).

as observed in the United States between 1975 and 2000; screening leads to a 15% mortality reduction and adjuvant treatment to a 21% mortality reduction. Could other plausible assumptions have led to quite different contributions? The assumptions about effectiveness of screening in MISCAN-Fadia are based on the analysis of the TCS results. Different screening trials found different degrees of screening effectiveness. The TCS estimate of screening efficacy fell in the midrange of all the Swedish trials. A next step could be to do similar analysis of other trials or do a meta-analysis of screening trials (23) similar to the analysis done with the standard MISCAN breast cancer model (8).

The effect of adjuvant treatment is modeled by increasing the fatal tumor diameter, which means that a larger proportion of the treated cases is cured. We estimated the increase from the results of the EBCTCG meta-analysis (20,21). The proportion cured corresponds to the asymptote of the breast cancer-specific

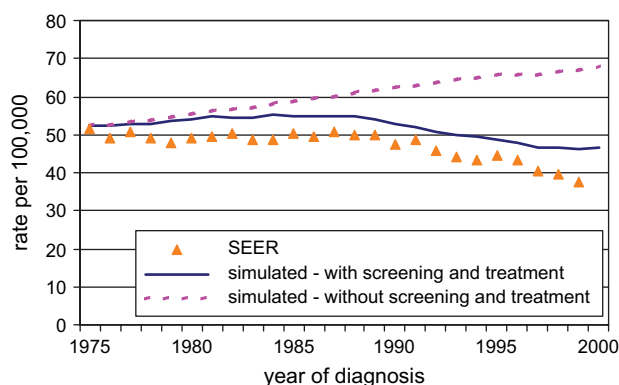


Fig. 5. MISCAN-Fadia model. Simulated age adjusted mortality rates with and without screening and adjuvant treatment (per 100 000) compared to Surveillance, Epidemiology, and End Results (SEER) data (age adjusted to U.S. 2000 standard population aged 30–79 years).

Table 13. MISCAN-Fadia: simulated effects of the base case interventions*

Intervention	Mortality reduction (%)
Actual screening	15
Adjuvant treatment (chemotherapy + tamoxifen)	21
Actual screening+ adjuvant treatment (chemotherapy + tamoxifen)	31
Annual screening	36
Chemotherapy only	10
Tamoxifen only	12
Actual screening + chemotherapy only	23
Actual screening + tamoxifen only	24

*Calculated as percent reduction in age-adjusted mortality with respect to the background run (age adjusted to U.S. 2000 standard population aged 30–79 years).

survival. However, the meta-analysis uses overall mortality, and there is some arbitrariness in deriving the cure fraction by correcting for death from other causes. We do not expect a major effect from this source of uncertainty, however.

Our model used only one survival curve, for the survival of a patient after the tumor has reached the fatal diameter, for incurable disease. This extremely parsimonious way of survival modeling was sufficient for a reasonably good fit of the TCS results by tumor size and by mode of detection. No independent evaluation of our model has yet been performed. We plan to do a first validation exercise using the results of the Canadian National Breast cancer Screening Study 2 (24).

In summary, the MISCAN-Fadia continuous tumor growth model gives a reasonably good fit of TCS data. On the basis of this fit, we estimate that the contributions of screening and adjuvant treatment to the decline in U.S. breast cancer mortality are similar in magnitude. We identified sources of uncertainty for these magnitudes. There are a few good explanations of why our prediction of mortality during 1975–2000 is too high. Modeling adjuvant treatment effectiveness proved to be more difficult than when using a discrete-stage model, like the standard MISCAN model. The biological model structure strengthens the interpretation possibilities of model results but leads to a less direct relationship between empirical data and model parameters. It is important to further investigate the advantages and disadvantages of the two approaches.

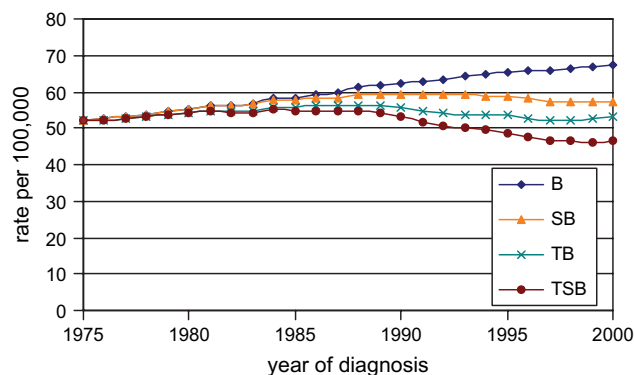


Fig. 6. MISCAN-Fadia model. Simulated age adjusted mortality rates (per 100 000) for base case runs (age adjusted to U.S. 2000 standard population aged 30–79 years): B = background risk only, SB = mammography screening and background risk, TB = adjuvant treatment and background risk, TSB = adjuvant treatment, mammography screening, and background risk.

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NOTES

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