Chapter 9:
The MISCAN-Fadia Continuous Tumor Growth Model for Breast Cancer

Sita Y. G. L. Tan, Gerrit J. van Oortmarssen, Harry J. de Koning, Rob Boer, J. Dik F. Habbema

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 two-fold. 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.

Affiliation of authors: Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands.

Correspondence to: J. Dik F. Habbema, PhD, Department of Public Health, Erasmus MC, University Medical Center Rotterdam, P.O. Box 2040, Rotterdam, 3000 CA, The Netherlands (e-mail: j.d.f.habbema@erasusmc.nl).

See “Notes” following “References.”

DOI: 10.1093/jncimonographs/lgj009
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56 Journal of the National Cancer Institute Monographs, No. 36, 2006
M  ODEL   DETAILS
results.
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used by the Cohort Model for parameter estimation, as well as
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adjuvant treatment component simulates dissemination of ad-
semination of mammography screening and its effects, and the
breast cancer tumor, the screening component simulates dis-
ponents (see  Fig. 1 ). The population component simulates the
natural history component simulates the natural history of a
demography and breast cancer incidence in the population, the
components (see  Fig. 1 ). The population component simulates the
natural history component simulates the natural history of a
breast tumors and ductal carcinoma in situ (DCIS). Invasive
treatment, were modeled for the Base Case analysis.

Fit Together

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 com-
ponents (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 disse-
mination of mammography screening and its effects, and the
adjuvant treatment component simulates dissemination of ad-
juvant 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, screen-
ing 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 as-
sumed 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 vari-
ables 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 diag-
nosis 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 di-
diameter at clinical diagnosis, and the survival after incep-
tion 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
From the Swedish Two County Study

result (see Fig. 2).

random variation in performance of the test or in reading the test

test result is governed entirely by the variability in the threshold
diameter for a screening test. Unpredictability of the screening
fatal diameter, the clinical diagnosis diameter, and the threshold
diameter determines the time since its initiation at which it reaches the

modeled since fatal diameter. For observed survival (shown), the time between
clinical diagnosis and the moment the tumor has reached its fatal diameter has
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 depen-
dencies, 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 detec-
tion rates and interval rates are corrected for the aging of the
women during the trial (11). For given values of the model pa-
rameters, 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 de-
derived by repeated evaluation of the simulated histories using the
score function method in combination with a quasi-Newton opti-
mization 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, multinom-
ial 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 pre-
dicted 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

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
diag 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
naturtal 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.
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, modeled as a fraction of the time between the moment at which the tumor reaches the fatal diameter and the death from breast cancer (0.68). 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).
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, 50–69, 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

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Method</th>
<th>Data used</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor growth rate</td>
<td>Estimated with cohort model</td>
<td>TCS</td>
<td>Table 1</td>
</tr>
<tr>
<td>Survival duration since fatal diameter</td>
<td>Estimated with cohort model</td>
<td>TCS</td>
<td>Table 1</td>
</tr>
<tr>
<td>Screening threshold</td>
<td>Estimated with cohort model + estimation of trend 1975-2000</td>
<td>TCS, HIP</td>
<td>Tables 1 and 6</td>
</tr>
<tr>
<td>Moment at which distant metastases lead to clinical diagnosis of the tumor</td>
<td>Estimated with cohort model</td>
<td>TCS</td>
<td>Table 1</td>
</tr>
<tr>
<td>Correlations between growth rate, diameter at clinical diagnosis because of primary tumor, and survival</td>
<td>Estimated with cohort model</td>
<td>TCS</td>
<td>Table 1</td>
</tr>
<tr>
<td>DCIS duration and progression</td>
<td></td>
<td>Dutch</td>
<td>Table 8</td>
</tr>
<tr>
<td>DCIS survival</td>
<td></td>
<td></td>
<td>100%</td>
</tr>
</tbody>
</table>

*TCS = Two County Study of Sweden; HIP = Health Insurance Plan of Greater New York; DCIS = ductal carcinoma in situ.
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 $F_{oc}(t)$.

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

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.
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 10^5 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 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 6. MISCAN*

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

*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.

### Table 7. MISCAN-Fadia*

<table>
<thead>
<tr>
<th>Birth cohort</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1895–99</td>
<td>4.1</td>
</tr>
<tr>
<td>1900–04</td>
<td>4.6</td>
</tr>
<tr>
<td>1905–09</td>
<td>5.2</td>
</tr>
<tr>
<td>1910–14</td>
<td>5.3</td>
</tr>
<tr>
<td>1915–19</td>
<td>5.6</td>
</tr>
<tr>
<td>1920–24</td>
<td>6.0</td>
</tr>
<tr>
<td>1925–29</td>
<td>5.7</td>
</tr>
<tr>
<td>1930–34</td>
<td>5.2</td>
</tr>
<tr>
<td>1935–39</td>
<td>5.4</td>
</tr>
<tr>
<td>1940–44</td>
<td>6.5</td>
</tr>
<tr>
<td>1945–49</td>
<td>7.1</td>
</tr>
<tr>
<td>1950–54</td>
<td>8.5</td>
</tr>
<tr>
<td>1955–59</td>
<td>9.5</td>
</tr>
<tr>
<td>1960–64</td>
<td>10.1</td>
</tr>
<tr>
<td>1965–69</td>
<td>9.4</td>
</tr>
<tr>
<td>1970–71</td>
<td>1.8</td>
</tr>
</tbody>
</table>

*Proportion of the simulated population in each birth cohort.

### Table 8. MISCAN-Fadia*

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

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

### Table 9. MISCAN-Fadia*

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Cumulative probability</th>
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<tbody>
<tr>
<td>20</td>
<td>.000</td>
</tr>
<tr>
<td>25</td>
<td>.002</td>
</tr>
<tr>
<td>30</td>
<td>.005</td>
</tr>
<tr>
<td>35</td>
<td>.021</td>
</tr>
<tr>
<td>40</td>
<td>.046</td>
</tr>
<tr>
<td>45</td>
<td>.105</td>
</tr>
<tr>
<td>50</td>
<td>.169</td>
</tr>
<tr>
<td>55</td>
<td>.233</td>
</tr>
<tr>
<td>60</td>
<td>.328</td>
</tr>
<tr>
<td>65</td>
<td>.436</td>
</tr>
<tr>
<td>70</td>
<td>.563</td>
</tr>
<tr>
<td>75</td>
<td>.707</td>
</tr>
<tr>
<td>80</td>
<td>.852</td>
</tr>
<tr>
<td>85</td>
<td>1.000</td>
</tr>
</tbody>
</table>

*Age distribution of the incidence of the onset of preclinical breast cancer (including ductal carcinoma in situ).
Table 10. MISCAN-Fadia*

<table>
<thead>
<tr>
<th>Year</th>
<th>30–49</th>
<th>50–59</th>
<th>60–69</th>
<th>70–79</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975</td>
<td>2.2</td>
<td>1.7</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td>2000</td>
<td>1.5</td>
<td>1.1</td>
<td>0.9</td>
<td>0.6</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Type and duration, age (y)</th>
<th>&lt;50</th>
<th>50–59</th>
<th>60–69</th>
<th>≥70</th>
<th>&lt;50</th>
<th>50–59</th>
<th>60–69</th>
<th>≥70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy, 2</td>
<td>0.27</td>
<td>0.14</td>
<td>0.08</td>
<td>0.08</td>
<td>4.3</td>
<td>3.6</td>
<td>3.2</td>
<td>3.7</td>
</tr>
<tr>
<td>Tamoxifen, 2</td>
<td>0.11</td>
<td>0.14</td>
<td>0.14</td>
<td>0.15</td>
<td>3.2</td>
<td>3.6</td>
<td>3.9</td>
<td>5.1</td>
</tr>
<tr>
<td>Tamoxifen, 5</td>
<td>0.18</td>
<td>0.22</td>
<td>0.22</td>
<td>0.24</td>
<td>3.6</td>
<td>4.2</td>
<td>4.7</td>
<td>8.6</td>
</tr>
<tr>
<td>Both, 2</td>
<td>0.35</td>
<td>0.26</td>
<td>0.21</td>
<td>0.22</td>
<td>5.1</td>
<td>4.5</td>
<td>4.7</td>
<td>7.7</td>
</tr>
<tr>
<td>Both, 5</td>
<td>0.40</td>
<td>0.33</td>
<td>0.28</td>
<td>0.30</td>
<td>5.6</td>
<td>5.3</td>
<td>5.8</td>
<td>14.7</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>MISCAN</th>
<th>APC (16)</th>
<th>% Diff</th>
<th>MISCAN</th>
<th>SEER (14)</th>
<th>% Diff</th>
<th>MISCAN</th>
<th>SEER (14)</th>
<th>% Diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–34</td>
<td>28</td>
<td>28</td>
<td>–1</td>
<td>6</td>
<td>6</td>
<td>10</td>
<td>84</td>
<td>75</td>
<td>12</td>
</tr>
<tr>
<td>35–39</td>
<td>61</td>
<td>62</td>
<td>–2</td>
<td>14</td>
<td>13</td>
<td>6</td>
<td>235</td>
<td>268</td>
<td>–12</td>
</tr>
<tr>
<td>45–49</td>
<td>176</td>
<td>180</td>
<td>–2</td>
<td>49</td>
<td>43</td>
<td>12</td>
<td>1023</td>
<td>1096</td>
<td>–7</td>
</tr>
<tr>
<td>50–54</td>
<td>200</td>
<td>201</td>
<td>–1</td>
<td>64</td>
<td>59</td>
<td>8</td>
<td>1611</td>
<td>1527</td>
<td>6</td>
</tr>
<tr>
<td>55–59</td>
<td>224</td>
<td>224</td>
<td>0</td>
<td>74</td>
<td>74</td>
<td>0</td>
<td>2097</td>
<td>1993</td>
<td>5</td>
</tr>
<tr>
<td>60–64</td>
<td>259</td>
<td>264</td>
<td>–2</td>
<td>87</td>
<td>84</td>
<td>3</td>
<td>2643</td>
<td>2289</td>
<td>15</td>
</tr>
<tr>
<td>65–69</td>
<td>293</td>
<td>294</td>
<td>0</td>
<td>100</td>
<td>93</td>
<td>8</td>
<td>3241</td>
<td>2556</td>
<td>27</td>
</tr>
<tr>
<td>70–74</td>
<td>322</td>
<td>322</td>
<td>0</td>
<td>117</td>
<td>104</td>
<td>12</td>
<td>3856</td>
<td>2904</td>
<td>33</td>
</tr>
<tr>
<td>75–79</td>
<td>329</td>
<td>331</td>
<td>–1</td>
<td>119</td>
<td>118</td>
<td>1</td>
<td>4363</td>
<td>3058</td>
<td>43</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Mortality reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual screening</td>
<td>15</td>
</tr>
<tr>
<td>Adjuvant treatment (chemotherapy + tamoxifen)</td>
<td>21</td>
</tr>
<tr>
<td>Actual screening + adjuvant treatment (chemotherapy + tamoxifen)</td>
<td>31</td>
</tr>
<tr>
<td>Annual screening</td>
<td>36</td>
</tr>
<tr>
<td>Chemotherapy only</td>
<td>10</td>
</tr>
<tr>
<td>Tamoxifen only</td>
<td>12</td>
</tr>
<tr>
<td>Actual screening + chemotherapy only</td>
<td>23</td>
</tr>
<tr>
<td>Actual screening + tamoxifen only</td>
<td>24</td>
</tr>
</tbody>
</table>

*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).
REFERENCES


(17) HIP Study. HIP Breast Cancer Screening Study—Statistical Tape; 1981.


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NOTES

Supported by NCI/NHI grant U01-CA88202. We gratefully acknowledge the National Cancer Institute–funded Breast Cancer Surveillance Consortium for providing information on breast cancer screening practices and characteristics of screen-detected tumors (grant numbers U01CA63740, U01CA60676, U01CA86082, U01CA63736, U01CA70013, U01CA69976, U01CA63731, and U01CA70040). We also gratefully acknowledge the “Vereniging van Nederlandse Kankercentra” for providing information of tumor staging in The Netherlands in the period before implementation of the nationwide mammography screening program.