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Simulating the Impact of Risk-Based Screening and Treatment on Breast Cancer Outcomes with MISCAN-Fadia

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Abstract

The MISCAN-Fadia microsimulation model uses continuous tumor growth to simulate the natural history of breast cancer and has been used extensively to estimate the impact of screening and adjuvant treatment on breast cancer incidence and mortality trends. The model simulates individual life histories from birth to death, with and without breast cancer, in the presence and in the absence of screening and treatment. Life histories are simulated according to discrete events such as birth, tumor inception, the tumor's clinical diagnosis diameter in the absence of screening, and death from breast cancer or death from other causes. MISCAN-Fadia consists of 4 main components: demography, natural history of breast cancer, screening, and treatment. Screening impact on the natural history of breast cancer is assessed by simulating continuous tumor growth and the "fatal diameter" concept. This concept implies that tumors diagnosed at a size that is between the screen detection threshold and the fatal diameter are cured, while tumors diagnosed at a diameter larger than the fatal tumor diameter metastasize and lead to breast cancer death. MISCAN-Fadia has been extended by including a different natural history for molecular subtypes based on a tumor's estrogen receptor (ER) status and human epidermal growth factor receptor 2 (HER2) status. In addition, personalized screening strategies that target women based on their risk such as breast density have been incorporated into the model. This personalized approach to screening will continue to develop in light of potential polygenic risk stratification possibilities and new screening modalities.

Keywords

breast cancer epidemiology, microsimulation model, risk-based breast cancer screening

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Randomized trials are considered the gold standard to assess the efficacy of cancer screening interventions. However, ethical concerns, participants lost to follow-up, feasibility issues regarding the number of evaluated screening strategies, and limited quantification abilities of the harms of screening, such as overdiagnosis, emphasize the need for ways to complement randomized trials. The breast cancer models of the Cancer Intervention and Surveillance Modeling Network (CISNET) simulate the effects of screening and treatment for lifetime follow-up, with varying compliance rates, for an unlimited number of screening strategies and thereby extrapolate the findings from randomized trials.

MISCAN-Fadia, an acronym for Micro Simulation Screening Analysis–Fatal Diameter, has been part of CISNET since its start in 2000, usually referred to as

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Model E (i.e., Erasmus Medical Center). Before the development of MISCAN-Fadia, a microsimulation model with discrete tumor progression was developed at Erasmus already in the 1980s to evaluate the effects of breast cancer screening in the Netherlands.[1] However, compared with observed stage distribution data, the model overestimated the number of early stage cancers diagnosed at subsequent screens. Sensitivity analysis of screening sensitivity did not lead to better estimates.[2] Moreover, it was difficult to explore different natural history assumptions because tumor progression was directly linked to discrete stages. MISCAN-Fadia, with continuous tumor growth, was initiated to overcome this rigid property. This model was developed with the intent of creating a more biologically oriented breast cancer model to evaluate the impact of screening and treatment on breast cancer incidence and mortality. Since tumor size is measurable and tumor growth is continuous, these properties form the biological approach to modeling the natural history of breast cancer. In the model, a distinction is made between tumor biology (growth function) and other model variables that are more likely to vary by calendar year and possibly differ between geographical areas such as access to screening facilities, screening equipment and consequently screening test sensitivity, clinical diagnosis in the absence of screening due to fewer breast self-examinations, and less public awareness of breast cancer risk. Sensitivity of a screening test is translated into a diameter size at which tumors become screen detectable. In MISCAN-Fadia, ductal carcinoma in situ (DCIS) and invasive tumors are simulated. Tumor properties like exponential growth rate, clinical diagnosis diameter, minimal diameter for screen detection, and fatal diameter are drawn from probability distributions to account for variability between tumors. The fatal diameter concept implies that available treatment only cures tumors that are diagnosed at a smaller diameter than the tumor's fatal diameter. Available treatment options are not sufficient for tumors diagnosed past their fatal diameter, and these tumors will cause breast cancer death.

Disease processes such as the moment of onset of breast cancer and progression or regression of DCIS and breast cancer are unobservable in reality. These are nonetheless important determinants that influence the balance of harms and benefits of screening and treatment. Modeling allows us to explore the effect of changing one of these unobservable factors on modeled outcomes such as breast cancer incidence and mortality. Likewise, it is possible to study the effect of changing tumor onset and tumor growth while keeping all other parameters unchanged to gain insight into the natural history of breast cancer and its interaction with cancer control interventions. To quantify the harms and benefits of different screening and treatment strategies, the model simulates the same female population twice. First, a population is simulated in the absence of screening and, second, in the presence of screening. Key outcomes such as the number of breast cancers, the number of breast cancer deaths, and overdiagnosed breast cancers can be calculated for lifetime follow-up for any possible screening strategy.

Population demography, natural history of breast cancer, screening, and treatment are the 4 main parts of the model. All model inputs and model parameters belong to one of these components and are either calibrated to data from trials or are based on empirical research.[3–5] This article presents the current model status and in particular the progress and extensions with respect to the first model study,[6] as well as the latest model applications that explore the possibilities of risk-based breast cancer screening.

Methods

Discrete Event–Driven Microsimulation

Discrete event simulation implies that the model moves from the time of one event (e.g., birth) to the next event (e.g., tumor onset). The events in a woman's lifetime are discrete and mutually exclusive. Microsimulation modeling entails simulation of independent life histories that can be aggregated to estimate the effects of screening and treatment at the population level. Life histories are simulated according to discrete events such as birth, a possible tumor inception, the diameter of the tumor when it would be clinically diagnosed in the absence of screening, a date of death from other causes, or, for a woman with breast cancer, a date of breast cancer death. Events that affect the natural history of breast cancer, such as screening and treatment, are tied to the tumor's continually growing diameter (i.e., screen detection of the tumor may take place from a certain tumor size and treatment may treat tumors successfully up to a certain tumor size). Each woman is simulated from birth and followed until death, and time plays an essential role in the order of events in a woman's life.

Parallel Universe Approach

In randomized controlled trials, randomization of participants is a key step to reduce the chance of systematic differences between study participants in the intervention and control groups. In MISCAN-Fadia, this is imitated

by simulating the same female population twice. First, the population is simulated in a no-screening world; then, the identical population is simulated again and subjected to screening to evaluate the effects of screening and treatment on incidence and mortality. In microsimulation modeling, this approach is often referred to as a parallel universe structure. Usually, populations of tens of millions of women are simulated with a model runtime of approximately 15 minutes.

Breast Cancer Onset

The risk of developing breast cancer increases as women get older, while at the same time breast cancer risk may differ by birth cohort.[7,8] Therefore, breast cancer onset in Model E is mainly driven by an age risk factor combined with a birth cohort risk factor to account for variations in the prevalence of risk factors that are related to the birth cohort. The model uses as input breast cancer incidence (invasive and DCIS) in the absence of screening to derive breast cancer onset probabilities that vary by age and cohort. Considering breast cancer incidence in the absence of screening has not been available at the population level in the United States since routine mammography screening started in the 1980s, most CISNET breast models have used breast cancer incidence in the absence of screening derived by Holford and others.[9] Currently in Model E, the breast cancer onset parameters are calibrated to the US incidence in the absence of screening that was derived and estimated by Gangnon and others,[10] who extended the work by Holford and others[9] by disentangling breast cancer incidence by cohort- and age-related factors, as well as the impact of mammography screening dissemination in the United States.

Continuous Tumor Growth Natural History Model

Among women who develop breast cancer, the natural history of the disease is simulated as a continuously growing tumor. At tumor inception, the tumor's diameter is 0.1 mm, and based on the time it takes for the tumor to double in size (i.e., the tumor volume doubling time), it grows exponentially. The DCIS model was originally based on the DCIS model of the Erasmus MISCAN breast model.[11] Once a breast lesion emerges from normal breast tissue, a woman is in the preclinical undetectable DCIS phase (Figure 1). The 2 possible transitions from there are either preclinical screen-detectable DCIS, the state that all CISNET breast models that include DCIS have in common,[12] or preclinical invasive breast cancer. From the preclinical screen-detectable state, 3 different transitions are possible: regression to a breast cancer–free life, progression to preclinical invasive breast cancer, or progression to the clinical DCIS state. The duration (years) in each DCIS state is assumed to be exponentially distributed, and transitions between DCIS states happen at exponential rates. These transition rates were estimated using Surveillance, Epidemiology, and End Results Program (SEER) American Joint Committee on Cancer (AJCC) data on stage distributions and age-specific DCIS and invasive incidence rates between 1975 and 1999.[3]

The tumor diameter at which available treatment options no longer result in cure is the fatal disease diameter and reflects the spread of breast cancer (i.e., distant metastasis). If the disease is fatal at the moment of diagnosis (i.e., the tumor diameter at diagnosis is larger than the tumor's fatal diameter), the time until death from breast cancer is determined by a draw from the survival distribution at the moment the disease became fatal (Figure 2). Tumors that are diagnosed at a smaller diameter than their fatal diameter are surgically removed and possibly radiated, and adjuvant treatment ensures the woman will not die of breast cancer. Each tumor is unique and has different diameter sizes for clinical diagnosis, screen detectability, and metastasis (fatal diameter). As listed under "the life course of a tumor," these tumor properties are governed by probability distributions to bring about variation between tumors.

Our natural history approach makes a distinction between tumor biology (i.e., growth rate of the tumor) and variables that are more likely to change over time, change by age, or differ by geographical region. The advantage of this approach is that it readily lends itself to define separate distributions for different parameters based on risk groups and molecular tumor subtypes, for example.[13] As such, adapting the model to simulate subgroups of more aggressive and faster growing tumors (e.g., estrogen receptor [ER]/human epidermal growth factor receptor 2 [HER2] molecular subtypes of breast cancer) was done by changing the growth rate of tumors while keeping other tumor aspects such as the clinical diagnosis diameter and tumor diameter threshold for screen detectability unchanged.

The life course of a tumor is described by the following:

1. Tumor growth rate $\sim$ lognormal (μ_1, σ_1)
2. Fatal diameter of the tumor $\sim$ Weibull (λ_1, K_1)
3. Survival time after reaching fatal diameter $\sim$ lognormal (μ_2, σ_2)

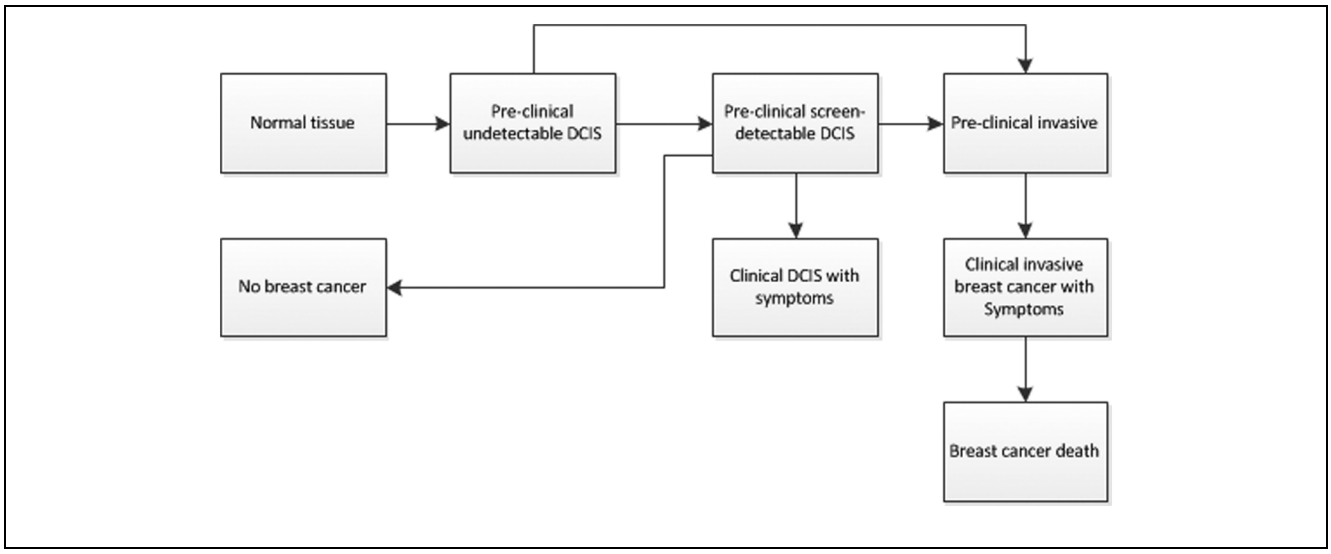

Figure 1 Ductal carcinoma in situ (DCIS) model in MISCAN-Fadia. Once a breast lesion emerges from normal breast tissue, a woman is in the preclinical undetectable DCIS phase. The 2 possible transitions from there are either preclinical screen-detectable DCIS or preclinical invasive breast cancer. From the preclinical screen-detectable DCIS phase, the tumor may regress and the woman will end up in the "No Breast Cancer" pool. However, from the preclinical screen-detectable DCIS phase, the tumor may also progress to preclinical invasive breast cancer or the tumor may cause clinical symptoms and a DCIS case will be diagnosed as a result of clinical symptoms. If a tumor is in the preclinical invasive breast cancer state, the cancer may be screen detected or cause clinical symptoms that lead to a clinical breast cancer diagnosis. Depending on the moment of diagnosis and the type of treatment, a women may be cured or die of breast cancer.

4. Screen-detectable (threshold) tumor diameter $\sim$ Weibull (λ_2, K_2)
5. Clinical diagnosis diameter of the tumor $\sim$ lognormal (μ_3, σ_3)
6. Clinical diagnosis of the tumor caused by distant metastasis. This is modeled as a constant fraction of the survival after reaching the tumor's fatal diameter.
7. Correlation between tumor growth rate and the tumor's clinical diagnosis diameter: ρ_1 (e.g., fast-growing tumors are diagnosed at larger diameters)
8. Correlation between tumor growth rate and survival time after reaching the tumor's fatal diameter: ρ_2 (e.g., fast-growing tumors have a shorter survival)
9. Correlation between tumor diameter at clinical diagnoses and survival time after reaching the tumor's fatal diameter: ρ_3 (e.g., tumors with a large size at clinical diagnosis have a shorter survival)
10. The tumor diameter at which N1 lymph node disease becomes detectable $\sim$ Weibull (λ_3, K_3)
11. Difference in tumor size at which N1 and N2 lymph node disease becomes detectable

When a breast tumor is initiated in a simulated woman, values of the six (1–6) tumor variables are generated. For each simulated tumor, the clinical diagnosis diameter is determined by the smallest tumor diameter of either the diameter at clinical diagnosis or the diameter at clinical diagnosis because of fatal metastases. After tumor initiation, the growth rate of the tumor determines the times at which the tumor reaches the threshold diameter for detectability by screening, the clinical diagnosis diameter, and the fatal diameter. If the tumor diameter at diagnosis is larger than the fatal diameter, then the survival time after reaching the fatal diameter will give the time at which a woman will die of breast cancer. On the other hand, if a tumor is detected, either clinically or through screening, before the fatal diameter is reached, the woman will be cured of cancer and die of other causes. A graphical representation of how the natural history of breast cancer is modeled in MISCAN-Fadia is provided in Figure 2. In MISCAN-Fadia, initially, Weibull distributions were assumed for all variables. However, when it became apparent that correlations had to be assumed, the more convenient multivariate lognormal distribution was used for 3 correlated variables. The

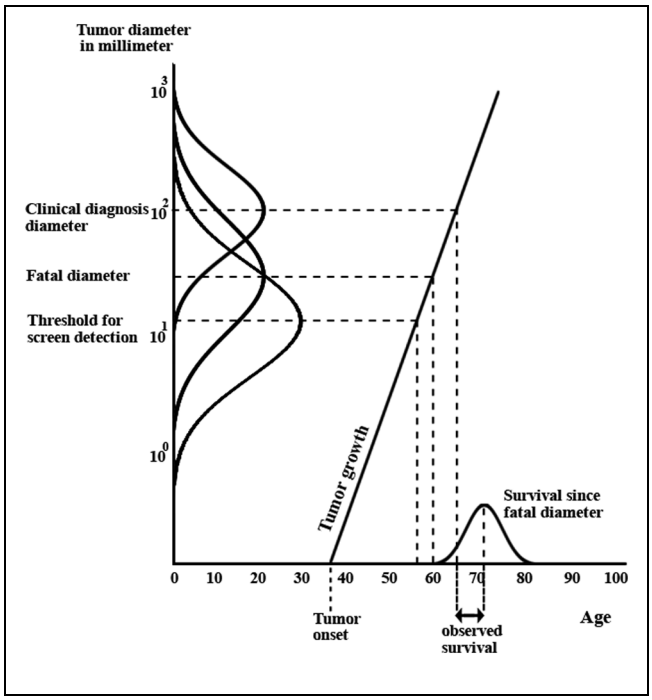

Figure 2 The MISCAN-Fadia breast cancer natural history model. After tumor onset, the values of 6 tumor characteristics are generated: growth rate of the tumor, the tumor's fatal diameter that represents distant metastasis, survival time after reaching the fatal diameter, screen detectability diameter (threshold), the clinical diagnosis diameter of the primary tumor, and clinical diagnosis caused by distant metastasis. The distribution curves on the y-axis demonstrate the probabilistic nature of the simulations and the variation between the screen detection, fatal, and clinical diagnosis diameter of tumors. The growth rate of the tumor determines the times since its initiation at which the tumor reaches the screen detectability diameter, the clinical diagnosis diameter, and the fatal diameter. If in the absence of screening, the clinical diagnosis diameter is larger than the fatal diameter, the woman will die of breast cancer, and the observed survival time is given as depicted in Figure 2. A woman will be cured if the breast cancer is detected, either clinically or through screening, before the fatal diameter is reached. Treatment (not shown in Figure 2) is modeled as a shift in fatal diameter and may affect survival and, in the best scenario, cause of death.

main reason was to get a better fit on the data of the base case analysis.

For the CISNET breast "base case" analysis,[14,15] the maximum likelihood estimates of MISCAN-Fadia for the natural history parameters were initially based on detailed data from the Swedish Two County Study.[4,5] These included estimates for tumor growth, tumor fatal diameter, survival duration since fatal diameter, clinical diagnosis diameter, and screen detectability diameter. The tumor size distribution and number of screen-detected cancers and interval cancers per screening round were simulated and compared with the findings of the trial. A detailed description and estimation of these natural history parameters can be found elsewhere.[6] Since the base case analysis, the natural history parameters such as tumor growth rate, tumor fatal diameter, survival duration after reaching the fatal diameter, and the threshold for screen detection have been reestimated for the simulation of various breast cancer molecular subtype combinations of ER and HER2.[13]

Population Demographics

MISCAN-Fadia can simulate one specific birth cohort, or, to account for varying demographic characteristics, a dynamic population consisting of multiple birth cohorts can be simulated. Certain birth cohorts may be assigned a different relative risk of developing breast cancer when cohort effects are present in the population. Nevertheless, each birth cohort is assigned an all-cause mortality table from which breast cancer as a cause of death is removed. These mortality tables determine the date of non–breast cancer–related death. A woman dies either of breast cancer or of other causes, whichever comes first. MISCAN-Fadia uses population parameters such as the number of birth cohorts and the proportion of each birth cohort in the overall US population. These model inputs, as well as the other-cause mortality tables, are common CISNET model inputs.[3]

Screening and Screen Detection

Characteristics of organized screening programs, such as screening ages, intervals, screening modality, and attendance by first and subsequent screens, can be inserted directly into the model. The mammography screening dissemination that reflects the historic opportunistic screening patterns observed in the United States can also be simulated.[16,17] Parameters to simulate screen detection, such as the sensitivity of the screening test, are translated into a diameter size at which tumors become screen detectable. By means of model calibration of tumor size distributions to observed tumor size distributions, the model estimates the screen detection (threshold) parameter. By varying only the screen detection parameters, the model finds the parameter values that resemble the best match between the simulated data and observed data.

If a woman is screened after a tumor onset but before the threshold tumor diameter of screen detectability, the result of the screening test is false negative. If that woman would be screened when the tumor diameter is larger than the tumor's screen detectability diameter, the result of the screening test is true positive. This structure for screen detection implies that no false positives are registered as direct output from the model. The number of false-positive mammograms is calculated based on the total number of mammograms performed in the model and the observed false-positive rates. Screening sensitivity differences between screening modalities, as well as improvements in screening performance, are modeled as a shift in the threshold diameter for screen detectability. The advent of digital mammography between 2000 and 2010 has been incorporated into the model by calibrating the threshold to digital mammography data.[18]

Overdiagnosis is defined as screen-detected DCIS or invasive breast cancer that would not have been diagnosed in a woman's life in the absence of screening. The parallel universe approach, simulating the same population of women twice, implies that the women in the screened population are exactly the same women as in the unscreened population. This allows for exact quantification of overdiagnosis due to screening because of the lifetime follow-up of all women.

Breast Cancer Staging

In MISCAN-Fadia, the severity of breast cancer is described by the diameter of the primary tumor and the extent to which the cancer has spread to lymph nodes or distant organs. This corresponds to the Tumor Node Metastasis (TNM) staging system that was developed and is maintained by the AJCC union that classifies tumors based on the size of the primary tumor (T), the nearby lymph nodes that are involved (N), and the spread of cancer as distant metastasis (M). To get to a stage at diagnosis, MISCAN-Fadia links tumor diameter to staging by including 3 parameters. First, continuous growth of the tumor diameter, the main concept of the natural history model, covers the T part of the staging system by the unique size of the tumor at diagnosis. Second, the lymph node status of tumors is covered by the inclusion of 2 parameters: N1 (the size of the tumor that reflects the spread to 1–3 nearby lymph nodes) and N2 (the size of the tumor that corresponds to the diameter at which breast cancer has spread to 4–9 lymph nodes). This is modeled as a fixed diameter size larger than N1. Third, metastasis of the primary tumor is modeled and covered by the unique fatal diameter of each tumor. The values of N1 and N2 were calibrated to SEER data on stage at diagnosis of cancers diagnosed between 1975 and 2000 as part of the base case analysis.[6] The definition of the AJCC staging system determines how cancers are staged at diagnosis; all DCIS diagnoses are staged as 0. Tumors smaller than 2 cm that have not spread to any nearby lymph nodes are staged as 1, tumors that are between 2 and 5 cm at diagnosis that have not spread to nearby lymph nodes are staged as 2a, and so on.

Adjuvant Treatment

The benefit of adjuvant treatment is modeled as a shift in the fatal diameter. For each adjuvant treatment, an age-specific cure proportion is estimated using the common CISNET model inputs[3] based on treatment effectiveness data from the meta-analyses by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG).[19,20] The cure proportions are translated into tumor diameters so that more effective treatment can cure a larger tumor. Women diagnosed at a tumor diameter greater than the tumor's fatal diameter benefit from adjuvant treatment by a shift to a larger fatal disease diameter. If the new fatal diameter is larger than the diameter at diagnosis, the treatment results in cure and ultimately death from other causes. However, if the new fatal diameter is still smaller than the diameter at diagnosis, surgery and radiation combined with adjuvant treatment will not result in cure, and the tumor will eventually cause breast cancer death. The dissemination of adjuvant treatment is modeled as the probability of being treated with a certain type of treatment (e.g., chemotherapy, tamoxifen) given the stage at diagnosis, calendar year, age at diagnosis, and ER and HER2 status.

Parameter Estimation

Parameter estimates are obtained by optimizing the goodness of fit between simulated data and observed data. The stochastic nature of the model output and duration of the model runs make the process of finding solid parameter estimates time-consuming. For selected starting values of the parameters, one microsimulation run will produce, for instance, age-specific breast cancer incidence trends over time and compare it with the observed breast cancer incidence levels. Maximum likelihood estimates of the model parameters are obtained by repeated evaluation of the simulated breast cancer incidence for different sets of parameter values. Parameters are estimated by minimizing the sum of squared

differences between observed and simulated data. This weighted sum measures the goodness of fit of the simulation results and is defined as a chi-squared distributed statistic.[21] Minimization of the goodness-of-fit statistic leads to the optimal parameters but requires frequent and time-consuming evaluations of the objective function. We used the Nelder and Mead Simplex (NMSM) algorithm,[22] which has the advantage that it only uses the value of the objective function (i.e., the goodness of fit of the model) to find the minimum. In the NMSM approach, each step in the optimization algorithms is based on output from previous simulation runs in which large numbers of life histories have been simulated, and it performs quite well in locating the optimum.

Extensive model calibration for the CISNET base case analysis provided parameter estimates that resulted in a close match between the simulated US incidence and mortality over time and the observed trends in incidence and mortality from 1975 to 2000.[15] These parameter estimates from the base case analysis were only recalibrated for a limited number of parameters at a time and within logical parameter bounds (e.g., new screening modalities with higher sensitivity of screening correspond to, and resulted in, a smaller threshold diameter for screen detectability).

Validation

Establishing the degree to which MISCAN-Fadia is an accurate representation of the real world is validation. Five types of validation[23] are addressed: face validity, internal validity, cross-validity, external validity, and predictive validity. Face validity means the model makes sense at face value. MISCAN-Fadia's structure with a biological entry of continuous tumor growth makes sense at face value. The model structure and data sources used as input lead to credible results that show no logical contradictions such as screening resulting in the diagnosis of more late-stage tumors or decreasing risk of developing breast cancer as women get older. Internal consistency, or verification, examines the mathematical calculations performed and its consistency with what could be expected based on the model's specification. MISCAN-Fadia, programmed in Delphi, is a microsimulation model in which disease processes are mainly driven by clearly specified probability distributions that are widely used in modern programming software packages. Results of mathematical calculations for published parameter values can easily be verified when using these probability distributions.

Cross-validity covers the aspect of comparing model results to the results of other modeling groups. As MISCAN-Fadia has been part of CISNET since the start of its collaboration, this form of validation of the model has been done extensively.[14,24,25] External validity is the comparison of model outcomes to observed data that were not used for calibration and development of the model. MISCAN-Fadia is currently part of an independent external validation exercise wherefore we validated the results of 5 CISNET breast cancer models against the UK Age trial.[26] In the past, we conducted a dependent model validation against the UK Breast Screening Frequency trial.[27] UK-specific breast cancer incidence and life tables were used, and the threshold diameter and the diameter of clinical diagnosis were reestimated based on the trial's data. The model accurately reproduced the cumulative incidence in the intervention and control groups. Also, the percentages of screen-detected and clinically diagnosed breast cancers were similar to the observed percentages in both groups, as were the number of breast cancer deaths.[28] Predictive validation is done by making model predictions for future outcomes of, for example, patterns in incidence and mortality. MISCAN-Fadia has made predictions about future trends in incidence and mortality,[29] but it still remains to be seen how these predictions unfold.

Model Input and Output of MISCAN-Fadia

Differences in patterns of breast cancer incidence and mortality can often be traced back to different screening and treatment regimens, adherence patterns, and different underlying risks. To simulate the harms and benefits of screening and treatment at the population level, the model requires data for the 4 major model components: population demographics, natural history of breast cancer, screening, and treatment. A list of inputs of MISCAN-Fadia is provided and described as common CISNET model inputs.[3]

The outcomes listed in Table 1 can be produced for any screening scenario with different start and stop ages of screening, screening frequency, and screening modality. In addition to different screening strategies, the model output can also be broken down by calendar year, age group, and tumor size or breast cancer stage such as AJCC. By assigning health utilities to specific health states and unit costs to specific events, total costs and quality-adjusted life years (QALYs) can be calculated. Consequently, cost-effectiveness analyses can be performed.[30] In addition, radiation-induced breast cancers

Table 1 Model Output in the MISCAN-Fadia Model

	Output Description
1	Invasive breast cancer cases diagnosed clinically
2	Invasive breast cancer cases diagnosed by screening
3	DCIS cases diagnosed clinically
4	DCIS cases diagnosed by screening
5	Life years in the absence of screening
6	Life years in the presence of screening
7	DCIS overdiagnosed cases (in the presence of screening)
8	Invasive overdiagnosed cases (in the presence of screening)
9	Breast cancer deaths in the absence of screening
10	Breast cancer deaths in the presence of screening
11	Deaths from other causes in the absence of screening
12	Deaths from other causes in the presence of screening
13	Number of mammograms
14	Number of cancers diagnosed in AJCC stages I, II, III, and IV
15	Number of cancers diagnosed in SEER stage: local, regional, and distant
16	Number of cancers diagnosed by tumor size: 0 to 20 mm, 20 to 50 mm, and 50 + mm
17	Number of cancers treated with adjuvant treatment
18	Intervals between events—for example, lead time (time between screen detection and diagnosis in the absence of screening) and survival (time between diagnosis and death)

AJCC, American Joint Committee on Cancer; DCIS, ductal carcinoma in situ; SEER, Surveillance, Epidemiology, and End Results Program.

and breast cancer deaths can be calculated using model output together with radiation dose.[31]

Extensions and Applications of the Model

Targeting screening to women with the highest potential benefit and lowest potential harm can improve the overall balance between benefits and harms in the population. In recent years, we explored the effects of obesity and race on US breast cancer mortality,[29,32] as well as the cost-effectiveness of ultrasonography screening.[30] In the past years, we also examined the contributions of screening and treatment to reduction in molecular subtype-specific breast cancer mortality by evaluating different screening scenarios, including risk-based screening strategies. We present some examples of the model adaptations that formed the basis of these collaborative modeling studies.

Personalizing Screening

To evaluate screening outcomes while taking into account advances in mammography and treatment of breast cancer, several screening strategies were modeled differing by age at which screening starts and screening interval. Biennial screening from age 50 to 74 years avoided a median of 7 breast cancer deaths per 1000 women screened compared with no screening and is generally considered to have a favorable balance between benefits and harms. More intensive screening leads to more benefits (breast cancer deaths averted) but also more harms (false positives and overdiagnosis). For example, annual screening from age 40 to 74 years avoided an additional 3 deaths but yielded 1988 more false-positive results and 11 more overdiagnosed cases per 1000 women screened.[25] Women aged 40 years with a 2-fold risk (compared to average risk) can expect the same balance of benefits and harms as average-risk women who receive biennial screening starting from age 50 years.[24]

Breast Density and Breast Cancer

Breast density has been proposed to personalize mammography screening. Dense breast tissue is prevalent and associated with a higher risk of developing breast cancer.[33] Moreover, since breast density is relatively easy to measure on a mammogram, it can be used for risk stratification. Some studies have found that tumors in dense breasts (categorized as BI-RADS 3 and 4) may progress more rapidly than those in fatty breasts, categorized as BI-RADS 1 and 2.[34] Based on this, breast density could be taken into account when personalizing a woman's screening frequency. Breast density affects not only the risk of developing breast cancer but also screening test sensitivity as dense breast tissue comprises less fat and

more connective breast tissue, which appears white on a mammogram. Moreover, cancer appears white on a mammogram and is therefore easier overlooked by radiologists, resulting in a lower screening test sensitivity.

Breast Density in MISCAN-Fadia

Breast density has been incorporated into MISCAN-Fadia to assess the effects of personalized screening; breast density was assumed to influence the sensitivity of the screening test (threshold diameter) as well as the onset of breast cancer. We also incorporated the decrease in breast density as women age because mammographic density decreases after menopause, when ovarian function declines. When modeling both risk and density, we found that average-risk women (low breast density) undergoing triennial screening and higher risk women (high breast density) receiving annual screening will maintain a similar or better balance of benefits and harms compared to biennially screening average-risk women.[35]

Simulating Molecular Subtypes of Breast Cancer

It has been widely acknowledged that breast cancer is a heterogeneous disease, and more knowledge is emerging on distinct molecular subtypes. Combinations of ER and HER2 status have different tumor growth and are associated with different treatment responses that have been found to be important in targeting the treatment of breast cancer. To understand the relative contributions of screening and treatment to US breast cancer mortality, first the major subtype combinations of ER positive and ER negative have been included in MISCAN-Fadia. Across CISNET models, we found that greater absolute breast cancer mortality declines in ER-positive cancers than among ER-negative cancers. The relative contribution of adjuvant treatment v. screening to breast cancer mortality reductions was higher for ER-positive cases; for ER-negative cases, the relative contributions were similar.[13] We have recently also included HER2 in the model, as well as the treatment trastuzumab (Herceptin), which is an antibody that interferes with the HER2 receptor.

Future Directions of Miscan-Fadia

Risk-Based Screening Based on Genetic Risk Profile

Genomic discoveries of genes associated with breast cancer risk may have the potential to personalize screening based on a woman's genetic risk profile. It is one of our primary goals in the upcoming years to continue our research on estimating the population impact of using polygenic risk to tailor screening strategies. A growing group of single-nucleotide polymorphisms (SNPs) are discovered that are associated with an elevated risk for breast cancer.[36] Individual SNPs identify a small increase in risk, but multiple SNPs combined together can be translated into a polygenic risk score to stratify women based on their polygenic risk. We divide the population into risk groups based on observed polygenic risk score distributions. For each risk group, the models simulate routine digital mammography screening strategies by varying starting and stopping ages of screening and screening frequency. To warrant a more intense screening scenario for high-risk groups and a less intense screening strategy for low-risk groups, we compare the benefits and harms of the different screening strategies. The polygenic risk distribution in the US female population determines how many women are eligible for each selected screening strategy and what the overall harms and benefits of polygenic risk-based screening will be.

A simplified analysis of using polygenic risk to inform screening strategies can be performed by dividing the population into 3 (low, median, high) risk groups with varying prevalence (Figure 3). Targeted screening based on polygenic risk leads to a redistribution of benefits and harms. A more in-depth analysis will be performed in the near future within CISNET. MISCAN-Fadia will be used to quantify the benefits such as the breast cancer deaths averted, quality-adjusted life years saved, breast cancer mortality reduction, costs, and harms such as the false-positive mammograms, overdiagnosed cases, unnecessary biopsies, and false negatives.

Strategies to Reduce Overtreatment of DCIS

While early detection of breast cancer and consequently less invasive treatment are often mentioned as benefits of screening, overtreatment of DCIS lesions that otherwise would not have clinically surfaced without screening is an increasing harm of screening since DCIS rates have increased dramatically over the past 30 years. Studies have shown that an increase in breast cancer mortality reduction due to screening comes with a substantially increased number of overdiagnosed DCIS cases.[11,37] MISCAN-Fadia will be extended to investigate if, how, and to what extent the harms of screening and treatment of DCIS can be reduced. By simulating "watchful waiting" strategies and exploring risk factors for progression to invasive breast cancer such as

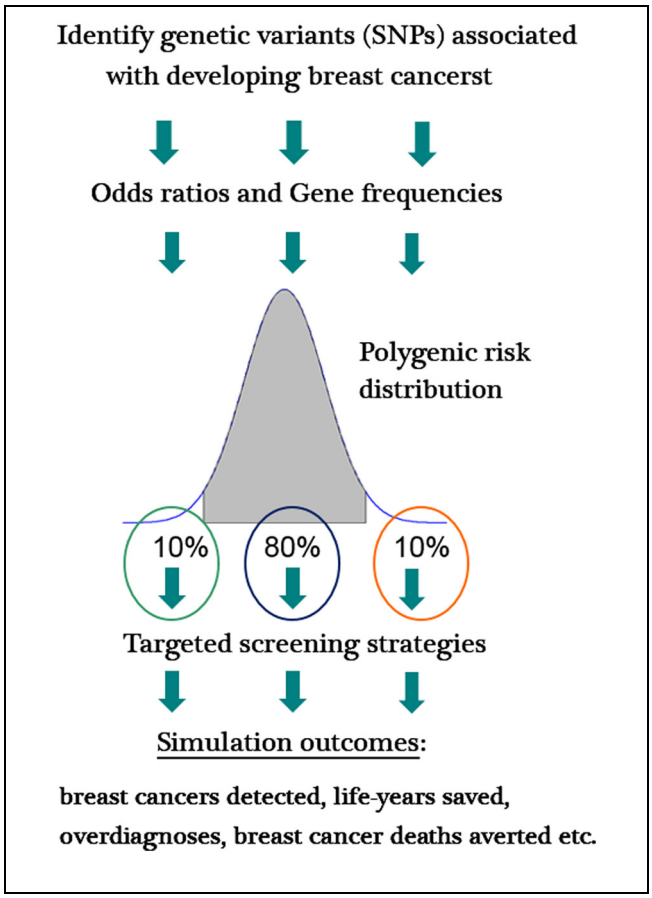

Figure 3 Simulating a personalized approach to breast cancer screening based on genetic risk profile. Genetic variants for breast cancer have different risk alleles. Multiple single-nucleotide polymorphisms (SNPs) combined together can be translated into a polygenic risk score to stratify women based on their polygenic risk. A simplified analysis of the potential population impact of using polygenic risk to inform screening strategies is demonstrated by dividing the population into 3 (low, median, high) risk groups with varying prevalence. In this simplified example, 10% of the population has a low risk of developing breast cancer, 80% an average risk, and 10% a high risk. More frequent screening could be offered to the high-risk group and less frequent screening (compared to the average-risk group) could be offered to the low-risk group. With more risk groups or even a continuous risk distribution, we could potentially optimize the tailoring of screening strategies based on polygenic risk, which would lead to a redistribution of benefits and harms compared to current practice. A more in-depth analysis will be performed in the near future within the Cancer Intervention and Surveillance Modeling Network.

cytological grade, ER status, age at diagnosis, and ethnicity, MISCAN-Fadia will be used to assess how different screening strategies and treatment routines may affect incidence and mortality for varying progression and regression rates of DCIS.

Conclusion

Trends in breast cancer incidence and mortality depend on many factors related to the biology and natural history of breast cancer. As tumor size is observable at diagnosis and tumors are considered to grow in continuous time rather than discrete time, these 2 aspects form MISCAN-Fadia's biological entry to modeling the effects of screening and treatment on breast cancer incidence and mortality. The advantage of this biologically oriented approach is that it allows for simple hypothesis testing because the core biological mechanisms are separated from cancer control interventions. Changes or improvements in screening and treatment that may vary by age or over time can be implemented directly and be dealt with without changing breast cancer onset or tumor growth parameters. On the other hand, simulating less or even more aggressive tumor subtypes with a different growth function is also possible. Moreover, correlations that were added to the base case model to get a good overall fit with observed data were plausible and, with a biological reasoning, intuitive to understand. In particular, one may expect faster growing tumors to be diagnosed at larger tumor diameters and faster growing tumors to have a shorter survival as well as a larger clinical diagnosis diameter.

However, MISCAN-Fadia also has limitations and makes use of simplifying assumptions. We model only 1 tumor per woman, while it may be possible that breast cancer develops in both breasts independently or at the same time, although such cancer development is not prevalent. Also, recurrence of breast cancer is not simulated in our model. We do not model specific factors associated with an elevated risk for breast cancer such as reproductive history, alcohol use, hormone therapy use, or familial risk. These different risk groups are assumed to be captured by the distribution we simulate tumors from. The spread between slower and faster growing tumors with unique tumor characteristics is assumed to capture the entire population risk profile.

Future development of the model will focus on evaluating the impact of using polygenic risk to inform screening strategies, evaluating the clinical management of screen-detected DCIS, and incorporating alternative and emerging screening modalities such as breast magnetic resonance imaging and tomosynthesis.

References

1. Habbema JD, van Oortmarssen GJ, Lubbe JT and van der Maas PJ. The MISCAN simulation program for the evaluation of screening for disease. *Comput Methods Programs Biomed*. 1985;20(1):79–93.
2. Boer R, de Koning H, van Oortmarssen G, Warmerdam P and van der Maas P. Stage distribution at first and repeat examinations in breast cancer screening. *J Med Screen*. 1999;6(3):132–8.
3. Mandelblatt JS, Near AM, Miglioretti DL, et al. Common model inputs used in CISNET collaborative breast cancer modeling. *Med Decis Making*. 2018;38(1S):9–23.
4. Tabar L, Fagerberg G, Duffy SW, Day NE, Gad A and Grontoft O. Update of the Swedish two-county program of mammographic screening for breast cancer. *Radiol Clin North Am*. 1992;30(1):187–210.
5. Tabar L, Fagerberg G, Day NE and Duffy SW. The Swedish two-county trial of mammographic screening for breast cancer: recent results on mortality and tumor characteristics. *Pathol Biol* (Paris). 1992;39(9):846.
6. Tan SY, van Oortmarssen GJ, de Koning HJ, Boer R and Habbema JD. The MISCAN-Fadia continuous tumor growth model for breast cancer. *J Natl Cancer Inst Monogr*. 2006;(36):56–65.
7. Clemmesen J. Carcinoma of the breast; results from statistical research. *Br J Radiol*. 1948;21(252):583–90.
8. Weedon-Fekjaer H, Bakken K, Vatten LJ and Tretli S. Understanding recent trends in incidence of invasive breast cancer in Norway: age-period-cohort analysis based on registry data on mammography screening and hormone treatment use. *BMJ*. 2012;344:e299.
9. Holford TR, Cronin KA, Mariotto AB and Feuer EJ. Changing patterns in breast cancer incidence trends. *J Natl Cancer Inst Monogr*. 2006;(36):19–25.
10. Gangnon RE, Sprague BL, Stout NK, et al. The contribution of mammography screening to breast cancer incidence trends in the United States: an updated age-period-cohort model. *Cancer Epidemiol Biomarkers Prev*. 2015;24(6):905–12.
11. de Gelder R, Fracheboud J, Heijnsdijk EA, et al. Digital mammography screening: weighing reduced mortality against increased overdiagnosis. *Prev Med*. 2011;53(3):134–40.
12. van Ravesteyn NT, van den Broek JJ, Li X, et al. Modeling ductal carcinoma in situ (DCIS): an overview of CISNET model approaches. *Med Decis Making*. 2018;38(1S):126–139.
13. Munoz D, Near AM, van Ravesteyn NT, et al. Effects of screening and systemic adjuvant therapy on ER-specific US breast cancer mortality. *J Natl Cancer Inst*. 2014;106(11).
14. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med*. 2005;353(17):1784–92.
15. Feuer EJ. Modeling the impact of adjuvant therapy and screening mammography on U.S. breast cancer mortality between 1975 and 2000: introduction to the problem. *J Natl Cancer Inst Monogr*. 2006;(36):2–6.
16. Cronin KA, Mariotto AB, Clarke LD and Feuer EJ. Additional common inputs for analyzing impact of adjuvant therapy and mammography on U.S. mortality. *J Natl Cancer Inst Monogr*. 2006;(36):26–9.
17. Cronin KA, Yu B, Krapcho M, et al. Modeling the dissemination of mammography in the United States. *Cancer Causes Control*. 2005;16(6):701–12.
18. Stout NK, Lee SJ, Schechter CB, et al. Benefits, harms, and costs for breast cancer screening after US implementation of digital mammography. *J Natl Cancer Inst*. 2014;106(6):dju092.
19. Early Breast Cancer Trialists' Collaborative Group,Peto R, Davies C, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet*. 2012;379(9814):432–44.
20. Yin W, Jiang Y, Shen Z, Shao Z and Lu J. Trastuzumab in the adjuvant treatment of HER2-positive early breast cancer patients: a meta-analysis of published randomized controlled trials. *PLoS One*. 2011;6(6):e21030.
21. Barton RR and Ivey JS. Nelder-Mead simplex modifications for simulation optimization. *Management Sci*. 1996;42:954–73.
22. Tan SYGL, Van Oortmarssen GJ and Piersma N. Estimating parameters of a microsimulation model for breast cancer screening using the score function method. *Ann Oper Res*. 2003;119(1):43–61.
23. Eddy DM, Hollingworth W, Caro JJ, et al. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7. *Med Decis Making*. 2012;32(5):733–43.
24. van Ravesteyn NT, Miglioretti DL, Stout NK, et al. Tipping the balance of benefits and harms to favor screening mammography starting at age 40 years: a comparative modeling study of risk. *Ann Intern Med*. 2012;156(9):609–17.
25. Mandelblatt JS, Stout NK, Schechter CB, et al. Collaborative modeling of the benefits and harms associated with different U.S. breast cancer screening strategies. *Ann Intern Med*. 2016;164(4):215–25.
26. Moss SM, Wale C, Smith R, Evans A, Cuckle H and Duffy SW. Effect of mammographic screening from age 40 years on breast cancer mortality in the UK Age trial at 17 years' follow-up: a randomised controlled trial. *Lancet Oncol*. 2015;16(9):1123–32.
27. Breast Screening Frequency Trial Group. The frequency of breast cancer screening: results from the UKCCCR Randomised Trial. United Kingdom Co-ordinating Committee on Cancer Research. *Eur J Cancer*. 2002;38(11):1458–64.
28. van Ravesteyn NT, Heijnsdijk EA, Draisma G and de Koning HJ. Prediction of higher mortality reduction for the UK Breast Screening Frequency Trial: a model-based approach on screening intervals. *Br J Cancer*. 2011;105(7):1082–8.

29. Mandelblatt J, van Ravesteyn N, Schechter C, et al. Which strategies reduce breast cancer mortality most? Collaborative modeling of optimal screening, treatment, and obesity prevention. *Cancer*. 2013;119(14):2541–8.
30. Sprague BL, Stout NK, Schechter C, et al. Benefits, harms, and cost-effectiveness of supplemental ultrasonography screening for women with dense breasts. *Ann Intern Med*. 2015;162(3):157–66.
31. Miglioretti DL, Lange J, van den Broek JJ, et al. Radiation-induced breast cancer incidence and mortality from digital mammography screening: a modeling study. *Ann Intern Med*. 2016;164(4):205–14.
32. van Ravesteyn NT, Schechter CB, Near AM, et al. Race-specific impact of natural history, mammography screening, and adjuvant treatment on breast cancer mortality rates in the United States. *Cancer Epidemiol Biomarkers Prev*. 2011;20(1):112–22.
33. McCormack VA and dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2006;15(6):1159–69.
34. Aiello EJ, Buist DS, White E and Porter PL. Association between mammographic breast density and breast cancer tumor characteristics. *Cancer Epidemiol Biomarkers Prev*. 2005;14(3):662–8.
35. Trentham-Dietz A, Kerlikowske K, Stout NK, Miglioretti DL, Schechter CB, Ergun MA, et al. Tailoring breast cancer screening intervals by breast density and risk for women aged 50 years or older: Collaborative modeling of screening outcomes. *Ann Intern Med*. 2016;165(10):700-12.
36. Mavaddat N, Pharoah PD, Michailidou K, et al. Prediction of breast cancer risk based on profiling with common genetic variants. *J Natl Cancer Inst*. 2015;107(5):djv036.
37. van Luijt PA, Heijnsdijk EA, Fracheboud J, et al. The distribution of ductal carcinoma in situ (DCIS) grade in 4232 women and its impact on overdiagnosis in breast cancer screening. *Breast Cancer Res*. 2016;18(1):47.