The validation of a simulation model incorporating radiation risk for mammography breast cancer screening in women with a hereditary-increased breast cancer risk

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ABSTRACT

Introduction: For women with a BRCA1 or BRCA2 mutation or a strong family history of breast cancer, there is no clear estimation of the risk of tumour induction versus the beneficial effects of mammography screening available. This study aims to validate the Simulation Model on Radiation Risk and breast cancer Screening (SiMRiSc) model in these women, which can provide information on the benefits and risks of screening for breast cancer for various screening scenarios.
Methods: The simulation model for breast cancer screening was developed and the values for model parameters including cancer induction due to radiation were derived from the literature. The simulation model was validated by comparing the outcome data of the model with the data from three published screening studies of women with an increased hereditary breast cancer risk. A sensitivity analysis was used to estimate the error margins of the outcome data and to analyse the sensitivity of the simulation model to each parameter.
Results: The model predicted 71 ± 4% of the reported tumours. When excluding the excess number of incident tumours detected in the first screening round, the model predicted 85 ± 6% of the tumours reported. The model was most sensitive to changes in the parameters related to lifetime breast cancer risk and sensitivity of mammography.
Conclusions: We conclude that the simulation model is suitable for the provision of accurate benefits' and risks' estimations necessary for the refinement of the screening guidelines for women at an increased risk of breast cancer.

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1. Introduction

Breast cancer is the most common cancer in women in Western European countries, and will develop in 1 in 9 to 1 in 11 women by age 80.[1] Women with a mutation in a BRCA1 or BRCA2 gene or women with a strong family history of breast cancer are at an increased hereditary breast cancer risk. For these women the risk to attain breast cancer is substantially higher and their mean age at diagnosis is younger than that in the general population.[2] Recognition of this has led to several guidelines regarding the screening of women with an increased breast cancer risk, based on the family history of breast and/or ovarian cancer, or the presence of a mutation in either BRCA1 or BRCA2 in themselves or a close relative. The actual extend of benefit of (annual) mammography surveillance, offered to these women, is controversial due to several aspects. First, there is the reduced sensitivity of breast imaging in pre-menopausal women, secondly there is the medical and psychological burden of false positive results and thirdly there is debate whether earlier detection does indeed lead to improved survival.[3–6] Another problem of mammography for these women is the risk of radiation-induced tumours, which is one of the possible side-effects of mammographic screening.

The risk of radiation-induced breast tumours is inversely related to the age at exposure: exposure before the age of 20 results in a higher risk of breast cancer than in those exposed at older ages. In addition, high doses of radiation evoke a higher risk of radiation-induced tumours than do low doses.[7–9] In most national breast cancer screening programmes, in which women are screened from 50 to 70 years of age,[10] it is confirmed that the impact of radiation-induced tumours on the total incidence is small.[8] However, women with a BRCA1 or BRCA2 mutation or with a strong family history of breast cancer are screened from younger ages, often more frequently, and usually for a longer period of time. Moreover, these women are thought to be more sensitive to radiation tumour induction.[11,12] It is expected that the balance between benefits and risks in these cases is less favourable.

To date, for the women with a BRCA1 or BRCA2 mutation or a strong family history of breast cancer, no studies have given a clear estimation of the risk of tumour induction versus the beneficial effects of mammography screening. Here we present the validation of a Simulation Model on Radiation Risk and breast cancer Screening (SiMRiSc), which aims at providing information on the benefits and the risks of screening for breast cancer in these populations for various screening scenarios. The purpose of this study was to validate the outcomes of this model using published data on the screening of women at hereditary-increased risk of breast cancer.

2. Materials and methods

2.1. A simulation model for screening

A previously developed simulation model for mammographic screening served as a base for this study.[13] In this simulation model, breast cancer screening was simulated using two age-dependent sensitivities for mammography and one fixed value for the risk to develop breast cancer due to low doses of ionising radiation. Therefore, for the current analysis, the model was extended with a more realistic function for the sensitivity of mammography and an assumption regarding the risk to develop breast cancer due to the low doses of ionising radiation. This assumption was based on an excess relative risk (ERR) model, which is developed based on breast cancer incidence rates after radiation exposure in eight large cohorts of 1502 breast cancers among 77,527 women (about 35,000 of whom were exposed) with 1.8 million woman-years of follow-up.[7,8] The ERR of ionising radiation (expressed per Sievert) is generally expressed as a risk relative to the background risk and states that the ERR is inverse quadratic dependent on the attained age. For a more detailed description of the model, see Appendix A.

In the model, three categories of women with a hereditary-increased breast cancer risk were considered: (1) women with a BRCA1 mutation, (2) women with a BRCA2 mutation and (3) women with a strong family history of breast cancer and possibly an unknown mutation (BRCAu). For each woman in either of these simulated groups, it was randomly assigned whether she would develop breast cancer or not, depending on her category-related cumulative lifetime risk. If a woman was considered to develop breast cancer, the age at which she would have clinically detectable breast cancer was randomly assigned depending on her lifetime risk. Next, the preclinical phase (i.e. the time between tumour onset age and clinical detection age) was randomly assigned depending on the tumour-doubling time.[14] For each screening round, it was simulated whether a tumour would be detected depending on a random sampling based on an exponential sensitivity model for mammography. For a tumour to be detected through screening, the screening had to take place between the tumour onset age and the clinical detection age.

2.2. Parameters of the model

Eight parameters were incorporated in the model (Table 1). The values for these parameters were based on the literature:

> The tumour induction model: the mean estimate for radiation dose was based on the mean glandular doses for a two-view mammogram on women exposed in 2002–2004 in the Dutch screening programme.[15] The probability of tumour induction is given by the parameter β in the ERR model (Appendix A, Eq. (2)).
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> The preclinical tumour growth model: the mean and standard deviation of the preclinical period were based on the average tumour-doubling time of primary breast cancers diagnosed in women younger than 50 years.[16] The function which describes the preclinical tumour growth is defined in Eq. (4) in Appendix A.
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> The risk to develop breast cancer during life: for the BRCA1 and BRCA2 mutation carriers, the baseline estimates for the lifetime risk were based on Easton and colleagues and Ford and colleagues.[17,18] The baseline estimates for the lifetime

Table 1 – Overview of the baseline parameters used in the model and the minimum and maximum estimates that were used for the sensitivity analysis.

	Parameter	Baseline estimate	Minimum estimate	Maximum estimate
Tumour induction model	*Radiation-induced tumour parameters*			
	Dose (d) [mSv]	3	1	5
	Probability of tumour induction (β)	0.51	0.28	0.83
Tumour growth model	*Preclinical period*			
	Mean (μ_{pc}) [years]	1.9	0.66	3.14
	Standard deviation (σ_{pc}) [years]	0.6	0.21	0.99
The risk to develop breast cancer during life	*BRCA1 probability function*			
	Lifetime risk at age 70 (f_1)	0.8	0.56	0.85
	Mean age (μ_1) [years]	40	24	67
	Standard deviation (σ_1) [years]	16.5	12	21
	Chi-square	0.041	0.005	0.054
	BRCA2 probability function			
	Lifetime risk at age 70 (f_2)	0.76	0.46	0.76
	Mean age (μ_2) [years]	40	25	65
	Standard deviation (σ_2) [years]	16.5	14	19
	Chi-square	0.018	0.001	0.047
	BRCAu probability function			
	Lifetime risk at age 70 (f_u)	0.38	0.19	0.57
	Mean age (μ_u) [years]	41	22	66
	Standard deviation (σ_u) [years]	17.2	16.9	17.5
	Chi-square	0.001	0.233	0.001
The sensitivity of mammography	*Programme sensitivity*			
	Modena (95% CI)			
	BRCA1 – 0.40 (0.00–0.83)	0.48	0.48	0.84
	BRCA2 – 0.40 (0.00–0.83)	0.47	0.47	0.84
	BRCAu – 0.68 (0.52–0.83)	0.67	0.55	0.83
	MRISC			
	BRCA1 – 0.32 (0.12–0.49)	0.52	0.52	0.52
	BRCA2 – 0.32 (0.12–0.49)	0.52	0.52	0.52
	BRCAu – 0.44 (0.26–0.63)	0.5	0.5	0.61
	MARIBS			
	BRCA1 – 0.23 (0.00–0.46)	0.51	0.51	0.51
	BRCA2 – 0.43 (0.06–0.80)	0.52	0.52	0.82
	BRCAu – 0.53 (0.28–0.79)	0.49	0.49	0.79

risks for the BRCAu populations were based on Jonker and colleagues.[19] The mean age (and the standard deviation) of the women in screening were derived from the validation cohorts.[20–22] The function which describes the risk to develop breast cancer during life is defined in Eq. (3) in Appendix A.

The sensitivity of mammography: the estimates for the programme sensitivity of annual mammography were based on the validation cohorts.[20–22] The function which describes the sensitivity of mammography is defined in Eq. (7) in Appendix A.

2.3.　Output of the model

The output of the model was given in terms of the number of detected breast cancers during the screening period (including screen-detected cancers in the first screening round and subsequent screening rounds) plus the number of breast cancers that became clinical between the screening sessions (interval cancers).

2.4.　Validation of the model

A systematic search in MEDLINE was done with the following strategy [breast cancer AND genetic predisposition to disease AND (mammography OR MRI OR ultrasound)] up to April 2007. MeSH headings as well as title words were explored. In this way we identified 11 cohorts concerning women with a BRCA1/2 mutation or a strong family history of breast cancer that were being screened with at least mammography. In case of more reports regarding one cohort, the most up-to-date publication was selected. Eight studies had to be excluded: studies that had not stratified screening populations for BRCA1 or BRCA2 mutation and family history of breast cancer;[23–27] studies including less than 10 mutation carriers;[28] and studies including women with a previous diagnosis of breast cancer.[29,30]

In this way, three studies could be used to validate our simulation model for screening: the Modena Study,[20] the MRISC study[21] and the MARIBS study[22] (Table 2). Data regarding the number of women included, the age distribution of the women under screening, the follow-up time in women

Table 2 – Overview of the studies that were used to validate our simulation model for screening. All studies used annual mammography.

Cohort	Stratum	Number of women included	Age (range) [years]	Follow-up time [person years]	Number of screen-detected breast cancers	Number of interval breast cancers	Total number of breast cancers	Total number of breast cancers in first round	Programme sensitivity (%)
Modena	BRCA1 and 2	48	42 (20–75)	158	2	3	5	1[a]	40
	Family history	931	42 (15–75)	4464	23	11	34	3[a]	68
MRISC	BRCA1 and 2	358	38 (20–72)	867	7	16	23	10	25
	Family history	1551	41 (19–72)	4382	12	15	27	14	39
MARIBS	BRCA1	82	40 (33–55)	278	3	10	13	8	23
	BRCA2	34	41 (34–49)	115	3	4	7	4	43
	Family history	533	41 (31–50)	2185	8	7	15	6	53

a Due to the design of the Modena study these data were not used in this analysis.

years, the number of screen-detected and interval cancers, the number of breast cancers diagnosed in the first screening round and the sensitivity of the annual mammography were derived from the papers, and 95% confidence intervals (95% CIs) were calculated. In the MARIBS study, data were available for patients with (1) a BRCA1 mutation, or (2) a BRCA2 mutation or (3) a family history for breast cancer. In the Modena and the MRISC study, data were available for patients with (1) a BRCA1 or BRCA2 mutation or (2) a family history for breast cancer. Where not all data were presented in the original papers, the authors were contacted for further information.

To validate the model, the data of the selected studies regarding the age distribution of the women under screening, the screenings interval and the sensitivity of the annual mammography were used as input to the simulation model, all stratified by BRCA1, BRCA2 or a family history for breast cancer. For each study, the screening was simulated given the input as presented in the study and the output of the simulation model for screening was compared to the results presented in that study. Because the data were not stratified by BRCA1 and BRCA2 in the MRISC study and the Modena study, the pooled number of tumours as predicted by the simulation model for these two populations was presented as the model estimate. To make a correct comparison, we compared the output of the simulation model for screening to (1) the data as presented in the studies and (2) the data as presented in the studies excluding the excess number of screen-detected tumours found in the first screening round.

2.5. Sensitivity analyses

To test the effect of the various assumptions in the simulation model for screening, sensitivity analyses were performed on the eight parameters in the model (Table 1) for BRCA1, BRCA2 and BRCAu separately.

The tumour induction model: The range of estimates for dose were based on mean glandular doses for a two-view mammogram on women exposed in 2002–2004 in the Dutch screening programme.[15] The range of the probability of

tumour induction was based on the 95% confidence interval fitted to the observed data.[7]

The preclinical tumour growth model: The minimum estimate for the preclinical period was based on tumour-doubling times as published by Tilanus-Linthorst and colleagues.[31] For the maximum estimate, a symmetrical interval around the baseline estimate was chosen. The minimum and maximum estimates for the standard deviation of the preclinical period were linear scaled to the minimum and maximum estimates.

The risk to develop breast cancer during life: For the BRCA1 and BRCA2 mutation populations, the minimum estimate of the lifetime risk was based on Chen and colleagues.[2] For the maximum estimate, a symmetrical interval around the baseline was chosen. For the BRCAu population, the maximum estimate of the lifetime risk was based on the model published by Jonker and colleagues.[19] For the minimum estimate, again a symmetrical interval around the baseline was chosen.

The sensitivity of mammography: For the minimum estimate of the sensitivity, a value was chosen so that the minimum sensitivity approached the minimum value of the confidence interval as given in Table 1 (see Appendix A). The maximum estimate of the sensitivity was chosen in a similar way.

For each study, the screening was simulated using the baseline estimates as given in Table 1, and the output of the simulation model for screening was compared to the data presented in that study. To gain sufficient precision each simulation was performed with an average 3.5–8.1 million women and each simulation was performed 10 times. Based on the minimum and maximum number of screen-detected and interval cancers due to the minimum and maximum estimates for each of the eight parameters listed in Table 1, the individual error margin in the number of screen-detected and interval tumours was calculated for each parameter. Thereafter, the total error margin was set equal to the maximum value of each of the eight individual error margins. Finally, the change in the number of detected tumours as predicted by the simulation model was assessed as a function

of variation of the model parameters in order to quantify the sensitivity of the model to each of the eight parameters separately.

Ethical approval was not required for this study.

3.   Results

3.1.   Observed data

In Fig. 1 the results of the screening simulation are shown for the Modena study, the MRISC study and the MARIBS study. In the published cohorts, the following data were observed: 5 (95% CI: 1–9) and 34 (95% CI: 22–44) tumours for the Modena cohort and 23 (95% CI: 14–32) and 27 (95% CI: 15–34) tumours for the MRISC cohort of pooled *BRCA1/2* mutation carriers and BRCAu, respectively. In the MARIBS cohort the following data
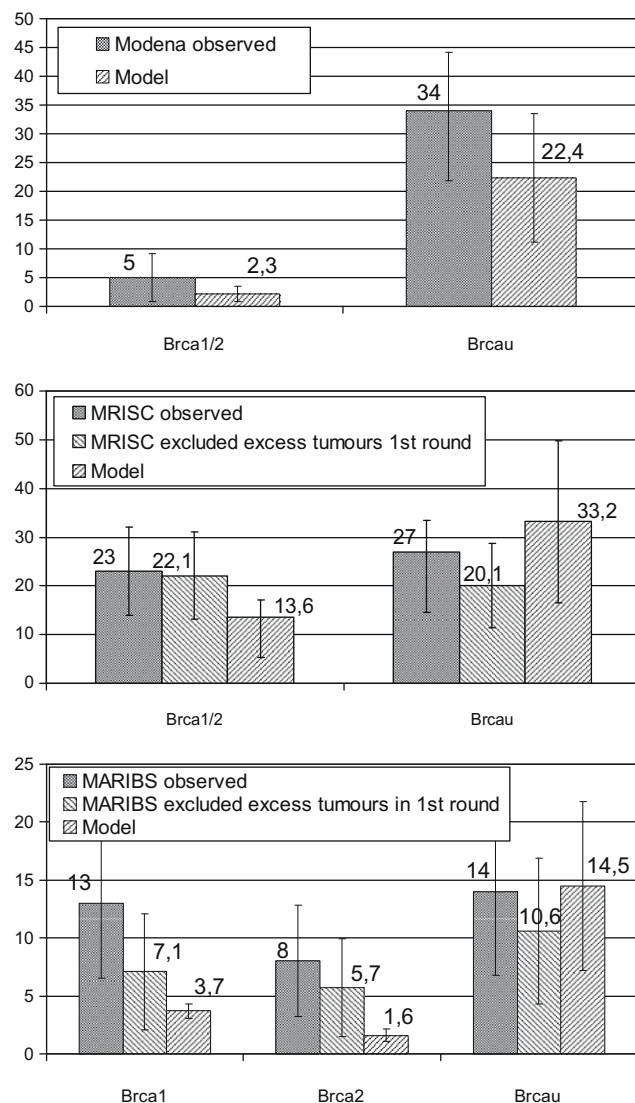

Fig. 1 – Comparing the number of tumours found in the published studies (Modena, MRISC and MARIBS) to the results as predicted by the Model with exclusion of the excess number of screen-detected tumours found in the first screening round.

were observed: 13 (95% CI: 7–20) tumours for *BRCA1*, 8 (95% CI: 3–13) for *BRCA2* and 14 (7–21) for BRCAu.

3.2.   Predicted data, including and excluding the first round yield

The model predicted 2.3 (95% CI: 1.4–3.4) and 22.4 (95% CI: 11.3–33.5) tumours for the respective Modena cohorts and 13.6 (95% CI: 5.2–17.1) and 33.2 (95% CI: 16.6–49.9) tumours for the respective MRISC cohorts. The model predicted 3.7 (95% CI: 2.3–4.3), 1.6 (95% CI: 0.9–2.1) and 14.5 (95% CI: 7.2–21.7) tumours for the MARIBS cohort for *BRCA1*, *BRCA2* and BRCAu, respectively. In the MRISC cohort, excluding the excess number of incident tumours found in the first screening round yielded 22.1 (95% CI: 13.1–31.0) and 20.1 (95% CI: 11.4–28.8) tumours for *BRCA1/2* combined and BRCAu, respectively. In the MARIBS cohort, excluding the excess number of screen-detected tumours found in the first round yielded 7.1 (95% CI: 2.1–12.1), 5.7 (95% CI: 1.4–9.9) and 10.6 (95% CI: 4.3–16.9) tumours for *BRCA1*, *BRCA2* and BRCAu, respectively.

3.3.   Fit of the model

Using the published screening scenarios, the model predicted a weighted average of 71 ± 4% of the number of tumours published. When excluding the excess number of screen-detected tumours found in the first round, the model predicted a weighted average of 85 ± 6% of the number of tumours published. When the incident cancers from the first screening round was excluded the outcome of the model was not significantly different from the published data for all carriers' simulations.

3.4.   Sensitivity analyses

The sensitivity analyses showed similar results for BRCA1, BRCA2 and BRCAu separately. Therefore, the results of the sensitivity analyses were given as a mean of the pooled data of the mutation carrier groups. The results of the sensitivity analyses showed that a decrease of 4 years (10%) in the mean age of onset of breast cancer resulted in an increase of 21% in the number of tumours expected in the model (Fig. 2). An increase of 10% in the lifetime risk and the programme sensitivity of annual screening with mammography resulted in a change of +11% and +4.9%, respectively, in the number of tumours expected in the model. Changes in the other assumptions regarding the standard deviations resulted in relatively smaller changes in the number of tumours expected in the model: of mean age of breast cancer (–3.1%), the mean preclinical period (+2.2%), the dose (+0.07%), the standard deviation in the mean preclinical period (+0.05%) and the tumour induction parameter (+0.04%).

4.   Discussion

A simulation model for breast cancer screening was developed with the incorporation of radiation-induced tumour probability, preclinical tumour growth rate, lifetime breast cancer risk and sensitivity of annual mammography. The
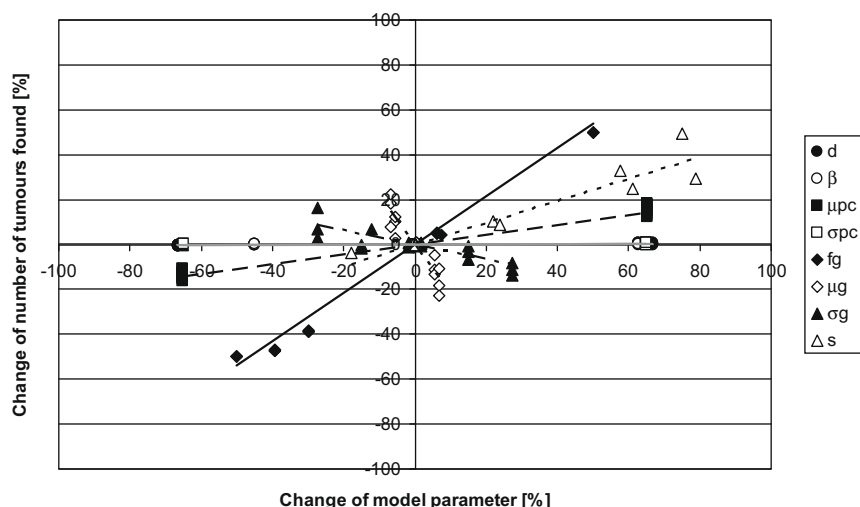
Fig. 2 – Result of the sensitivity analysis which shows the change of the number of tumours as predicted by the model as a function of change of each of the eight parameters used in the model listed in Table 2. Tumour induction model: dose (*d*), probability of tumour induction (*β*), tumour growth model: mean preclinical period (x_{pc}), standard deviation of mean preclinical period (σ_{pc}), the risk to develop breast cancer during life: lifetime risk (f_g), mean age (μ_g), standard deviation (σ_g) and the sensitivity of mammography (*s*).

values for these parameters were derived from published estimates. The simulation model was validated by comparing the outcome data of the model with the published data in three studies with cohorts of women with a *BRCA1* or *BRCA2* mutation or a strong family history of breast cancer (BRCAu). The model predicted a weighted average of 71 ± 4% of the number of tumours published. When excluding the excess screen-detected cancers of the first round, the model predicted a weighted average of 85 ± 6% of the number of tumours published. Excluding the excess number of screen-detected tumours found in the first round, no significant different results were observed between the expectations under the model and the published data. The model was most sensitive to changes in the parameters related to lifetime risk and the programme sensitivity of annual screening with mammography.

Three published studies fulfilled our criteria, presenting their data stratified for *BRCA1/2* mutations and family history of breast cancer (BRCAu) and these were considered as validation cohorts. Since the baseline estimates in our model for the lifetime risks for *BRCA1/2* and BRCAu strongly vary over the three categories, exact information regarding the distribution of patients and tumours over the three groups was of utmost importance in the validation of our model. The baseline estimates for the lifetime risks for *BRCA1* and *BRCA2* were based on Easton and colleagues for *BRCA1* and Ford and colleagues, for *BRCA2*.[17,18] The baseline lifetime risk for BRCAu was estimated according to Jonker and colleagues.[19] All these baseline estimates concern women without a personal history of breast cancer, because women with a personal history of breast cancer are at an increased risk to develop a second breast cancer, locoregional recurrence and/or metastatic disease. Since this risk is not yet quantifiable studies including women with previous breast cancer were excluded. Limitations of the validation cohorts were that the exact distribution of age was estimated based on the published means and stan-

dard deviations and that the follow-up time was relatively short in comparison to the mean tumour induction time. In addition, in the Modena and the MRISC cohorts the results were not stratified for *BRCA1* and *BRCA2*. Therefore, we performed a pooled analysis for *BRCA1* and *BRCA2* in these two cohorts for validation.

A possible explanation for the differences between the predicted and observed number of breast cancers in the *BRCA1* and *BRCA2* mutation cohorts can be that in the MRISC cohort 24 of 50 (48%) and in MARIBS 18 of 35 (51%) tumours were found in the first round.[21,22] In the Modena cohort, only 5 of 39 (13%) tumours were detected in the first round.[20] In the MRISC and MARIBS studies, recruitment of patients began in the end of the nineties and the first screen always included mammography as well as a dynamic MRI, which is highly sensitive for the presence of breast cancer.[32] In the Modena cohort, however, screening started in 1994 with mammography, ultrasonography and clinical breast examination. It was only after 2000 that MRI was offered to women with a *BRCA1/2* mutation or at a very high risk for breast cancer due to a family history. In our analysis it was found that excluding the excess number of screen-detected tumours found in the first round increased the fit of the model.

In our computation we used a linear no threshold (LNT) model for the effect of radiation. This model is favoured by most organisations who quantified the biological effect of low-dose ionising radiation.[57–59] In addition, we used an excess relative risk model to compute the multiplicative risk due to multiple mammography examinations and the underlying breast cancer rates (see Appendix A). Although the BEIR VII committee preferred an excess absolute risk model, the committee also stated that the excess relative risk model can be used for estimating risks for the population of United States and European women, and the lifetime cancer mortality estimates for female breast cancer are comparable to the corresponding values given by other models.[54,57–59]

The sensitivity of the annual mammographic screening programme had a major impact on the predictions of the simulation model. An increase of 10% in this programme sensitivity resulted in an increase of 4.9% in the number of tumours expected in the model. The main explanation is that in our study the model was based on the published screening scenarios with a rather low number of screening rounds per woman (estimated range 2.4–4.8).

In our simulation model, the mean tumour-doubling time was based on Peer and colleagues and assumed to be 1.9 years.[16] This is in line with a recent publication by Weedon-Fekjær in which the mean time a tumour needed to grow from 10 mm to 20 mm in diameter was estimated as 1.7 years.[33] There was, however, a considerable variation between subjects and tumour-doubling time which increased with age. Women with a BRCA1 or BRCA2 mutation or a strong familial aggregation for breast cancer tend to have their breast cancer at a relatively young age. In the sensitivity analyses the minimum estimate for tumour-doubling time was based on a recent study of Tilanus-Linthorst and colleagues.[31] They concluded that tumours grow faster in women with a BRCA1 mutation as well as in BRCAu women under the age of 50.[31] Since changes in the mean length of the preclinical period only had a minor impact on the predictions of our model, we do not expect that the differences observed between the predicted and observed number of breast cancers in women with a BRCA1 or BRCA2 mutation can be explained by an effective shorter tumour-doubling time.

Based on Dutch data, we used an estimated mean dose of 3 mGy per screening round (i.e. two exposures), while for the sensitivity analysis a range of 1–5 mGy was used, based on the data by Van der Helm and colleagues.[15] Comparable estimates have been published by Young and colleagues,[34] Kruger and colleagues.[35] Our model was less sensitive to changes in the radiation dose and the radiation risk. A main explanation is that the time of follow-up in the cohorts is too short to study the effects of dose on the model outcome. Since effects on radiation-induced tumours are expected to become manifest predominantly after 15–20 years,[7] we extended the screening of the three cohorts in our simulation to 75 years. From this simulation we found that the number of tumours in the screened population increased up to 6.2% depending on the specific mutation. This increase reflected the influence of cumulative dose during an extended time period which was long enough for radiation-induced tumours to become manifest.

In our study, we developed a model for the screening of women with a BRCA1/2 mutation or family history for breast cancer, including the latest BEIR VII excess relative risk model on radiation-induced breast tumour risk. Many simulation models have been published aiming at calculating the effectiveness of screening in the general population.[36–51] However, none of these studies include the potential harmful effect of X-rays on tumour induction. Tumours induced by X-rays were included in only two model study for evaluation of breast cancer screening[52,53] Jansen and colleagues concluded that screening between 40 and 80 years of age is beneficial in terms of survival using an absorbed dose of 2 mGy per session.[52] Beemsterboer and colleagues published the benefit risk ratio of mammography screening in the general population, also taking into account the risk of dying from breast cancer induced by low-dose mammography.[53] Their induced breast cancer mortality calculation, however, was based on the BEIR V model,[54] and they concluded that for screening under the age of 50 the benefit risk ratio was less favourable in comparison to screening at older ages.

Limitations of the here proposed model are that the model does not include screening with MRI and physical examination. In addition, the specificity of mammography was not included. The latter might not be important given the high specificity of mammography in these patient groups. Due to the short follow-up time in the validation cohorts, we were not able to test the model regarding overall mortality and breast cancer-specific mortality. Finally, the impact of life events such as salpingo-oophorectomy and preventive mastectomy was not incorporated in our model. It is expected that these life events will decrease the lifetime risk to develop breast cancer. However, since the aim of our study was to provide a model for breast cancer screening for women at a high lifetime risk, these life events have not been included in the current simulation.

Simulation models of benefit and risk estimation for screening of BRCA1/2 mutation carriers have been published in two studies. In the first study, Jacobi and colleagues concluded that annual breast cancer screening with mammography for women under the age of 50 is cost-effective in women with a strong family history of breast cancer.[13] They included a radiation risk model in their simulation based on a constant radiation risk 1.65×10^{-5} below the age of 50, and 1.14×10^{-5} above the age of 50. In the second study, Plevritis and colleagues included the use of MRI in their screening simulation and concluded that the cost per quality-adjusted life-year gained is 55,420 dollars for BRCA1 mutation carriers and 130,695 dollars for BRCA2 mutation carriers.[55] However, both these studies did not include the influence of tumour induction by frequent mammographic examinations based on the latest BEIR VII model.

The next step in our study is to compare different screening strategies to assess the benefit risk ratio. The benefit can be expressed in terms of number of screen-detected small tumours whereas the risk can be expressed in terms of number of radiation-induced tumours, the costs of the different screening strategies and the number of false positive findings. This benefit risk ratio can then be used to find the optimal screening strategy for women with a hereditary-increased breast cancer risk.

5.   Conclusion

Although several studies have been published on benefit and risk simulation of mammographic screening in the general population or in BRCA1/2 mutation carriers or about radiation-induced tumours, this is the first study which presents a simulation model for screening of women with a mutation in the BRCA1/2 genes or a strong family history of breast cancer incorporating the potential harmful radiation effects of X-rays based on the latest excess relative risk model for radiation-induced breast cancer. Our model is validated against the data published from three cohorts and predicts the

outcomes to a high degree. Therefore, the simulation model is suitable for the provision of accurate benefits and risks and useful for the refinement of the screening guidelines for women at an increased risk of breast cancer.

Conflict of interest statement

None declared.

Acknowledgements

Appendix A

A.1.   Radiation risk

The excess relative risk (ERR) of ionising radiation is generally expressed as a risk relative to the background risk. With a linear dose–response function, the general model for ERR is given by[7]

$$\lambda(c, s, a, b, d) = \lambda(c, s, a, b)[1 + \beta_s ERR(e, a)d] \tag{1}$$

where $\lambda(c, s, a, b)$ denotes the background rate at zero dose, and depends on city (c), sex (s), attained age (a) and birth cohort (b). The term $\beta_s\, ERR(e, a)$ is the excess relative risk per unit dose d expressed per Sievert, which may depend on sex (s), age at exposure (e) and attained age (a).

Preston and colleagues[8] found that a common model could be used to describe the radiation-induced breast cancer risk for several cohorts, among which the Life Span Study (LSS) cohort includes more than 47,000 women. From this model the BEIR VII committee's preferred model was derived for ERR:

$$ERR(e, a) = \beta\left(\frac{a}{60}\right)^{-2} \tag{2}$$

where β was fitted to the data and found to be $\beta = 0.51$ with a 95% confidence interval of (0.28, 0.83). In contrast to the model for ERR described in BEIR V,[54] the BEIR VII model depends only on attained age (a) and not on age at exposure (e).

A.2.   BRCA probability function

The probability density function $p(a_{bc}, g)$ of breast cancer at age a_{bc} and genetic predisposition g (where g is equal to BRCA1, BRCA2 or BRCAu) is modelled by a normal distribution given by

$$p(a_{bc}, g) = \frac{f_g}{\sigma_g \sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{a_{bc} - \mu_g}{\sigma_g}\right)^2} \tag{3}$$

where the mean breast cancer age is given by μ_g, the standard deviation is given by σ_g and the integral of Eq. (3) is given by f_g. The values for these parameters are given in Table 1.

A.3.   Preclinical period

The preclinical age is calculated using a log-normal distribution. The probability distribution of this function is given by a normally distributed logarithm of the preclinical breast cancer period x_{pc}:

$$p(x_{pc}) = \frac{1}{x_{pc}\sigma_{pc}\sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{\ln x_{pc} - \mu_{pc}}{\sigma_{pc}}\right)^2} \tag{4}$$

where μ_{pc} and σ_{pc} are the mean and standard deviation of the logarithm of the preclinical breast cancer period x_{pc}. Given the expected value E_{pc} and the variance var_{pc} of the preclinical breast cancer period distribution $p(x_{pc})$, the mean μ_{pc} and standard deviation σ_{pc} of the logarithm of the preclinical breast cancer period are given by

$$\mu_{pc} = \ln E_{pc} - \frac{1}{2}\ln\left(1 + \frac{var_{pc}^2}{E_{pc}^2}\right)$$
$$\sigma_{pc} = \sqrt{\ln\left(1 + \frac{var_{pc}^2}{E_{pc}^2}\right)} \tag{5}$$

A Box–Müller transformation is used in order to generate a pair of independent standard normally distributed random numbers (z_1, z_2) given a pair of uniformly distributed random numbers (u_1, u_2):[56]

$$z_1 = \sqrt{-2\ln u_1}\cos(2\pi u_2)$$
$$z_2 = \sqrt{-2\ln u_1}\sin(2\pi u_2) \tag{6}$$

A.4.   Sensitivity

The sensitivity $s(t)$ during the preclinical period is modelled by an exponential growth equation given by

$$s(t) = s_0\left(\frac{s_1}{s_0}\right)^{t/T} \tag{7}$$

where s_0 is the sensitivity at tumour onset, $s_1 = 1$ is the sensitivity at the clinical breast cancer age and $T = x_{pc}$ is the preclinical period.

A.5.   Screening loop

Now a loop is started where N women are included in a screening programme. In the simulation a screening is simulated for a certain age interval given by the starting age a_{start} and end age a_{end}. For each woman, the age at clinical breast cancer and the preclinical breast cancer age are calculated using Eqs. (3) and (4).

The cumulative excess relative risk $CumERR(d, a_i)$ of tumour induction by mamma screening with dosis d at age a_i after i screening rounds is given by the multiplication of the individual ERR at the ages a_1 to a_i in the screening programme.

$$CumERR(d, a_i) = \prod_{j=1}^{i}(1 + ERR(a_j) \cdot d) - 1 \tag{8}$$

Now the total excess relative risk $TotERR$ of breast cancer is given by the multiplication of the radiation induced risk and the genetic risk.

$$TotERR(d, a_i, g) = p(a_i, g)(1 + CumERR(d, a_i)) \tag{9}$$

From Eq. (9) the probability $p(d, a, g)$ of breast cancer at age a and gen g can be calculated using a Monte Carlo simulation. The probability $p(d, a, g)$ is given by:

$$p(d, a, g) = \int_{a'=0}^{a} TotERR(d, a', g) da' \qquad (10)$$

Now choose a random number R where $0 \leqslant R \leqslant 1$ and solve for the breast cancer age a_{bc}:

$$R = p(d, a_{bc}, g) \qquad (11)$$

Eq. (11) yields the breast cancer age a_{bc} due to a genetic predisposition given by gen g and a screening programme with dose d.

Now the preclinical age a_{pc} is randomly sampled:

$$a_{pc} = a_{bc} - e^{\mu_{pc} + z_1 \sigma_{pc}} \qquad (12)$$

where the random variable z_1 is given by Eq. (6).

Assuming an exponential growth model, the probability p_{det} that the preclinical tumour will be detected is given by

$$p_{det} = R < s(a) \qquad (13)$$

where again, R is a random number $0 \leqslant R \leqslant 1$ and $s(a)$ is the sensitivity of the screening modality at age a given in Eq. (7).

Finally, the output of the model is given in terms of the number of breast cancers before the screening starts, N_{pre}, the number of detected breast cancers in the screening N_{det}, the number of breast cancers which become clinical during the screening period, the so called interval cancers N_{int}, and the number of breast cancers which become clinical after the end of the screening period N_{end}, where $N_{pre} + N_{det} + N_{int} + N_{end} = N$.

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