Differences in Natural History between Breast Cancers in BRCA1 and BRCA2 Mutation Carriers and Effects of MRI Screening-MRISC, MARIBS, and Canadian Studies Combined


Abstract

**Background:** It is recommended that BRCA1/2 mutation carriers undergo breast cancer screening using MRI because of their very high cancer risk and the high sensitivity of MRI in detecting invasive cancers. Clinical observations suggest important differences in the natural history between breast cancers due to mutations in BRCA1 and BRCA2, potentially requiring different screening guidelines.

**Methods:** Three studies of mutation carriers using annual MRI and mammography were analyzed. Separate natural history models for BRCA1 and BRCA2 were calibrated to the results of these studies and used to predict the impact of various screening protocols on detection characteristics and mortality.

**Results:** BRCA1/2 mutation carriers (N = 1,275) participated in the studies and 124 cancers (99 invasive) were diagnosed. Cancers detected in BRCA2 mutation carriers were smaller [80% ductal carcinoma in situ (DCIS) or ≤10 mm vs. 49% for BRCA1, P < 0.001]. Below the age of 40, one (invasive) cancer of the 25 screen-detected cancers in BRCA1 mutation carriers was detected by mammography alone, compared with seven (three invasive) of 11 screen-detected cancers in BRCA2 (P < 0.0001). In the model, the preclinical period during which cancer is screen-detectable was 1 to 4 years for BRCA1 and 2 to 7 years for BRCA2. The model predicted breast cancer mortality reductions of 42% to 47% for mammography, 48% to 61% for MRI, and 50% to 62% for combined screening.

**Conclusions:** Our studies suggest substantial mortality benefits in using MRI to screen BRCA1/2 mutation carriers aged 25 to 60 years but show important clinical differences in natural history.

**Impact:** BRCA1 and BRCA2 mutation carriers may benefit from different screening protocols, for example, below the age of 40. Cancer Epidemiol Biomarkers Prev; 21(9): 1458–68. © 2012 AACR.

Introduction

Women with a BRCA1 or BRCA2 mutation have a 45% to 87% risk of being diagnosed with breast cancer by the age of 70 (1–3). In comparison with the general population, breast cancer often develops at a younger age and probably with a higher growth rate (4, 5).

Several large studies have evaluated screening of BRCA1/2 mutation carriers using mammography and MRI (6–11). MRI has a much higher sensitivity for detecting invasive cancers especially in dense breasts (12); however, the costs and false-positive rate are higher (13, 14). Because the sensitivity for detecting low-grade...
ductal carcinoma in situ (DCIS) by MRI may be lower, a combination of MRI and mammography screening has been suggested (15–17). Two studies showed that annual screening including MRI significantly reduced the incidence of advanced-stage breast cancer in comparison with control groups outside (7) and within a regular screening program without MRI (18). Because of the expected mortality benefit, breast cancer screening with mammography and MRI is being offered to BRCA1 and BRCA2 mutation carriers, usually starting from the age of 25 to 30 years.

For clinical practice, determination of the optimal use of MRI and mammography at different ages would be very beneficial to prevent high costs for over- or underscreening. MRI without mammography may be sufficient in certain age groups. Also, there may be differences in the optimal screening protocol for BRCA1 and BRCA2 mutation carriers (19, 20) because of differences in natural history of the tumors.

In this study, we combined the results of 3 large studies, the Dutch MRI Screening Study (MRISC: refs. 7, 10), the Canadian study (11), and the UK Magnetic Resonance Imaging Breast Screening Study (MARIBS; ref. 9) to examine screen-detected cancers by mutation, stage, and age. Then, we created separate models for the natural history of BRCA1 and BRCA2 mutation carriers. Using these models, differences in natural history were evaluated. And breast cancer mortality reductions achievable with different screening protocols were predicted, leading to suggestions for possible adaptations of the current screening recommendations.

Materials and Methods

Data from 3 BRCA1/2 screening projects in the Netherlands (MRISC), Canada, and United Kingdom (MARIBS) were combined. Each study included at least 200 BRCA1/2 mutation carriers. Women with breast cancer symptoms were excluded. Women with a history of breast cancer were excluded in MRISC and MARIBS. In the Canadian study, women with a history of breast cancer were eligible if the contralateral breast was not affected. In women who had multiple cancers diagnosed, only the first (if metachronous) or largest tumor (if synchronous) was included.

Description of the studies

The Netherlands (NL). The MRISC study (7, 10) which started in 1999 was designed to assess the efficacy of mammographic and MRI screening in 2,157 women (including 594 BRCA1/2 mutation carriers) with an increased risk of breast cancer due to a family history or a BRCA mutation. Screening consisted of annual mammography and MRI with clinical breast examination (CBE) every 6 months. The target screening ages were 25 to 70 years but could be younger depending on the age the youngest family member was diagnosed. For the present analysis, the data from the BRCA1/2 mutation carriers up to March 2006 are used.

Canada (CA). The Canadian study (11, 18) started in 1997 and included only BRCA1/2 mutation carriers between the ages of 25 and 65 years. The screening consisted of annual mammography, MRI, and ultrasound conducted on the same day with CBE every 6 months. Ultrasound was discontinued after May 2005. The data up to January 2008 are used in our analysis.

United Kingdom (UK). The MARIBS study (9) started in 1997 and included carriers of a BRCA1/2 or TP53 mutation, first-degree relatives, and women with a strong family history of breast and/or ovarian cancer. The screening ages for the BRCA1/2 mutation carriers were in principle 35 to 49 years but could be younger, depending on the age at which a first-degree relative was diagnosed with breast cancer. Screening consisted of annual mammography and MRI, preferably on the same day. For our analysis, the data from the BRCA1/2 mutation carriers up to January 2005 are used.

Statistical analyses

Breast cancer detection rates were calculated as the total number of breast cancers detected (including DCIS) per 1,000 woman-years at risk. A Poisson distribution was used to calculate the 95% confidence intervals (CI). Differences in age at entry and age at diagnosis, stage distribution, interval cancers, and nodal status between the different studies and between BRCA1 and BRCA2 mutation carriers were analyzed by t tests, χ² tests, or Fisher exact tests. A 2-sided P value of <0.05 was considered statistically significant.

MISCAN model

MISCAN is a well-validated microsimulation model used to evaluate various screening programs (21–24). In MISCAN, individual life histories are simulated. The natural history of breast cancer is modeled as a progression through 5 preclinical and invasive disease stages. From each preclinical stage, a tumor may be clinically diagnosed or may grow into the next preclinical stage. By applying screening, the tumor may be detected by screening. Further information on the model can be found in the Supplementary Data.

Application of the model

BRCA1 and BRCA2 were modeled separately for the 3 studies. The number of women participating, the age distribution at entry, the duration of follow-up, and the screening protocols were inputs to the models. The inclusion of women year by year was simulated by reproducing the total number of screening tests conducted. The average screening attendance of the total cohort was 90%. The sensitivity of the tests depended on age, stage of the tumor, and the screening method but was initially assumed to be equal for all studies. Mammographic sensitivities for premenopausal women (under 50 years) and MRI sensitivities were first estimated from the (largest) MRISC study. Stage-specific sensitivities of CBE in women 55 years or older were based on the Canadian Natural History of BRCA1 and BRCA2 Cancers and MRI Screening
National Breast Screening study (23). For women under 50 years, the CBE sensitivity was assumed to be 50% of the sensitivity for women >55 years. For women aged 50 to 55 years, all test sensitivities were linearly interpolated. The estimated values for sensitivities are shown in the Supplementary Table S1.

The models were calibrated using the number of screenings, the number of screen detected cancers and interval cancers, the stage distribution, and the age at diagnosis within each study. Parameters for the onset probability, the distribution of onset of the disease by age, stage durations, and transition probabilities were varied to fit the data of the BRCA1 and BRCA2 mutation carriers separately. Likelihood ratio tests were used to compare the goodness-of-fit.

With the calibrated models, predictions of the number of screen detected and interval cancers, the stage distribution in the study, the mortality reduction and the probability of dying from breast cancer were made for the following screening protocols: (i) annual mammography, (ii) both annual mammography and MRI (screening protocol of the studies), (iii) annual MRI only until the age of 40 and combined annual mammography and MRI thereafter, (iv) annual MRI, and (v) combined annual mammography and MRI until the age of 50, and only annual mammography above the age of 50. In all protocols, women aged 60 to 74 were screened biennially using mammography only. For the Netherlands and Canada, CBE every 6 months was added in all screening protocols.

Results

Combined analysis of the three studies

In total, 1,275 BRCA1/2 mutation carriers (801 BRCA1 and 474 BRCA2) participated in the studies, with 3,432 woman-years at risk. The mean age of the participants at first screening was 41.2 years and the mean age at diagnosis 43.9 years (Fig. 1). The participants completed 5,100 screenings. In total, 124 cancers were detected, of which 108 (87%) were screen-detected (46 in the first round). The detection rate in the first round was 36.1, and in the subsequent rounds, 28.3 per 1,000 woman-years at risk. The cumulative rate was 36.1 per 1,000 woman-years at risk (Table 1).

Several differences between the studies were found. In the Canadian study, the age at entry was significantly higher: mean 44.1 (95% CI, 43.3–45.0) versus 39.2 (95% CI, 38.4–40.0) for the MRISC study and 40.5 (95% CI, 39.9–41.1) for the MARIBS study. More interval cancers were detected for BRCA1 (A) and BRCA2 (B). The bars represent all women, the white bars are the women with breast cancer diagnosed during the study.
Table 1. Number of women, number of screening visits, age at entry and at diagnosis, total number of breast cancers detected, divided into screen-detected (first and subsequent rounds) and interval cancers in the 3 trials

<table>
<thead>
<tr>
<th></th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>Total</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>Total</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>Total</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>Total</th>
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<tr>
<td>Number of women</td>
<td>801</td>
<td>474</td>
<td>1,275</td>
<td>422</td>
<td>172</td>
<td>594</td>
<td>244</td>
<td>212</td>
<td>456</td>
<td>135</td>
<td>90</td>
<td>225</td>
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<td>Woman-years at risk</td>
<td>2,222</td>
<td>1,210</td>
<td>3,432</td>
<td>1,178</td>
<td>408</td>
<td>1,586</td>
<td>789</td>
<td>645</td>
<td>1,434</td>
<td>255</td>
<td>157</td>
<td>412</td>
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<tr>
<td>Mean follow-up, y</td>
<td>2.77</td>
<td>2.55</td>
<td>2.69</td>
<td>2.79</td>
<td>2.37</td>
<td>2.67</td>
<td>3.23</td>
<td>3.04</td>
<td>3.14</td>
<td>1.89</td>
<td>1.74</td>
<td>1.83</td>
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<tr>
<td>Mean age at entry</td>
<td>40.5</td>
<td>42.4</td>
<td>41.2</td>
<td>38.8</td>
<td>40.1</td>
<td>39.2</td>
<td>43.5</td>
<td>44.9</td>
<td>44.1</td>
<td>40.3</td>
<td>40.7</td>
<td>40.5</td>
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<tr>
<td>Number of visits</td>
<td>3,423</td>
<td>1,677</td>
<td>5,100</td>
<td>2,250</td>
<td>780</td>
<td>3,030</td>
<td>825</td>
<td>685</td>
<td>1,510</td>
<td>348</td>
<td>212</td>
<td>560</td>
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<td>Mean age at diagnosis</td>
<td>42.7</td>
<td>45.7</td>
<td>43.9</td>
<td>40.3</td>
<td>42.0</td>
<td>40.9</td>
<td>47.7</td>
<td>50.4</td>
<td>48.9</td>
<td>38.9</td>
<td>43.4</td>
<td>41.1</td>
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<td>Number of cancers</td>
<td>73</td>
<td>51</td>
<td>124</td>
<td>32</td>
<td>17</td>
<td>49</td>
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<td>9</td>
<td>21</td>
<td>9</td>
<td>7</td>
<td>16</td>
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<tr>
<td>Detection ratea</td>
<td>32.5</td>
<td>42.2</td>
<td>36.1</td>
<td>11.8</td>
<td>23.3</td>
<td>15.2</td>
<td>49.2</td>
<td>42.5</td>
<td>46.1</td>
<td>66.7</td>
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<td>71.1</td>
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<td>Subsequent rounds</td>
<td>33</td>
<td>28</td>
<td>61</td>
<td>15</td>
<td>11</td>
<td>26</td>
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<td>11</td>
<td>24</td>
<td>5</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Detection ratea</td>
<td>23.2</td>
<td>38.0</td>
<td>28.3</td>
<td>19.8</td>
<td>46.6</td>
<td>26.2</td>
<td>23.9</td>
<td>25.4</td>
<td>24.5</td>
<td>41.6</td>
<td>89.6</td>
<td>58.8</td>
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<tr>
<td>Interval</td>
<td>8</td>
<td>2</td>
<td>10</td>
<td>6^a</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cumulative rateb</td>
<td>32.9</td>
<td>42.1</td>
<td>36.1</td>
<td>27.2</td>
<td>41.7</td>
<td>30.9</td>
<td>33.0</td>
<td>31.0</td>
<td>32.1</td>
<td>58.8</td>
<td>89.2</td>
<td>70.4</td>
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<tr>
<td>95% CI</td>
<td>25.8–41.3</td>
<td>31.4–55.4</td>
<td>30.1–43.1</td>
<td>18.6–38.4</td>
<td>24.3–66.7</td>
<td>22.9–40.9</td>
<td>21.5–48.3</td>
<td>18.9–47.9</td>
<td>23.5–42.8</td>
<td>32.9–97.0</td>
<td>48.7–149.6</td>
<td>47.1–101.1</td>
</tr>
</tbody>
</table>

aDetection rate per 1,000 woman-years at risk.

bCumulative rate of breast cancer (screen-detected and interval cancers) shown per 1,000 woman-years at risk and 95% CIs.

cIn addition, 4 cancers were interval-detected in women who had not followed the protocol exactly (too long screening interval or no MRI screen) and 2 cancers were detected by prophylactic mastectomy. These 6 interval cancers have not been used in the meta-analysis but have been used in comparisons with the model.

dIn addition, one cancer was detected by prophylactic mastectomy. This cancer has not been used in the meta-analysis but has been used in comparisons with the model.
diagnosed in the MRISC study (7/49 = 14% vs. 1/46 = 2% for the Canadian study and 2/29 = 7% for the MARIBS study). The detection rate per 1,000 woman-years in the MARIBS study was highest with 70.4 (95% CI, 47.1–101.1) versus 30.9 (95% CI, 22.9–40.9) for the MRISC study and 32.1 (95% CI, 23.5–42.8) for the Canadian study.

The age at entry was significantly higher for the BRCA2 mutation carriers than with the BRCA1 mutation carriers: 42.4 (95% CI, 41.6–43.2) for BRCA2 and 40.5 (95% CI, 39.8–41.1) for BRCA1. Below the age of 30, there was only one cancer detected in BRCA2. There was no statistically significant difference in the proportion of interval cancers to the total number of cancers (8/73 = 11% for BRCA1 vs. 2/51 = 4%, P = 0.16).

The tumor stage distribution (DCIS), T1A/T1B (<10 mm), T1C (11–20 mm), T2+ (>20 mm) differed significantly between BRCA1 and BRCA2 (Fig. 2, black bars). The percentages of DCIS and T1A/B tumors were higher for BRCA2 (31% and 49%, respectively) than for BRCA1 (13% and 36%, P < 0.001), whereas the percentages of T1C and T2+ tumors were higher in BRCA1 (29% and 22%, compared with 16% and 4%).

There were no clear trends in stage distribution or nodal status by age group, although the data suggested that the proportion of smaller tumors increased with age (Table 2).

Below the age of 40, only one invasive tumor of 25 screen-detected tumors of BRCA1 mutation carriers was detected by mammography alone, whereas this figure was 7 (3 invasive) tumors of 11 screen-detected tumors in BRCA2 mutation carriers younger than 40 (P < 0.0001, data not shown).

**Modeling of BRCA1 and BRCA2**

First, the model was calibrated to the BRCA1 data (Fig. 3A). The model predicted the age distribution at diagnosis well for this group. When using the same natural history assumptions in the BRCA2 model, the predicted age distribution was less accurate (Fig. 3B). Parameters for the natural history had to be changed considerably to calibrate to the observed cancers by age for BRCA2 (Fig. 3C).

The estimated parameters for the onset probability, the age of onset of the disease, and the stage durations of the best fitted models for the BRCA1 and BRCA2 study data are listed in Supplementary Table S2. Compared with BRCA1, the parameter for the onset probability of breast cancer was lower for BRCA2 (0.543 vs. 0.771 for BRCA1),
leading to predicted lifetime risks of breast cancer diagnosis by the age of 70 of 60% for \textit{BRCA1} and 32% for \textit{BRCA2} in a situation without screening. In particular, the preclinical stage durations, the period during which the cancer is screen detectable, had to be substantially increased for \textit{BRCA2}. The predicted mean preclinical detectable phase for \textit{BRCA1} was 1 to 4 years and for \textit{BRCA2}, 2 to 7 years, increasing with age (data not shown in table). Therefore, the mean preclinical duration in \textit{BRCA2} was 1.6 times longer for women younger than 50 and 2.2 times longer for women older than 50 years, as compared with \textit{BRCA1}.

The revised models predicted the stage distributions for both \textit{BRCA1} and \textit{BRCA2} very well (Fig. 2, white bars).

\textbf{Effects of other screening protocols}

The number of screen-detected and interval cancers, the stage distribution in the studies, the steady-state breast cancer mortality reduction, and the reduction after 25 years of screening were then predicted for various screening protocols (Table 3).

Compared with mammography alone, adding annual MRI resulted in much more favorable stage distributions, with more T1A/B, fewer interval cancers, and larger mortality reductions (from 41.9% to 50.1% for \textit{BRCA1} and from 46.8% to 61.6% for \textit{BRCA2}). Almost the same benefits were obtained when mammography was omitted below the age of 40. When mammography was omitted completely, the predicted mortality reductions were only slightly lower (49.0% for \textit{BRCA1} and 61.0% for \textit{BRCA2}). Mammography screening until the age of 50 and mammography between ages 25 and 60 resulted in a slightly lower mortality reduction for \textit{BRCA1} (48.3%) and a slightly higher mortality reduction for \textit{BRCA2} (61.2%). The probability of dying from breast cancer decreased from 14.0% to 12.2% for \textit{BRCA1} comparing mammography screening with the study screening protocol and from 7.1% to 5.1% for \textit{BRCA2}.

\textbf{Discussion}

The combined data of 3 large trials showed important differences between \textit{BRCA1}- and \textit{BRCA2}-associated breast cancer. \textit{BRCA2} mutation carriers were diagnosed with relatively more DCIS and T1A/T1B tumors and fewer interval cancers, findings which have been found before (4–6, 10, 20). One possible explanation is that the sensitivity of mammography for \textit{BRCA1} tumors may be lower, due to different tumor characteristics (5, 12, 25, 26). These tumors show more continuous pushing margins, thereby mimicking benign lesions on a mammogram. The second explanation is that the growth rate of \textit{BRCA2} tumors is slower (5, 20). Within the model, these 2 explanations have been assessed. Because the separate models for \textit{BRCA1} and \textit{BRCA2} that best fit the study data showed different estimates for the stage durations and transition probabilities (Supplementary Table S2), the second explanation is most plausible. Moreover, by fitting only the mammography and MRI sensitivities and using the same natural history for \textit{BRCA1} and \textit{BRCA2}, the model could not reproduce the results of the studies (data not shown). Therefore, it is unlikely that only a difference in test sensitivity between \textit{BRCA1} and \textit{BRCA2} explains the observed difference in stage distribution and interval cancers in these screening studies.

On the basis of the empirical observations, predictions are made for the duration of the preclinical detectable phase of the tumors and for the lifetime risks. The predicted duration of the preclinical detectable phase was 1.6 to 2.2 times longer for \textit{BRCA2} than for \textit{BRCA1}, which means that \textit{BRCA2} cancers grow more slowly and therefore have a higher probability of being screen-detected. The predicted lifetime risk of breast cancer by the age of 70 without screening was 60% for \textit{BRCA1} and 32% for \textit{BRCA2}. For \textit{BRCA1}, these results comply with published lifetime risks at the age of 70 of 55% to 75% (1–3, 27); for \textit{BRCA2}, the results are close to 45% to 47% (1, 27) but much lower than more recent results of 87% to 88% (2, 3). Although the published estimates also include screen-detected cases, it is possible that the lifetime risk is higher than estimated in our model, which means that screening should detect more cancers and the mortality reduction may be higher.
The study data provide some support for omitting mammography in BRCA1 mutation carriers younger than 40, although mammographic prescreening of women in our studies may have reduced incident mammographic detection. This would comply with recommendations from studies reporting increased breast cancer risk in mutation carriers following exposure to diagnostic radiation at younger age, specifically before the age of 30 (28, 29). The simulations confirmed that for BRCA1/2 mutation carriers, screening with MRI is a valuable addition to mammography screening, especially by detecting more T1A/B tumors. Compared with the study protocol, protocols with MRI and less mammography showed only slightly lower mortality reductions in the models, which means that annual MRI and less mammography screening may be as effective. Several other modeling studies have also found that the effectiveness of screening using MRI is only slightly lower than the effectiveness of screening.

**Figure 3.** The number of diagnoses observed in the 3 trials compared with the number of diagnoses predicted by the MISCAN models: (A) BRCA1, (B) BRCA2 assuming no differences in natural history, and (C) BRCA2 assuming a different natural history.
Table 3. The effects of various annual screen protocols on the number of screen-detected cancers and interval cancers and node positives, as would be detected in the studies, as well as the predicted mortality reduction and probability of breast cancer death.

<table>
<thead>
<tr>
<th></th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Screen</td>
<td>Interval</td>
<td>Screen</td>
</tr>
<tr>
<td>Mammography age (25–60)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCIS</td>
<td>6.6</td>
<td>1.0</td>
<td>13.4</td>
</tr>
<tr>
<td>T1A/B</td>
<td>10.3</td>
<td>3.5</td>
<td>9.0</td>
</tr>
<tr>
<td>T1C</td>
<td>16.5</td>
<td>8.0</td>
<td>7.4</td>
</tr>
<tr>
<td>T2+</td>
<td>11.7</td>
<td>7.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>45.1</td>
<td>20.2</td>
<td>29.9</td>
</tr>
<tr>
<td>Node-positive</td>
<td>11.7</td>
<td>8.1</td>
<td>3.4</td>
</tr>
<tr>
<td>Mortality reductiona</td>
<td>41.9%</td>
<td></td>
<td>46.8%</td>
</tr>
<tr>
<td>Probability BC deathb</td>
<td>14.0%</td>
<td></td>
<td>7.1%</td>
</tr>
<tr>
<td>MRI and mammography (study protocol)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>DCIS</td>
<td>8.5</td>
<td>0.9</td>
<td>16.5</td>
</tr>
<tr>
<td>T1A/B</td>
<td>24.2</td>
<td>2.5</td>
<td>23.0</td>
</tr>
<tr>
<td>T1C</td>
<td>16.4</td>
<td>5.0</td>
<td>6.4</td>
</tr>
<tr>
<td>T2+</td>
<td>11.3</td>
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<tr>
<td>Total</td>
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<td>Node-positive</td>
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<td>Mortality reductiona</td>
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<td>61.6%</td>
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<tr>
<td>Probability BC deathb</td>
<td>12.2%</td>
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<td>5.1%</td>
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<td>MRI age (25–60) mammography age (40–60)</td>
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<tr>
<td>DCIS</td>
<td>6.8</td>
<td>1.1</td>
<td>14.4</td>
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<td>T1A/B</td>
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<td>6.3</td>
</tr>
<tr>
<td>T2+</td>
<td>11.2</td>
<td>5.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>58.3</td>
<td>13.8</td>
<td>43.6</td>
</tr>
<tr>
<td>Node-positive</td>
<td>13.5</td>
<td>5.3</td>
<td>4.6</td>
</tr>
<tr>
<td>Mortality reductiona</td>
<td>49.5%</td>
<td></td>
<td>61.1%</td>
</tr>
<tr>
<td>Probability BC deathb</td>
<td>12.3%</td>
<td></td>
<td>5.2%</td>
</tr>
<tr>
<td>MRI age (25–60) mammography age (25–60)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCIS</td>
<td>5.4</td>
<td>1.2</td>
<td>12.6</td>
</tr>
<tr>
<td>T1A/B</td>
<td>24.0</td>
<td>2.6</td>
<td>22.8</td>
</tr>
<tr>
<td>T1C</td>
<td>15.9</td>
<td>5.4</td>
<td>6.2</td>
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<tr>
<td>T2+</td>
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<td>5.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>56.5</td>
<td>14.4</td>
<td>41.6</td>
</tr>
<tr>
<td>Node-positive</td>
<td>13.4</td>
<td>5.5</td>
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<tr>
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<td>12.5%</td>
<td></td>
<td>5.3%</td>
</tr>
</tbody>
</table>

Abbreviation: BC, breast cancer.

aThe breast cancer mortality reduction in a steady state situation (after 25 years of screening), compared with a situation without screening. Annual screening is assumed from the age of 25 to 60 years with every 6-month CBE. From age 60 to 74, biennial mammography screening is assumed.

bThe probability of breast cancer death is calculated for women who start screening at the age of 30.
using MRI and mammography (30–32), and that screening \( BRCA1/2 \) mutation carriers using MRI and mammography is cost-effective (20, 30–33). However, these modeling studies did not make a distinction between \( BRCA1 \) and \( BRCA2 \). Despite the differences in natural history between \( BRCA1 \) and \( BRCA2 \) in our model, this resulted in only small changes in recommended screening protocols. The predicted mortality reductions are larger for \( BRCA2 \), but due to the increased probability of breast cancer death for \( BRCA1 \), both groups would benefit from (MRI) screening.

At older ages, the proportion of small tumors seemed higher, which corresponds to the estimated increasing preclinical durations and therefore slower growth rate with age. Therefore, higher sensitivity imaging may perhaps be conducted less frequently with increasing age, although we have insufficient data for mutation carriers older than 60.

There were some notable differences between the 3 screening studies. The cumulative incidence was highest in the MARIBS study, especially for the first screening round. This could be due to the stricter selection criteria of the women (34) or because the women received less screening before entering the study. In the Canadian and MRISC study, around 80% of the participating women had already received screening. It is also possible that the breast cancer incidence for \( BRCA1/2 \) mutation carriers in the UK is higher (1). In addition, the mean follow-up was shorter in the MARIBS study. In the MRISC study, more interval cancers were found for \( BRCA1 \). This can possibly be explained by the large proportion of \( BRCA1 \) mutation carriers younger than 35 years (42%, compared with 19% for Canada and 10% for MARIBS).

In the Canadian study, more DCIS and stage T1A/T1B tumors and fewer node-positive tumors were found. This could be due to age differences because women in the Canadian study were somewhat older and 23% were treated for breast cancer before entering the study. Other possible explanations are higher screen test sensitivities, a higher experience level of radiologists, or differences in adherence to the protocol and follow-up.

The optimal screening strategy may also depend on race/ethnicity, because of differences in natural history (24); however, there are not enough data to include race/ethnicity in our mutation carrier models. \( BRCA1/2 \) mutation prevalence is comparable across race/ethnicity, but there are differences in access to genetic testing, screening, and prophylactic surgery (35), which may influence the effects of screening.

The strength of this study is the large data set from the combined studies. This allows for the estimation by modeling of different natural history of these tumors and predictions of the effects of screening strategies. This method also has several limitations, due to the estimation of model parameters on data from relatively small studies. The models are based on the number of cancers found in the studies. Although 3 studies with \( BRCA1/2 \) mutation carriers have been combined, the overall numbers are still relatively small, and there was only a small proportion of women older than 50. In addition, prior prophylactic mastectomy and screening history of the participating women could not be taken into account. A substantial proportion of the women was screened with mammography before entering the study. Also, the breast cancer incidence without screening is unknown, and because women treated for breast cancer before entering the study are mostly excluded from the studies, these cancers are missing in the model, which will affect the screening results. The survival estimates are based on the age- and stage-specific survival for noncarriers, but \( BRCA1 \) mutation carriers particularly may have a different survival because of different tumor characteristics but higher sensitivity to (adjuvant) chemotherapy (36, 37). Furthermore, some parameters in the model are interchangeable. This means that with different combinations of parameters, the same outcomes can be obtained, for example, the combination of incidence, sensitivity, and transition durations. Despite the uncertainties, the models reproduce the study results and therefore can be used to predict the effects of screening, which are difficult to obtain by trials.

In conclusion, this study suggests substantial mortality benefits in using MRI to screen \( BRCA1/2 \) mutation carriers aged 25 to 60 but showed that there are important differences in the natural history of breast cancers in \( BRCA1 \) as compared with \( BRCA2 \) mutation carriers which suggests that the optimal screening regimen may be different. For both \( BRCA1/2 \) mutation carriers, at least annual MRI until the age of 60 is recommended because of the substantial estimated mortality reduction. We have insufficient data for or against MRI screening of mutation carriers older than 60.

Disclosure of Potential Conflicts of Interest

E. Warner had reported receiving consulting/advisory fees from Bayer Pharmaceuticals. P.A. Causer and D.B. Plewes have reported receiving consulting/advisory fees from Sentinelle Medical. D.B. Plewes reported ownership interest for Sentinelle Medical and General Electric. R.A. Eeles has received an educational grant from Vista diagnostics. M.O. Leach has received salary as a Director of a company (Specialty Scanners) developing dedicated MRI scanners for breast cancer. The company also receives grant funding from the UK Technology Strategy Board. M.O. Leach is employed by the Institute of Cancer Research (University of London) which holds patents on density measurement using MRI and may reward staff should these be licensed. His department has research agreements with Philips, Siemens, and General Electric, who may contribute to travel funding. M.O. Leach has performed paid consultancy for Roche. No potential conflicts of interest were disclosed by the other authors. None of the funders had any role in the conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Authors’ Contributions


Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): E.A.M. Heijnsdijk, E. Warner, F.J. Gilbert, M.M.A. Tilanus-Linthorst (did not conduct the statistical analyses but did


Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): R. Kaas, E.A. Ramsay, K.A. Hill, M.J. Hoping, D.B. Plewes.

Study supervision: M.M.A. Tilanus-Linthorst, E.J.T. Rutgers, M.O. Leach, H.J. de Koning.

Study coordinator (MRISC study): J.G.M. Klijn.

Development and support of MRI technology throughout the study: D.B. Plewes.

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References


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Eveline A.M. Heijnsdijk, Ellen Warner, Fiona J. Gilbert, et al.


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