ARTICLE

Impact of Early Breast Cancer Screening on Mortality Among Young Survivors of Childhood Hodgkin’s Lymphoma

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Abstract

Background: Female survivors treated with thoracic radiation therapy (RT) for childhood cancer experience increased risks of breast cancer (BC). There are currently no data quantifying the potential mortality gains of early BC screening among such survivors.

Methods: A mathematical model of BC development was used to evaluate the marginal benefit of early-initiated screening of female survivors of adolescent Hodgkin’s lymphoma (HL) starting at age 25 years on BC mortality compared with screening initiated at age 40 years. Sensitivity analyses were performed to evaluate the robustness of the estimates over a plausible range of conditions.

Results: For survivors treated at age 15 years, the absolute risk of BC mortality by age 75 years was predicted to decrease from 16.65% with no early screening to 16.28% (annual mammography), 15.40% (annual MRI), 15.38% (same-day annual mammography and MRI), and 15.37% (alternating mammography and MRI every six months). Approximately 80 patients would need to be invited to MRI-based screening to prevent one BC death. In sensitivity analyses, the number needed to invite to MRI-based screening to prevent one BC death ranged from 71 to 333. Combinations of MRI plus mammography were predicted to produce 99.52 false positives per 1000 screenings done between age 25 to 39 years.

Conclusions: These findings are the first to indicate that early MRI-based screening should reduce BC mortality among women treated with RT for adolescent HL. The magnitude of this benefit is superior to that described for other accepted screening indications although MRI can produce a substantial rate of false-positive results.
undertaken in the foreseeable future. To address this clinical uncertainty, we conducted mathematical simulations under a range of clinically plausible conditions to quantify the potential benefit of early BC screening using different screening modalities among women treated with mediastinal RT for Hodgkin’s lymphoma in adolescence.

Methods

Description of the Model

We modeled the health outcomes of a simulated cohort of 100,000 female patients treated at age 15 years with mediastinal RT for HL and followed from age 25 to 75 years under different BC screening protocols. We evaluated the benefit of the early initiation of high-risk screening beginning at age 25 years, consistent with Children’s Oncology Group guidelines (4), compared with average-risk screening initiated at age 40 years (8). Screening was continued until age 74 years in all scenarios. We assumed that all women did not have clinically detectable BC when they started screening at age 25 years. A schematic of the simulation model is shown in Figure 1.

Breast Cancer Incidence and Natural History

The annual incidence of BC among survivors was derived from epidemiologic studies of female HL survivors treated with mediastinal RT (1–9,13). Relative risks (declining in a piecewise linear fashion from 60 at age 25 years to 7.5 at age 40 years to 2.0 at age 65 years) were used as multipliers to the age-specific BC incidence rates for the general US female population age 25 to 75 years to derive cumulative incidence rates, adjusted to account for competing risks of death (10–12,14–16). The model was calibrated to produce a cumulative incidence of BC compatible with that described in cohort studies of adolescent females treated with mediastinal RT (10–12). From these incidence models, we estimated the number of survivors in our simulated cohort who would be expected to develop BC and the age of their BC occurrence.

The growth of breast tumors was simulated using a continuous time, parametric, stochastic model described previously (17,18). We programmed the model in R following the detailed specifications given in Flevritis et al. (18) and include additional details in the Supplementary Methods (available online). The model generates an individual growth rate and simulates the time course, stage, and volume for the growth of a tumor starting from a diameter of 2 mm to eventual detection, with possible transitions to regional and metastatic stages. Based on available evidence, the baseline model assumed that breast tumors arise earlier in life in HL survivors than in the general population but with a similar growth rate once occurring. These assumptions were tested as described below. The generated age at clinical detection was aligned with the BC incidence from the epidemiologic incidence model. This yields a cohort in which some women develop BC with an age-specific incidence and stage distribution that is controlled by the underlying natural history model, and consistent with available data.

Screening and Detection

Once an individual patient’s BC natural history was simulated, various screening protocols starting at age 25 years were overlaid to predict when and how the tumor would be detected. The sensitivity and specificity of mammography and MRI were derived from studies of average- and high-risk populations (Table 1; Supplementary Methods, available online) (19–25). When an enlarging tumor exceeded specific size thresholds, it became screen-detectable. Based on work described previously, 5 mm tumors were considered potentially MRI detectable and mammographically visible tumors had a median detection size of 10 mm (17,18).

We evaluated the following screening scenarios: 1) average-risk screening: annual mammography from age 40 to 74 years; 2) early mammography: annual mammography from age 25 to 74 years;
Table 1. Parameter input values for breast cancer screening model

<table>
<thead>
<tr>
<th>Description of input parameter/source</th>
<th>Values</th>
<th>Range of values in sensitivity analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-specific breast cancer incidence rates for US female population age 25–75 y (14)*</td>
<td>From SEER</td>
<td>N/A</td>
</tr>
<tr>
<td>Relative risk of breast cancer incidence for HL survivors vs the general population (assumed to be a piecewise linear function) (10–12,14–16)*</td>
<td>60 at age 25 y to 7.5 age 40 y to 2.0 at age 65+ y</td>
<td>Risk reduction by 65%, 75%</td>
</tr>
<tr>
<td>Plevritis model parameters fitted to historical breast cancer data (18,43,44)</td>
<td>8.32</td>
<td>(4.16, 16.64)</td>
</tr>
<tr>
<td>Mean tumor doubling time (mo)</td>
<td>10 mm</td>
<td>Not varied</td>
</tr>
<tr>
<td>Mammogram screening characteristics (19–23,25)†</td>
<td>Sensitivity (at age &lt; 50, age 50+ y) Specificity (at age &lt; 50, age 50+ y) Mammogram tumor size detection threshold (median)</td>
<td>(75,85) (97,97) 10 mm</td>
</tr>
<tr>
<td>MRI screening characteristics (22–25)†</td>
<td>Sensitivity (first 2 screens, all subsequent) Specificity (first 2 screens, all subsequent) MRI tumor size detection threshold</td>
<td>(92,90) (91,93) 5 mm</td>
</tr>
<tr>
<td>Compliance with screening protocols (20,21,24–28) (% complete compliance, % partial compliance, % noncompliance)</td>
<td>(65/25/10)</td>
<td>(33/33/34), (90/0/10)</td>
</tr>
<tr>
<td>Age- and stage-specific breast cancer cumulative survival rates in general population (31–33)</td>
<td>50% increase</td>
<td>Equivalent to general population, 20% reduction</td>
</tr>
<tr>
<td>Relative mortality of HL survivors with breast cancer patients have 50% higher mortality than general population (30,31)*</td>
<td>From SEER</td>
<td>N/A</td>
</tr>
<tr>
<td>Age-specific US female mortality rates (34)*</td>
<td>From NCHS</td>
<td>N/A</td>
</tr>
<tr>
<td>Annual relative survival for HL survivors, survived to age 25 y, who did not die of breast cancer (31,34)*</td>
<td>From SEER</td>
<td>Risk reduction by 10%, 65%</td>
</tr>
<tr>
<td>Model-estimated cumulative breast cancer incidence in a simulated unscreened cohort, % (10–12)†</td>
<td>At age 40 y At age 50 y At age 60 y</td>
<td>13.51 27.29 36.66</td>
</tr>
<tr>
<td>Model-estimated 10-year mortality after breast cancer diagnosed age 25–39 y, in a simulated unscreened cohort, % (32,33)</td>
<td>Local stage Regional stage Distant stage</td>
<td>N/A (model output) 31.26 58.53 92.43</td>
</tr>
<tr>
<td>Model-estimated cumulative mortality because of all other causes in a simulated unscreened cohort</td>
<td>At age 40 y At age 50 y At age 60 y</td>
<td>8.3 22.0 34.4</td>
</tr>
</tbody>
</table>

* Detailed annual inputs are available in the Supplementary Methods (available online). NCHS = National Center for Health Statistics; SEER = Surveillance Epidemiology and End Results.
† Comparative values from published studies available in the Supplementary Methods (available online).

3) early MRI: annual MRI from age 25 to 39 years, then annual mammography + MRI from age 40 to 74 years; 4) early same-day mammography + MRI: annual mammography + MRI performed at same time from age 25 to 74 years; 5) early alternating mammography + MRI: annual mammography + annual MRI alternating q6 monthly from age 25 to 74 years. The baseline schedule of average-risk screening reflects recommendations from the American Cancer Society (8) that were selected because they recommend starting earlier and imaging more frequently than other analogous recommendations, which seemed appropriate given the nature of the cohort. Compliance rates were based on published reports of compliance in clinical trials of BC screening (22,23,26–30), with 65% of women fully compliant, 25% partly compliant (attending half of their annual screenings), and 10% noncompliant.

A tumor was designated as “screen-detected” when the survivor attended screening, her tumor was larger than the mammographic or MRI detection threshold, and the screening test returned a positive result. Alternatively, a tumor was designated as “clinically detected” at the simulated age of BC incidence, provided no previous positive screening tests had occurred. There was a small increase in MRI specificity and a decrease in sensitivity after the first two screening rounds, but otherwise we assumed that the results of repeated screens on the same woman were independent.

Mortality Component

For the modeled cohort, two survival times were calculated, one for BC-related deaths and one for all other causes of death. Age- and stage-matched BC survival rates for patients with BC in the general population were obtained from SEER (31). In the baseline scenario, HL survivors were modeled to have 50% higher stage- and age-specific BC mortality rates than the general population.
based on published studies (32,33). Using these sources, survival times from BC diagnosis were calculated for all subjects developing BC in the simulations. Given that SEER provides survival times in five-year increments, we assumed a uniform distribution of survival within each five-year interval following diagnosis. Breast cancer survival was only determined for subjects labeled in the model iteration as developing BC.

To account for competing risks of non-BC death, we extracted annual relative survival data from SEER for women with a primary HL diagnosis before age 18 years who were diagnosed between 1973 and 2008, known to have survived to age 25 years, and did not die of BC. The annual relative survival rates for age 25 to 40 years ranged from between 98.56% and 100.07% (median = 99.59%). Because of sparse data after age 40 years, we assumed a relative survival of 98.50%. Annual survival rates were then calculated by comparison with standard 2008 age-specific US mortality rates obtained from the National Center for Health Statistics (34). The final simulated age at death was the lesser of age at death because of BC (for those developing BC) and age at death because of any non-BC cause. Mortality was considered up to age 75 years, at which point the simulation model stopped. Breast cancer mortality and mortality from all other causes were treated as competing risks for death.

Outcome Measures

The screening protocols were assessed by estimating the cumulative mortality because of BC up to age 75 years in the entire cohort invited to screening and among those diagnosed with BC from age 25 to 39 years. We also examined the number of BC deaths prevented per 1000 screened (or invited) from age 25 to 39 years compared with average-risk mammographic screening starting at age 40 years, and the number needed to screen with an early-onset screening protocol to prevent one BC death. BC deaths prevented was calculated by comparing the number of BC deaths occurring among the same cohort of women simulated to undergo either one of the early-screening scenarios or average-risk screening. For each early-onset screening scenario, we determined the number of BC deaths occurring in the subcohort of women screened at least once from age 25 to 40 years and compared this with the number of BC deaths occurring had the same women undergone the average-risk screening scenario. Note that the set natural histories of disease in the cohorts are the same; only the screening scenarios differ. The difference between these two numbers was the number of BC deaths prevented through early screening. Dividing this by the subcohort size and multiplying by 1000 gives the number of BC deaths prevented per 1000 screened. The number needed to invite is a comparable comparison but compares BC deaths among all “invited” subjects, including those who are modeled as completely non-compliant with screening.

We also report the lead time (years between a screen diagnosis and the potential clinical diagnosis) and the false positives per 1000 screens and per woman screened. The latter is the proportion of screens in breast-cancer-free women age 25 to 39 years who are incorrectly positive, reported as the average number of false positives an ever-screened woman experiences over the course of the screening protocol from age 25 to 74 years. Finally, we report the proportion of overdiagnosed cases. A BC casework as defined as overdiagnosed if screen-detected before age 40 years in a women who, in the absence of screening, would have died from non-BC related causes before her BC would have been clinically detected.

For the primary analyses, median estimates and bootstrap 95% confidence intervals were based on 250 Monte Carlo replicates of 100 000 individuals. Estimates for the sensitivity analyses were based on 50 replicates. All statistical analyses were performed with R 2.14.2 (http://cran.r-project.org).

Sensitivity Analyses

One-way sensitivity analyses were run to evaluate the stability of our results to variations in the model inputs. Factors that were varied included tumor growth rate, BC incidence, BC mortality, all-cause mortality in HL survivors, the sensitivity and specificity of the screening tests, and compliance rates (Supplementary Table 1, available online). The goal of the one-way sensitivity analysis was to evaluate the effect of changing model inputs to what were deemed to be extreme levels. Additional best- and worst-case scenarios were run, in which all input variables were set to maximize or minimize the effect of screening or to examine the most extreme results produced by the model. This gives upper and lower bounds on what one might expect the effects of screening to be over a wide range of clinically plausible settings.

Results

Model Performance Compared With Published Epidemiologic and Clinical Data

The model-estimated cumulative incidence of BC among survivors at ages 40, 45, 50, and 60 years were 13.51%, 20.74%, 27.29%, and 36.66% respectively, which are consistent with observed outcomes in observational studies (Supplementary Methods, available online) (1,11,26,27). With the assumption of 90% compliance with mammographic screening alone, 64.14% of BCs were identified with mammography, with 75.87% node-negative, 22.67% node-positive, and 1.46% metastatic disease, respectively. The overall five-year survival after a BC diagnosis between age 25 and 39 years was 73.64%. These estimates are consistent with clinical reports of female HL survivors with good compliance to early mammographic screening protocols (23,28).

Early Mammographic Screening

Early annual mammographic screening with moderate (65/25/10) compliance increased the proportion of cases diagnosed at localized stages prior to age 40 years (Table 2). In the whole cohort screened to age 75 years, the early initiation of annual mammographic screening was estimated to reduce the absolute risk of BC death from 16.65% to 16.28% by age 75 years compared with average-risk screening starting at age 40 years (Table 3 and Figure 2A). With moderate compliance, just over 259 women would have to be invited to early mammographic screening to prevent one BC death over the full course of the screening program, or, alternatively, 3.86 BC deaths would be prevented per 1000 women invited and moderately compliant with a mammographic screening program (Table 3).

Early MRI Screening

Moderate compliance with MRI screening alone further reduced the proportion of node-positive and metastatic disease, and increased the proportion of early-stage cancers diagnosed before age 40 years to 86.88%. Among all subjects, early MRI screening alone was predicted to reduce BC mortality by age 75 years to
Table 2. Modeled clinical characteristics of breast cancers diagnosed before age 40 years with different screening protocols among female survivors of childhood Hodgkin’s lymphoma

<table>
<thead>
<tr>
<th>Screening outcome†</th>
<th>Average-risk screening</th>
<th>Mammography only</th>
<th>MRI only</th>
<th>Same-day mammography + MRI</th>
<th>Alternating mammography + MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size distribution, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 cm</td>
<td>34.12</td>
<td>66.68</td>
<td>81.02</td>
<td>81.66</td>
<td>83.01</td>
</tr>
<tr>
<td>2–5 cm</td>
<td>52.78</td>
<td>24.21</td>
<td>12.40</td>
<td>11.94</td>
<td>11.38</td>
</tr>
<tr>
<td>&gt;5 cm</td>
<td>13.13</td>
<td>9.12</td>
<td>6.62</td>
<td>6.42</td>
<td>5.63</td>
</tr>
<tr>
<td>Tumor stage distribution, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>50.82</td>
<td>73.68</td>
<td>86.88</td>
<td>87.31</td>
<td>88.14</td>
</tr>
<tr>
<td>Regional</td>
<td>44.15</td>
<td>24.51</td>
<td>12.12</td>
<td>11.73</td>
<td>10.97</td>
</tr>
<tr>
<td>Distant</td>
<td>5.04</td>
<td>1.78</td>
<td>1.00</td>
<td>0.96</td>
<td>0.88</td>
</tr>
<tr>
<td>Protocol sensitivity, %</td>
<td>-</td>
<td>74.98</td>
<td>90.26</td>
<td>91.97</td>
<td>91.91</td>
</tr>
<tr>
<td>Protocol specificity, %</td>
<td>-</td>
<td>97.00</td>
<td>92.83</td>
<td>90.05</td>
<td>90.05</td>
</tr>
<tr>
<td>Mode of detection, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical detection</td>
<td>100.0</td>
<td>41.65</td>
<td>20.75</td>
<td>19.92</td>
<td>16.61</td>
</tr>
<tr>
<td>Mammogram only</td>
<td>0.0</td>
<td>58.35</td>
<td>0.00</td>
<td>2.14</td>
<td>7.19</td>
</tr>
<tr>
<td>MRI only</td>
<td>0.0</td>
<td>0.00</td>
<td>79.25</td>
<td>64.72</td>
<td>55.46</td>
</tr>
<tr>
<td>Mammogram + MRI</td>
<td>0.0</td>
<td>0.00</td>
<td>0.00</td>
<td>13.22</td>
<td>20.74</td>
</tr>
<tr>
<td>Lead time among cases, y</td>
<td>-</td>
<td>1.50</td>
<td>3.35</td>
<td>3.33</td>
<td>3.24</td>
</tr>
<tr>
<td>Proportion of cases overdiagnosed, %</td>
<td>-</td>
<td>1.76</td>
<td>3.58</td>
<td>3.57</td>
<td>3.51</td>
</tr>
<tr>
<td>No. false positives per 1000 screens</td>
<td>-</td>
<td>29.98</td>
<td>71.71</td>
<td>99.52</td>
<td>99.52</td>
</tr>
<tr>
<td>No. false positives per woman screened</td>
<td>-</td>
<td>0.35</td>
<td>0.83</td>
<td>1.15</td>
<td>1.15</td>
</tr>
</tbody>
</table>

* Average-risk screening = annual mammography age 40–74 years; early mammography only = annual mammography age 25–74 years; early magnetic resonance imaging (MRI) only = annual MRI age 25–39 years, then annual mammography + MRI age 40–74 years; early alternating mammography + MRI = annual mammography alternating q6 monthly with annual MRI age 25–74 years; MRI = magnetic resonance imaging.
† All results are for breast cancers detected during early screening from age 25–39 years.

15.40%. With moderate compliance, approximately 80 women would require invitation to early MRI screening to prevent one BC death by age 75 years compared with average-risk mammographic screening (ie, 12.48 BC deaths would be prevented per 1000 women invited for early screening).

Combinations of MRI and Mammography

Among all subjects, same-day MRI plus mammography reduced the absolute risk of death from BC mortality by age 75 years to 15.38%, and with moderate compliance approximately 79 women would require invitation to combined screening to prevent one BC death (Table 3). Compared with MRI alone, the benefit of early-initiated mammography required 7692 women to be invited to screening with both modalities over the full course of the screening program to prevent one additional BC death.

Alternating MRI and mammography every six months produced a negligible reduction in BC mortality compared with same-day imaging (15.37% vs 15.38% by age 75 years) and a slightly smaller number needed to invite (~78) to save one life (Table 3). Compared with MRI screening alone, an additional 2532 patients would need to be invited to additional alternating mammography to prevent one additional BC death.

False Positives and Overdiagnosis

MRI was predicted to substantially increase the proportion of false-positives to 71.71 per 1000 screens, as compared with mammography alone, which was predicted to produce 30 false positives per 1000 screens. Combinations of MRI plus mammography were predicted to produce 99.52 false positives per 1000 screens done between age 25 and 39 years (Table 2). Extended over the course of the screening program to age 75 years, at least one false positive result would be expected to occur in 48% of women when screened with mammography, 74% when screened with MRI alone, and 79% when screened with both modalities.

The proportion of overdiagnosed BC cases during age 25 to 39 years following screening with mammography, MRI, or both modalities was predicted to be 1.76%, 3.58%, and 3.57%, respectively (Table 2).

Sensitivity Analyses

Most young women treated for HL who are currently emerging into an age of screening eligibility will have received treatment that more effectively cures HL with lower normal tissue radiation doses and potentially lower risks of BC and other delayed causes of mortality than the treatments that are the epidemiologic basis for quantifying second cancer risk (2). Based on dosimetry and clinical outcome studies of patients treated with more modern RT techniques in the context of combined-modality therapy, we evaluated the effect of screening with the relative risk of BC reduced by 65% and the risk of non-BC mortality is reduced by 10% (2). The absolute BC mortality by age 75 associated with mammography alone, MRI alone, or both simultaneously was 5.87%, 5.57%, and 5.56%, respectively, compared with 6.00% with no early screening (Table 4 and Figure 2B). The relative reductions in BC mortality for these screening interventions vs no early screening were 2.17%, 7.17%, and 7.33 %, respectively (Table 4 and Figure 2B). The numbers needed to invite to early screening to prevent one BC death were 769, 231, and 231, respectively.

In one-way sensitivity analyses, the greatest loss of effectiveness was seen in the scenario of a 75% reduction in BC risk, in
Table 3. Results of early breast cancer screening from age 25 compared with average risk screening from age 40 in survivors of childhood Hodgkin’s lymphoma*

<table>
<thead>
<tr>
<th>Screening outcome</th>
<th>Average-risk screening starting age 40 y (95% CI)</th>
<th>Mammography only (95% CI)</th>
<th>MRI only (95% CI)</th>
<th>Same-day mammography + MRI (95% CI)</th>
<th>Alternating mammography + MRI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative mortality at age 75 y in breast cancer cases diagnosed from age 25-39 y, %*</td>
<td>71.38 (71.31 to 71.48)</td>
<td>65.08 (64.96 to 65.14)</td>
<td>59.23 (59.16 to 59.27)</td>
<td>59.09 (59.02 to 59.13)</td>
<td>58.87 (58.83 to 58.93)</td>
</tr>
<tr>
<td>Because of breast cancer</td>
<td>27.61 (27.53 to 27.67)</td>
<td>32.08 (32.00 to 32.15)</td>
<td>35.06 (34.99 to 35.13)</td>
<td>35.16 (35.10 to 35.27)</td>
<td>35.28 (35.25 to 35.37)</td>
</tr>
<tr>
<td>All other mortality</td>
<td>16.65 (16.64 to 16.67)</td>
<td>16.28 (16.26 to 16.29)</td>
<td>15.40 (15.39 to 15.42)</td>
<td>15.38 (15.37 to 15.41)</td>
<td>15.37 (15.36 to 15.40)</td>
</tr>
<tr>
<td>Cumulative mortality at age 75 y in full cohort, %†</td>
<td>52.53 (52.50 to 52.57)</td>
<td>52.93 (52.91 to 52.96)</td>
<td>53.35 (53.33 to 53.39)</td>
<td>53.36 (53.32 to 53.39)</td>
<td>53.37 (53.35 to 53.42)</td>
</tr>
<tr>
<td>Breast cancer deaths prevented per 1000 screened†</td>
<td>4.29 (4.12 to 4.41)</td>
<td>13.92 (13.76 to 14.04)</td>
<td>14.02 (13.86 to 14.18)</td>
<td>14.35 (14.13 to 14.48)</td>
<td></td>
</tr>
<tr>
<td>No. needed to screen to prevent one breast cancer death†</td>
<td>233.24 (226.90 to 242.48)</td>
<td>71.85 (71.20 to 72.66)</td>
<td>71.31 (70.39 to 72.08)</td>
<td>69.69 (69.15 to 70.76)</td>
<td></td>
</tr>
<tr>
<td>Breast cancer deaths prevented per 1000 invited to screen†</td>
<td>3.86 (3.71 to 3.97)</td>
<td>12.48 (12.36 to 12.63)</td>
<td>12.62 (12.49 to 12.75)</td>
<td>12.88 (12.72 to 13.00)</td>
<td></td>
</tr>
<tr>
<td>No. needed to invite to prevent one breast cancer death†</td>
<td>259.07 (251.89 to 268.46)</td>
<td>80.10 (79.24 to 80.91)</td>
<td>79.27 (78.43 to 80.19)</td>
<td>77.64 (76.95 to 78.62)</td>
<td></td>
</tr>
</tbody>
</table>

* Refers to cumulative mortality by age 75 years in patients diagnosed with breast cancer before age 40 years. Breast cancer mortality and all other causes of mortality are treated as competing risks of death. CI = confidence interval; MRI = magnetic resonance imaging.

† Refers to outcomes in full cohort screened from age 25-74 years, compared with the referent of average-risk screening with mammography starting at age 40 years.
which case approximately 333 patients would have to be invited to MRI screening or 1150 to mammographic screening in order to prevent one BC death. In a scenario in which all input variables were set to maximize the incidence of BC mortality, 94.07 to 96.95 patients would have to be invited to early MRI-based screening to prevent one BC death, whereas when BC mortality was minimized these values were 833.33 to 840.34 invitations per BC death prevented (Supplementary Table 1, available online).

Discussion

One of the most appealing methods of reducing the morbidity of late-onset treatment toxicity is to detect asymptomatic disease before it causes clinical problems. Consequently, expert consensus guidelines recommend early screening for BC, colorectal cancer, and heart disease among selected asymptomatic survivors based on treatment exposures (4,5,35). However, a major limitation of these recommendations is the lack of data to indicate the extent to which early screening will improve the health outcomes among survivors.

This study provides the first quantitative evidence that the early initiation of BC screening will reduce BC mortality among female survivors of adolescent HL treated with mediastinal RT. Two hundred and sixty high-risk survivors treated at age 15 years would have to be invited to start mammographic screening at age 25 years, or 80 invited to MRI screening, to prevent one BC death. In sensitivity analyses spanning a range of plausible clinical circumstances, early screening was consistently predicted to reduce absolute BC mortality, with the major limitation of MRI-based screening being the high risk of false positives over the course of a screening program.

Figure 2. Modeled cumulative incidence of breast cancer mortality among female survivors of adolescent Hodgkin’s lymphoma treated with mediastinal radiation therapy and moderate compliance to different screening regimens. A) Assuming breast cancer incidence and competing risks of death based on epidemiologic studies with long-term follow-up. B) Assuming reduced breast cancer incidence and competing risks of death based on studies describing reduced normal tissue dose with involved-field radiation therapy.
**Table 4.** Results of early breast cancer screening from age 25 years compared with average risk screening from age 49 years in survivors of childhood Hodgkin’s lymphoma - 65% reduction in breast cancer risk, 10% reduction in non-breast cancer mortality

<table>
<thead>
<tr>
<th>Screening outcome</th>
<th>Average-risk starting at age 40 y (95% CI)</th>
<th>Mammography only (95% CI)</th>
<th>MRI only (95% CI)</th>
<th>Same-day mammography + MRI (95% CI)</th>
<th>Alternating mammography + MRI (95% CI)</th>
</tr>
</thead>
</table>
| Cumulative mortality at age 75 y in breast cancer cases diagnosed from age 25–39 y, %  
Because of breast cancer | 72.97 (72.87 to 73.08) | 66.64 (66.58 to 66.73) | 60.78 (60.67 to 60.85) | 60.66 (60.58 to 60.76) | 60.51 (60.41 to 60.60) |
| All other mortality | 26.03 (25.95 to 26.14) | 30.35 (30.29 to 30.45) | 33.22 (33.14 to 33.31) | 33.24 (33.13 to 33.34) | 33.33 (33.20 to 33.45) |
| Cumulative mortality at age 75 y in full cohort, %†  
Because of breast cancer | 6.00 (5.99 to 6.02) | 5.87 (5.86 to 5.88) | 5.57 (5.56 to 5.58) | 5.56 (5.56 to 5.58) | 5.56 (5.55 to 5.56) |
| All other mortality | 54.22 (54.18 to 54.25) | 54.36 (54.32 to 54.38) | 54.50 (54.45 to 54.53) | 54.49 (54.46 to 54.52) | 54.51 (54.46 to 54.5) |
| Breast cancer deaths prevented per 1000 screened† | - | 1.44 (1.32 to 1.56) | 4.83 (4.71 to 4.95) | 4.81 (4.70 to 4.92) | 4.95 (4.86 to 5.04) |
| No. needed to screen to save one life† | - | 694.08 (635.71 to 748.31) | 207.07 (201.41 to 212.16) | 207.68 (203.28 to 212.69) | 201.98 (198.54 to 206.01) |
| Breast cancer deaths prevented per 1000 invited to screen† | - | 1.29 (1.20 to 1.41) | 4.34 (4.23 to 4.48) | 4.33 (4.23 to 4.42) | 4.45 (4.39 to 4.54) |
| No. needed to invite to save one life† | - | 769.28 (709.28 to 829.89) | 230.68 (223.71 to 236.69) | 230.95 (225.49 to 236.69) | 224.72 (220.26 to 227.79) |

* Refers to cumulative mortality by age 75 years in patients diagnosed with breast cancer before age 40 years. Breast cancer mortality and all other causes of mortality are treated as competing risks of death. MRI = magnetic resonance imaging.

† Refers to outcomes in full cohort screened from age 25–74 years, compared with the referent of average-risk screening with mammography starting at age 40 years.
The absolute reduction in BC deaths expected with early screening compares favorably with that described for well-established screening indications. For example, analyses of several BC screening trials suggest that that approximately 350 to 400 women would need 10 or more years of annual mammographic screening starting at age 50 years to prevent one BC death (36,37), and other studies have estimated that 1339 women age 50 to 59 years would need to be invited to a screening program to prevent one BC death (37). Duffy et al. estimated that the UK Breast Screening Program prevented 5.7 BC deaths prevented per 1000 women screened for 20 years starting at age 50 years (38), while our work suggests that 13.92 to 14.35 BC deaths are prevented with early MRI-based screening among young HL survivors screened over a 24-year period.

Our results support the use of MRI screening in HL survivors treated in adolescence, finding consistent with studies of other high-risk populations (36). However, the use of MRI was predicted to increase the proportion of women experiencing a false-positive test and 79% of women were predicted to experience at least one false positive over the course of the screening program when both modalities were used, and this could increase the anxiety associated with screening (39). In addition, approximately 3.6% of detected cancers were overdiagnosed, affecting less than 1% of screened patients. This rate is substantially lower than that estimated for average-risk screen-eligible patients (typically ~20%) (40), but slightly higher than the overdiagnosis rate estimated for BRCA2 carriers undergoing MRI screening (2.2%) (17), likely because of the higher risk of non-BC mortality among middle-aged HL survivors.

The incremental reduction in BC mortality because of mammography when added to MRI screening has not been evaluated for high-risk survivors. Our findings indicate that the absolute gain compared with MRI alone is likely to be very small, with a large number of patients requiring additional screening to save one additional life. However, the model employed did not include DCIS as part of the natural history because little is known about its progression, particularly in the setting of prior RT. Including a DCIS phase would require additional assumptions regarding the proportion of cases that progress to invasive disease and the rate at which this progression occurs. The model used here assumes that DCIS does not contribute to BC mortality and its detection and treatment would not substantially reduce BC mortality among screened patients. In our view, the most important limitation of this assumption arises from the observation that mammography can detect calcifications associated with DCIS that may be missed by MRI. Consequently, mammographic detection of DCIS may be beneficial by allowing premalignant lesions to be treated without systemic therapy, and this benefit would not be revealed in this study. Our view is that these issues should be discussed with patients when developing an individual screening strategy.

Among HL survivors undergoing mammographic screening, a substantial proportion of BCs are detected clinically in the interval between annual imaging (41,42). Our results estimated that 41.7% of survivors developing BC after being invited to undergo mammography would have their tumor detected clinically, compared with 20.8% of patients invited to undergo MRI screening. The high rate of clinical detection raises the possibility that alternating MRI with mammography every six months may be preferable, and while this screening protocol yielded the lowest BC mortality rate, the additional gain over MRI alone was small. Although the value of breast self-examination is controversial, our view is that patients should be made aware that even with screening some BCs will be detected clinically so that they do not ignore signs of malignancy.

The study has limitations that warrant consideration. Among the potential sources for inaccuracy is the challenge of matching the expected incidence of BC in HL survivors based on cohort studies in which the means of detection were not provided in detail (1,10–12). Given that early studies demonstrating increased BC risk preceded recommendations for early screening and the low rate of early screening even after the elevated risk was recognized in the medical community (6), we think it is unlikely that a meaningful proportion of survivors in early cohort studies participated in early screening programs. However, if this assumption is incorrect and a large majority of patients in these studies had their cancers detected on screening, then our model would overestimate the incidence of BC and inflate the potential benefit of screening. Given the results of our sensitivity analysis, however, we view this as unlikely to have a major impact on the long-term outcomes described.

Another limitation is the absence of cost considerations. Understanding cost-effectiveness is an important consideration when making treatment recommendations for patient populations. Future work should evaluate the occurrence and progression of DCIS and develop robust cost-effectiveness models for young survivors.

In addition, the work is based on an HL treatment age of 15 years, chosen based on the median age of pediatric HL studies. Existing data on second cancer risk as it relates to treatment age are not sufficiently granular to allow the model to be more finely calibrated to distinguish risk differences between different adolescent ages. Furthermore, additional work is required to explore in detail the optimal timing of starting and ending screening because guidelines differ in their recommendations in this regard.

In conclusion, early BC screening is predicted to reduce the risk of BC death among young female HL survivors, and the number needed to screen to prevent one BC death compares favorably with accepted breast screening indications. MRI screening is more effective in reducing BC mortality than mammography in these patients but increases the rate of false-positive results.

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