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Annual Screening Strategies in BRCA1 and BRCA2 Gene Mutation Carriers: A Comparative Effectiveness Analysis

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Abstract

Background—While breast cancer screening with mammography and MRI is recommended for BRCA mutation carriers, there is no current consensus on the optimal screening regimen.

Methods—We used a computer simulation model to compare six annual screening strategies [film mammography (FM), digital mammography (DM), FM and magnetic resonance imaging (MRI) or DM and MRI contemporaneously, and alternating FM/MRI or DM/MRI at six-month intervals] beginning at ages 25, 30, 35, and 40, and two strategies of annual MRI with delayed alternating DM/FM to clinical surveillance alone. Strategies were evaluated without and with mammography-induced breast cancer risk, using two models of excess relative risk. Input parameters were obtained from the medical literature, publicly available databases, and calibration.

Results—Without radiation risk effects, alternating DM/MRI starting at age 25 provided the highest life expectancy (BRCA1: 72.52 years, BRCA2: 77.63 years). When radiation risk was included, a small proportion of diagnosed cancers were attributable to radiation exposure (BRCA1: <2%, BRCA2: <4%). With radiation risk, alternating DM/MRI at age 25 or annual MRI at age 25/delayed alternating DM at age 30 were most effective, depending on the radiation risk model used. Alternating DM/MRI starting at age 25 also had the highest number of false-positive screens/person (BRCA1: 4.5, BRCA2: 8.1).

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Conclusions—Annual MRI at 25/delayed alternating DM at age 30 is likely the most effective screening strategy in BRCA mutation carriers. Screening benefits, associated risks and personal acceptance of false-positive results, should be considered in choosing the optimal screening strategy for individual women.

Keywords

BRCA1 gene; BRCA2 gene; Breast neoplasms; Mass screening; Computer simulation

Introduction

Women with BRCA1 and BRCA2 gene mutations have a significantly increased lifetime risk of developing breast cancer, with an estimated 40–65% of carriers developing breast cancer by the age of 70.¹ Because of their elevated risk, carriers are advised to begin routine annual breast cancer screening at younger ages with both mammography and breast magnetic resonance imaging (MRI).² However, there is no current consensus regarding the optimal age to begin annual screening or whether multimodality screening should occur contemporaneously or with alternating modalities every six months. In addition, concerns have been raised about the risks of earlier and repeated radiation exposure in women already at increased breast cancer risk.^{3, 4, 5}

Screening mammography has been shown to decrease breast cancer mortality in the general population^{6, 7}. The use of screening MRI has been shown to identify cancers at smaller sizes and earlier stages in women at increased breast cancer risk.⁸ Potential disadvantages of more intensive breast cancer screening include an increased number of false-positive screens, which may lead to additional imaging, biopsies, and patient anxiety in women without breast cancer. Additional potential harms of screening include the possibility of mammography-induced breast cancer and overdiagnosis/overtreatment of breast cancers which may not ultimately cause death⁹.

A randomized controlled trial of breast cancer screening in women with BRCA gene mutations would be difficult to perform, due in part to the large numbers of participants and long length of follow-up required to demonstrate significant effects on overall life expectancy and breast cancer mortality. In the absence of definitive randomized controlled trial data, we have developed a comprehensive simulation model to evaluate multimodality breast cancer screening with mammography and breast MRI, which provides estimates of both screening benefits in terms of life expectancy gains, as well as potential disadvantages of false-positive screens and radiation exposure effects. The purpose of this study was to evaluate the comparative effectiveness of breast cancer screening strategies using mammography (film or digital), alone or in combination with MRI, in women with BRCA 1/2 gene mutations.

Methods

No human subject data were collected from individual patients for this study; therefore, Institutional Review Board approval was not required.

Model Overview and Inputs

The Markov Monte Carlo simulation model includes breast cancer development, detection, and treatment in asymptomatic 25-year-old BRCA1/2 carriers. For each scenario, two million individual women are tracked until death, and their outcomes are aggregated to provide cohort estimates of average life expectancy, cumulative breast cancer incidence, and breast cancer mortality. For the base case analysis, it was assumed that no women had

prophylactic bilateral salpingo-oophorectomy, mastectomy, or chemoprevention. Competing mortality risks obtained from the United States 2005 life expectancy tables¹⁰ were adjusted to reflect the increased mortality rate from ovarian cancer.¹¹

Model input parameters were obtained through a review of published literature and model calibration. BRCA1-specific and most other model parameter values have been previously published^{12, 13}; BRCA2-specific parameters are provided in Table 1. Values for key model input parameters relating to diagnostic test performance and radiation dose are presented in Table 2. Sensitivity and specificity values for film and digital mammography were obtained from the Digital Mammographic Imaging Screening Trial (DMIST).^{14, 15} To approximate the test performance of mammography in BRCA mutation carriers, sensitivity and specificity from the subset of premenopausal women with dense breasts was used in the base case analysis. Sensitivity values were stratified by tumor invasiveness (ductal carcinoma in situ vs invasive carcinoma) and size. Diagnostic test performance for MRI was obtained from the Magnetic Resonance Imaging Breast Screening (MARIBS) screening trial.¹⁶ Sensitivity and specificity of combined mammography / MRI strategies were obtained by combining individual modality test performance under an assumption of conditional independence. Estimates of radiation dose to the breast from screening mammography were obtained from the DMIST study.¹⁷

Strategies Evaluated

Twenty-six screening strategies were compared to a reference strategy of clinical surveillance without imaging. Breast cancer screening modalities included film mammography (FM), digital mammography (DM), and MRI. Annual mammography (FM or DM) was evaluated, alone or in conjunction with annual MRI, which could be performed contemporaneously or at alternating six-month intervals. Each of these six strategies was evaluated beginning at ages 25, 30, 35, and 40. Two additional strategies of annual MRI starting at age 25, with annual FM or DM added at age 30, were also evaluated.

Radiation Risk

We used two models of excess relative risk (ERR), in which radiation-induced breast cancer risk is proportional to a population's underlying cancer risk: Attained Age (AA), and Age-at-Exposure (AE) models. These models were developed by Preston and colleagues¹⁸ using pooled data from eight different cohorts exposed to different levels of ionizing radiation, and found that no single ERR model described observed findings across all cohorts. In the AA model, ERR is a function of the cumulative dose (d_c) of radiation exposure and the current age (age_c) of the patient:

$$ERR_{AA} = 0.74 * d_c * (age_c / 50)^{-2}$$

In the AE model, the effect of each radiation exposure on ERR is a function of the dose of radiation exposure, d_e , and the age at which the person was exposed, age_e :

$$ERR_{AE} = 1.9 * d_e * \exp(-0.092 * (age_e - 25))$$

The cumulative ERR was then calculated by summing the ERR for all exposures. In the simulation model, total ERR due to radiation-exposure was re-calculated each time a woman underwent screening mammography. This risk was then multiplied by the baseline age-specific breast cancer risk.

Outcomes

The primary outcome projected for each strategy was average life expectancy (LE). No adjustments for quality of life or discounting were applied. Secondary health outcomes included percent reduction in breast cancer mortality (relative decrease in breast cancer deaths in screened vs unscreened cohorts) and the average number of false positive screens/woman for each strategy, without and then with radiation exposure risk. Overdiagnosis was defined as the proportion of detected cancers in the screening scenarios that were not detected in the clinical surveillance scenario.¹⁹

Efficiency of Strategies

To examine the benefits of each strategy in the context of potential disadvantages, we defined efficient strategies as those which resulted in maximum health benefit (life years) while minimizing false positive screens (FP). To compare screening strategy efficiency, we first ranked all strategies in order of increasing number of FP screens. For a given number of FP screens/woman, the screening strategy with the highest LE was considered the most efficient. Strategies that provided the greatest additional LE gain as the number of FP screens/woman increased were connected on an “efficiency frontier”. If a strategy with a higher number of FPs resulted in a smaller benefit than strategies with lower numbers of FPs, this strategy was considered dominated and was not included on the efficiency frontier.

Sensitivity Analyses

We evaluated the effect of uncertainty in model parameters on both the ranking of most efficient strategies and the LE gain from multimodality screening (alternating mammography/ MRI at age 25) compared to mammography alone. BRCA 1/2 mutation penetrance (which determines lifetime breast cancer risk) was varied over the 95% confidence interval reported in the literature.¹ The effects of prophylactic oophorectomy (PO) at ages 35, 40, or 45 were examined, assuming that PO would reduce breast cancer risk by 50% and ovarian cancer risk by 100%.²⁰ Diagnostic test performance for mammography was evaluated in two-way sensitivity analyses using alternative published values for FM¹⁶ and test performance for all women with dense breasts in the DMIST trial.¹⁴ MRI test performance was similarly varied using values reported from other prospective trials of MRI in high risk women.^{21–24} We also examined the effect of increasing DM and MRI specificity by 5% after the first screen and of positive and negative test correlation for combined modality strategies. Radiation exposure effects from mammography were assessed by varying radiation dose exposures from the 10th to the 90th percentile reported for DMIST participants¹⁷.

Results

Life Expectancy Gains with Screening

For both BRCA1 and BRCA2 mutation carriers, strategies using DM resulted in higher average LE than those with FM, and strategies using alternating mammography/MRI screening were more effective than contemporaneous mammography/MRI (Figure 1). When radiation risk was not included in the model, alternating DM/MRI produced the highest LE at all ages of screening initiation, with the maximum LE achieved when starting at age 25. Using this strategy, the LE gain compared with clinical surveillance was 1.89 years for BRCA1 and 1.76 years for BRCA2 mutation carriers (overall LE=72.52 and 77.63 years, respectively; Table 3).

Effects on Breast Cancer Mortality

When examining the effects of screening strategies on breast cancer mortality both without and with radiation risk, alternating DM/MRI starting at age 25 achieved the greatest reduction in breast cancer mortality in both BRCA1 and BRCA2 mutation carriers, with the BRCA2 cohort demonstrating greater benefit (Table 3). In the absence of radiation risk, this alternating DM/MRI strategy reduced breast cancer mortality by 16.7% in the BRCA1 cohort and 31.1% in the BRCA2 cohort. With radiation risk included, the AE model had a greater effect than the AA model; breast cancer mortality benefit decreased to 15.4% (BRCA1) and 28.6% (BRCA2).

Effect of Radiation Exposure on Lifetime Cancer Incidence

For both BRCA1 and BRCA2 mutation carriers, a small percentage of detected cancers may be attributed to radiation exposure from mammographic screening. In the BRCA1 model without radiation risk, lifetime cancer incidence increased from 66.0% with clinical surveillance to 71.2% with alternating DM with MRI screening starting at age 25, (Figure 2), with overdiagnosis at 7.3%. When radiation risk was added, the additional breast cancers with the same screening strategy comprised <2% of all detected breast cancers (lifetime cancer incidence of 71.7%, AA model, and 72.2% AE model). In the BRCA2 model without radiation risk, lifetime cancer incidence increased from 53.8% with clinical surveillance to 56.9% from alternating DM/MRI starting at age 25, with overdiagnosis at 5.6%. With radiation risk included in the BRCA2 model, the additional breast cancers were <4% of all detected breast cancers, (lifetime cancer incidence 57.9%, AA model, and 59.1%, AE model).

Efficiency of Screening Strategies

The most efficient screening strategies in BRCA1 and BRCA2 carriers without and with radiation risk are summarized in Table 3. For women with either BRCA mutation, LE was maximized with the alternating DM /MRI strategy starting at age 25. However, the incremental LE gain between the two most effective BRCA1 screening strategies was modest. The LE from annual MRI at age 25 / delayed DM at age 30 was 72.49 years, and 72.52 years from alternating DM/MRI starting at age 25. Similarly in BRCA2 carriers, LE from annual MRI at 25 / delayed DM at 30 was 77.60 years, and 77.63 years from alternating DM/MRI at 25.

When radiation risk (AA model) was included in the BRCA1 cohort (Figure 3), alternating DM/MRI at age 25 remained the most effective strategy (LE=72.46 years). However, in the AE model, annual MRI at 25 / delayed DM at age 30 produced the highest LE (72.41 years) with fewer FP screens than the alternating DM/MRI strategy. In the BRCA2 cohort, annual MRI at age 25 / delayed DM at age 30 was the most effective strategy in both the AA and AE models (77.59 and 77.58 years, respectively), providing greater LE with fewer FP screens than alternating DM/MRI at age 25. In both BRCA1 and BRCA2 cohorts the incremental gain in LE with annual MRI at age 25 / delayed DM at age 30 compared to alternating DM/MRI at age 30 was modest (0.04–0.06 years) relative to the increase in FP screens per person (0.7–0.8).

Sensitivity analyses

The ranking of the most effective strategies in both BRCA1 and BRCA2 carriers remained stable across the range of parameters examined. The range in LE gain from multimodality screening (alternating DM/MRI) compared to mammography alone was most dependent upon MRI test performance (Figure 4), with the LE benefit in BRCA1 carriers ranging from 0.45–0.72 years. Multimodality screening became more beneficial as breast cancer risk

increased, and less beneficial as breast cancer risk decreased. When BRCA1 lifetime breast cancer risk increased from the base case value of 65% to 74%, the LE benefit with multimodality screening compared to annual DM alone increased from 0.49 years (base case) to 0.53 years. Conversely, when BRCA1 lifetime risk was reduced to 42%, the LE gain decreased to 0.32 years.

Similarly, when risk-reducing PO was modeled, the benefits of multimodality screening in BRCA1 carriers decreased to 0.34 years (PO at age 35) and 0.47 years (PO at 45). Using test performance data from the DMIST patient sub-population with dense breast tissue compared to premenopausal women with dense breast tissue slightly decreased the additional benefit of multimodality screening to 0.46 years. The addition of radiation risk to the model increased the benefit from 0.49 years without radiation risk to 0.51 years (AE model) and 0.55 years (AA model).

Varying these parameters in the BRCA2 cohort had similar effects. Varying MRI test performance resulted in the widest range of LE benefit from multimodality screening (0.21–0.42 years, base case 0.26 years). When the lifetime breast cancer risk increased from 50% in the base case to 56%, the added LE benefit remained stable at 0.26 years. When the cumulative incidence decreased to 31%, the LE gain decreased to 0.13 years. When PO was modeled at ages 35, 40, and 45, the LE gain ranged from 0.18 to 0.20 years. Similar to the BRCA1 cohort, using test performance data from the entire dense breast subgroup in the DMIST population slightly decreased the multimodality screening benefit to 0.24 years. The addition of radiation risk also contributed a small additional multimodality screening benefit, from 0.26 to 0.29 years.

We also examined the effects of using the different natural history parameters identified in model calibration. When we simulated the strategies using all 172 well-fitting parameter sets identified during the model calibration process for BRCA1, the LE gain for alternating DM/MRI compared to annual DM ranged from 0.42 to 0.60 years. When we used 44 well-fitting parameter sets identified for the BRCA2 cohort, the LE gain ranged from 0.22 to 0.35 years.

Discussion

The results from this study suggest that in women with BRCA mutations, screening with mammography and MRI will provide greater life expectancy and breast cancer mortality reduction. In this analysis, we examined screening strategies both without and with the risk of radiation-induced breast cancer from screening mammography. While concerns about radiation risk from screening mammography have been raised, a recent meta-analysis demonstrated an increased but non-significant relationship between low-dose radiation exposure and breast cancer risk in women with a familial or genetic predisposition⁴. However, a significant association was identified among women reporting ≥ 5 exposures, the scenario most relevant for women choosing breast cancer screening.

When screening strategies are modeled without accounting for the risk of radiation-induced cancers, alternating DM/MRI starting at age 25 is the most effective strategy. The model included an excess relative risk model of radiation exposure risk, in which the radiation induced risk was proportional to the increased underlying cancer risks in women with BRCA mutations. When radiation risk is modeled, the most effective screening strategy differs between BRCA1 and BRCA2 carriers.

For BRCA1 carriers, either annual MRI at age 25 combined with alternating DM delayed until age 30, or alternating DM/MRI at age 25 provides the greatest life expectancy, depending on the radiation risk model used. While our results indicate that these two strategies provide comparable LE, delaying the start of mammographic screening until age

30 decreases the number of total mammographic examinations and expected false positive screens. For BRCA2 carriers, when radiation exposure risk was included in the model, the most effective strategy shifted from alternating DM/MRI starting at age 25 to annual MRI at age 25 with alternating DM added at age 30. This strategy provided the greatest LE with both radiation risk models, and had fewer false-positive screens. However, it is noteworthy that in both the BRCA1 and BRCA2 cohorts the additional LE gain with adding annual MRI between ages 25 and 30 compared to starting alternating multimodality screening at age 30 was small relative to the higher number of false positive screens. This suggests that for some of these high risk women, it may be reasonable to delay all imaging-based screening until age 30, such as women whose first degree relatives were diagnosed with breast cancer at age 40 or later, or women with high anxiety about false positive screens.

Our model further indicates that less than 4% of all diagnosed cancers would be attributable to radiation exposure. These findings were stable even when the 90th percentile of radiation exposure from mammography was modeled. Thus, the benefits of most screening strategies that include mammography appear to substantially exceed the risks associated with radiation exposure.

Other models have been used to quantify the benefits of multimodality screening in the BRCA1/2 population but have not examined these benefits in the context of radiation risk or false positives.^{25, 26} Moreover, neither model specifically examined the benefits of strategies using digital mammography and alternating with MRI at six month intervals, which proved most effective in our analysis. Berrington de Gonzalez, et al.⁵ used an ERR model to calculate the long-term risk of radiation-induced breast cancer mortality due to mammography alone in young women with BRCA1/2 mutations. Their results suggested that the benefits of mammography at ages younger than 30 did not outweigh the risk of radiation-induced cancers. Our model similarly suggests that while the use of MRI is beneficial in women as young as age 25, the additional gains of using mammography before the age of 30 are small and may be negligible.

As with all modeling studies, ours has some limitations. First, our model is an approximation of reality, with intrinsic simplifying assumptions. We assumed that radiation-induced breast cancers behave like other breast cancers in the BRCA1/2 populations in terms of growth rates, hormone receptor status, and prognosis since these characteristics of radiation-induced breast cancers are not currently well described. While we used input data specific to BRCA 1/2 carrier populations whenever possible, some data come from small, very select patient samples. In those instances, we chose base case input parameter estimates from studies of breast cancer in the general population, such as the large databases maintained by SEER,¹¹ the Breast Cancer Surveillance Consortium,²⁷ or meta-analyses of randomized trials.²⁸ Also, the model focuses on the development and detection of first primary breast cancer, and we assumed perfect adherence to screening and treatment protocols.

In conclusion, our results suggest that for women with BRCA mutations, starting MRI screening at age 25, combined with MRI with alternating DM (starting at either ages 25 or 30 in BRCA1, and starting at age 30 in BRCA2 carriers) provides the greatest life expectancy. The projected benefits of these strategies, along with their associated risks and patient acceptance of false-positive screening results, should be considered when making individual screening decisions.

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REFERENCES

1. Antoniou A, Pharoah PDP, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. *American Journal of Human Genetics*. 2003; 72:1117–1130. [PubMed: 12677558]
2. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA: A Cancer Journal for Clinicians*. 2007; 57:75–89. [PubMed: 17392385]
3. Ernestos B, Nikolaos P, Koulis G, et al. Increased chromosomal radiosensitivity in women carrying BRCA1/BRCA2 mutations assessed with the G2 assay. *International Journal of Radiation Oncology, Biology, Physics*. 2010; 76:1199–1205.
4. Jansen-van der Weide MC, Greuter MJW, Jansen L, Oosterwijk JC, Pijnappel RM, de Bock GH. Exposure to low-dose radiation and the risk of breast cancer among women with a familial or genetic predisposition: a meta-analysis. *European Radiology*. 2010; 20:2547–2556. [PubMed: 20582702]
5. Berrington de Gonzalez A, Berg CD, Visvanathan K, Robson M. Estimated risk of radiation-induced breast cancer from mammographic screening for young BRCA mutation carriers. *Journal of the National Cancer Institute*. 2009; 101:205–209. [PubMed: 19176458]
6. Nelson HD, Tyne K, Naik A, Bougatsos C, Chan BK, Humphrey L. Screening for breast cancer: An update for the U.S. Preventive Services Task Force. *Annals of Internal Medicine*. 2009; 151:727–737. [PubMed: 19920273]
7. Humphrey LL, Helfand M, Chan BKS, Woolf SH. Breast cancer screening: A summary of the evidence for the U. S. Preventive Services Task Force. *Annals of Internal Medicine*. 2002; 137:347–360. [PubMed: 12204020]
8. Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D. Systematic review: Using magnetic resonance imaging to screen women at high risk for breast cancer. *Annals of Internal Medicine*. 2008; 148:671–679. [PubMed: 18458280]
9. United States Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. *Annals of Internal Medicine*. 2009; 151:716–726. [PubMed: 19920272]
10. Arias, E.; Rostron, BL.; Tejada-Vera, B. National vital statistics reports. Hyattsville, Maryland: National Center for Health Statistics; 2010. United States life tables, 2005; p. 1-40.
11. Horner M, Ries L, Krapcho M. SEER Cancer Statistics Review, 1975–2006. National Cancer Institute, Bethesda, MD, based on November 2008 SEER data submission, posted to SEER website. 2009
12. Lee JM, Kopans DB, McMahon PM, et al. Effectiveness of MRI for breast cancer screening in BRCA1 gene mutation carriers: A Markov Monte Carlo Decision Analysis. *Radiology*. 2008; 246:763–771. [PubMed: 18309013]
13. Lee JM, McMahon PM, Kong CY, et al. Cost-effectiveness of breast MR Imaging and screen-film mammography for screening BRCA1 gene mutation carriers. *Radiology*. 2010; 254:793–800. [PubMed: 20177093]
14. Pisano ED, Gatsonis C, Hendrick E, et al. Diagnostic performance of digital versus film mammography for breast-cancer screening. *New England Journal of Medicine*. 2005; 353:1773–1783. [PubMed: 16169887]
15. Pisano ED, Hendrick RE, Yaffe MJ, et al. Diagnostic accuracy of digital versus film mammography: exploratory analysis of selected population subgroups in DMIST. *Radiology*. 2008; 246:376–383. [PubMed: 18227537]

16. Leach MO, Boggis CR, Dixon AK, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). *Lancet*. 2005; 265:1769–1778. [PubMed: 15910949]
17. Hendrick RE, Pisano ED, Averbukh A, et al. Parameters and breast dose in digital mammography and screen-film mammography in the American College of Radiology Imaging Network Digital Mammographic Imaging Screening Trial. *AJR*. 2010; 194:362–369. [PubMed: 20093597]
18. Preston DL, Mattsson A, Holmberg E, Shore R, Hildreth NG, Boice JDJ. Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. *Radiation Research*. 2002; 158:220–235. [PubMed: 12105993]
19. Welch HG, Black WC. Overdiagnosis in cancer. *Journal of the National Cancer Institute*. 2010; 102:605–613. [PubMed: 20413742]
20. Rebbeck TR, Kauff ND, Domcheck SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. *Journal of the National Cancer Institute*. 2009; 101:80–87. [PubMed: 19141781]
21. Kriege M, Brekelmans CT, Boetes C, et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. *N Engl J Med*. 2004; 351:427–437. [PubMed: 15282350]
22. Kuhl CK, Schrading S, Leutner CC, et al. Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. *J Clin Oncol*. 2005; 23:8469–8476. [PubMed: 16293877]
23. Sardanelli F, Podo F, D'Agnolo G, et al. Multicenter comparative multimodality surveillance of women at genetic-familial high risk for breast cancer (HIBCRIT study): interim results. *Radiology*. 2007; 242:698–715. [PubMed: 17244718]
24. Warner E, Plewes DB, Hill KA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. *JAMA*. 2004; 292:1317–1325. [PubMed: 15367553]
25. Plevritis SK, Kurian AW, Sigal BM, et al. Cost-effectiveness of screening BRCA 1/2 mutation carriers with breast magnetic resonance imaging. *JAMA*. 2006; 295:2374–2384. [PubMed: 16720823]
26. Grann VR, Patel PR, Jacobson JS, et al. Comparative effectiveness of screening and prevention strategies among BRCA1/2-affected mutation carriers. *Breast Cancer Research and Treatment*. 2011; 125
27. Breast Cancer Screening Consortium. [accessed 9/18/06] Frequency of node-positivity and metastatic cancer by primary tumor size and method of detection. Available from URL: <http://www.breastscreening.cancer.gov/>
28. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005; 365:1687–1717. [PubMed: 15894097]
29. Lakhani SR, van de Vijver MJ, Jacquemier J, et al. The pathology of familial breast cancer: Predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in BRCA1 and BRCA2. *Journal of Clinical Oncology*. 2002; 20:2310–2318. [PubMed: 11981002]

Figure 1.

A–1B. Projected life expectancy for annual screening strategies in BRCA1 (1A) and BRCA2 (1B) mutation carriers in the absence of radiation risk. For both populations, alternating DM with MRI produced the highest life expectancy at all ages of screening initiation, and the highest LE was achieved with alternating DM with MRI starting at age 25.

Figure 2.

Cumulative incidence of breast cancer (BC) in the alternating DM with MRI strategy starting at age 25. When compared to no screening, the cumulative incidence of BRCA1 cancers increased from 66.1% (without radiation risk, top dashed line) to 71.2% (light blue line). BRCA2 cancers increased from 54.0% (without radiation risk, bottom dashed line) to 57.0% (green line). When radiation effects were included, <2% of diagnosed cancers can be attributed to radiation exposure, using both Attained-Age (AA, pink and brown lines) and Age-At-Exposure (AE) models (navy and yellow lines).

Figures 3.

A–D. Efficiency frontiers for BRCA1 AA (3A) and AE (3B) models, and for BRCA2 AA (3C) and AE (3D) models. The strategies that maximized LE for a given level of FP screens are considered efficient and connected by the solid line. Open circles indicate dominated strategies. Strategies are notated as modality (age at first screen). Ann = Annual, Alt = Alternating at six month intervals, DM = Digital Mammography.

Figure 4.

A–4B. Influential parameters and effect on life expectancy (LE) gain, alternating DM/MRI at age 25 vs. annual DM alone at age 25. Results are presented in decreasing order of LE gain variation, with lifetime breast cancer risk estimates being the most influential factor in estimating LE gains from multimodality screening in both BRCA1 and BRCA2 carriers.

Vertical axes represent the LE gain in the base case (BRCA1 = 0.49 years, BRCA2 = 0.26 years). DM = Digital Mammography, ERR = Excess Relative Risk.

Table 1

BRCA2-related model parameters.

Parameter	Base case value	Range used in sensitivity analysis*	Source
Preclinical phase	6	3.0 – 17.0	Calibration
Incidence multiplier	1.59	1.25 – 3.18	Calibration
Probability of invasive cancer at onset	0.059	0.002 – 0.089	Calibration
Annual rate of DCIS becoming invasive cancer	0.297	0.25 – 0.39	Calibration
Annual rate of DCIS stabilization	0.061	0.03 – 0.27	Calibration
Probability of DCIS being non-palpable	0.159	0.14 – 0.22	Calibration
Mean tumor growth parameter (lognormal distribution)	−2.21	−2.10 to −2.26	Calibration
Probability of estrogen receptor-positive cancer	0.66	Not varied	Lakhani ²⁹

DCIS = ductal carcinoma in situ.

* Model calibration identified 44 good fitting parameter sets, with the parameter set best reproducing the expected stage distribution of clinically presenting cancers selected for use in the base case analysis. The remaining parameter sets were used in multi-parameter sensitivity analysis (Figure 4).

Table 2

Values and sources for test performance characteristics and radiation dose.

Input Parameter	Base Case	Values used for Sensitivity Analysis	Source
Film Mammography Sensitivity by Size			DMIST*
DCIS			
0–5mm	0.00	0.00	
>5mm	0.44	0.51 (for >3mm)	
Invasive cancers			
0–3mm	0.00	0.00	
>3mm	0.15	0.42	
Digital Mammography Sensitivity by Size			DMIST*
DCIS			
0–5mm	0.00	0.00	
>5mm	0.72	(>3mm) 0.65	
Invasive cancers			
0–3mm	0.00	0.00	
>3mm	0.50	(>3mm) 0.54	
MRI Sensitivity by Size			MARIBS ¹⁶ , Kriege ²¹ , Sardanelli ²³ , Kuhl ²² , Warner ²⁴
DCIS			
0–4mm	0.00		
5–10mm	0.25	(>5mm) 0.167–1.00	
>10mm	0.50		
Invasive cancers			
0–4mm	0.00		
5–9mm	0.64	(>5mm) 0.813–0.933	
10–15mm	0.78		
16–20	0.83		
21–30	0.85		
>30mm	0.86		
Correlation of mammography and MRI test performance	1.00 (test independence)	–0.38 to 0.18	Lee ¹³
Film mammography specificity	0.89	0.90, 0.95	DMIST*
Digital mammography specificity	0.90	0.91, 0.96	DMIST*
MRI specificity	0.81	0.898–0.972	MARIBS ¹⁶
Radiation dose for film screening mammogram, two-views (mGy)	4.98	2.00–8.00	Hendrick ¹⁷
Radiation dose for digital screening mammogram, two views (mGy)	4.15	1.70–6.80	Hendrick ¹⁷

* DMIST data obtained directly from authors EDP and CG.

Table 3

Outcomes for efficient screening strategies.

Strategy (Age at Initiation)	BRCA1			BRCA2		
	FP Screens / Person	Mean LE (years)	BC Mortality Reduction (%)	FP Screens / Person	Mean LE (years)	BC Mortality Reduction (%)
<i>No Radiation Risk</i>						
No imaging	0.0	70.66	N/A	0.0	75.87	N/A
Annual DM (30)	1.5	71.96	12.2	3.0	77.33	26.6
Annual DM (25)	2.0	72.03*	12.6	3.5	77.37	26.9
Alternating DM with MRI (30)	3.5	72.45	16.2	7.0	77.58	30.9
Annual MRI (25) with delayed DM (30)	4.2	72.49*	16.6	7.8	77.60*	31.1
Alternating DM with MRI (25)	4.6	72.52	16.7	8.2	77.63	31.2
<i>ERR AA Radiation Risk Model</i>						
No imaging	0.0	70.66	N/A	0.0	75.87	N/A
Annual DM (30)	1.4	71.91	11.4	2.9	77.26	25.1
Annual DM (25)*	1.9	71.91*	11.3	3.4	77.24*	24.6
Alternating DM with MRI (30)	3.4	72.38	15.8	7.0	77.54	30.0
Annual MRI (25) with delayed DM (30)	4.2	72.44	16.0	7.8	77.59	30.2
Alternating DM with MRI (25)	4.5	72.46	16.1	8.1	77.57*	30.1
<i>ERR AE Radiation Risk Model</i>						
No imaging	0.0	70.66	N/A	0.0	75.87	N/A
Annual DM (30)	1.4	71.91	11.4	2.9	77.28	25.1
Annual DM (25)*	1.9	71.88*	11.2	3.4	77.24*	24.6
Alternating DM with MRI (30)	3.4	72.37	15.5	6.9	77.52*	29.4
Annual MRI (25) with delayed DM (30)	4.1	72.41	15.9	7.7	77.58	29.9
Alternating DM with MRI (25)	4.5	72.39*	15.4	8.0	77.52*	28.6

FP = False Positive; LE = Life Expectancy; BC = Breast Cancer; DM = Digital Mammography; FM = Film Mammography; AA = Age-Attained

* Indicates dominated strategies