Cost-effectiveness of Breast MR Imaging and Screen-Film Mammography for Screening *BRCA1* Gene Mutation Carriers[1]

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Purpose: To evaluate the clinical effectiveness and cost-effectiveness of screening strategies in which MR imaging and screen-film mammography were used, alone and in combination, in women with *BRCA1* mutations.

Materials and Methods: Because this study did not involve primary data collection from individual patients, institutional review board approval was not needed. By using a simulation model, we compared three annual screening strategies for a cohort of 25-year-old *BRCA1* mutation carriers, as follows: *(a)* screen-film mammography, *(b)* MR imaging, and *(c)* combined MR imaging and screen-film mammography (combined screening). The model was used to estimate quality-adjusted life-years (QALYs) and lifetime costs. Incremental cost-effectiveness ratios were calculated. Input parameters were obtained from the medical literature, existing databases, and calibration. Costs (2007 U.S. dollars) and quality-of-life adjustments were derived from Medicare reimbursement rates and the medical literature. Sensitivity analysis was performed to evaluate the effect of uncertainty in parameter estimates on model results.

Results: In the base-case analysis, annual combined screening was most effective (44.62 QALYs), and had the highest cost ($110 973), followed by annual MR imaging alone (44.50 QALYs, $108 641), and annual mammography alone (44.46 QALYs, $100 336). Adding annual MR imaging to annual mammographic screening cost $69 125 for each additional QALY gained. Sensitivity analysis indicated that, when the screening MR imaging cost increased to $960 (base case, $577), or breast cancer risk by age 70 years decreased below 58% (base case, 65%), or the sensitivity of combined screening decreased below 76% (base case, 94%), the cost of adding MR imaging to mammography exceeded $100 000 per QALY.

Conclusion: Annual combined screening provides the greatest life expectancy and is likely cost-effective when the value placed on gaining an additional QALY is in the range of $50 000–$100 000.

Supplemental material: *http://radiology.rsna.org/lookup/suppl/doi:10.1148/radiol.09091086/-/DC1*

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Women with *BRCA1* or *BRCA2* gene mutations have a substantially increased lifetime risk of developing breast cancer (1–4). Although screening mammography is the current clinical standard for breast cancer screening in the general population, it aids in the detection of less than one-half of prevalent and incident breast cancers in high-risk women (5–7). This finding is thought to be related to multiple factors, such as the younger age at screening and increased breast density in these women, as well as to pathologic and imaging characteristics of breast cancers in this population (8–12).

Breast magnetic resonance (MR) imaging is highly sensitive, depicts many cancers not seen at mammography (13–19), and is recommended as an adjunct to mammography for screening women at increased genetic risk of breast cancer (20). Compared with mammography, breast MR imaging is more time consuming and more expensive. Further, MR imaging is less specific, which will invariably result in an increased number of false-positive test results. It is presumed that early detection with MR imaging decreases breast cancer mortality, although there is currently insufficient evidence to confirm this finding. A randomized controlled trial in which screening with the two modalities is compared is unlikely to be performed, because of the large number of women and length of follow-up required, as well as the expense that would be incurred. In the absence of a definitive randomized controlled trial to establish the comparative effectiveness of multimodality breast cancer screening, we have developed a computer simulation model of breast cancer natural history and outcomes to project long-term health outcomes and lifetime costs related to breast cancer screening with MR imaging.

The purpose of this study was to evaluate the clinical effectiveness and cost-effectiveness of screening strategies in which MR imaging and screen-film mammography were used, alone and in combination, in women with *BRCA1* gene mutations.

Advances in Knowledge

- When three annual screening strategies were compared, combined screening with MR imaging and screen-film mammography provided the greatest life expectancy gain and breast cancer mortality reduction and was also the most costly.
- Annual MR imaging was more cost-effective as an adjunct to annual mammographic screening rather than as a replacement.
- The projected cost-effectiveness of annual combined screening with MR imaging and screen-film mammography is strongly dependent on the cost of an MR imaging examination and the underlying breast cancer risk in the women being screened.

Materials and Methods

Because this study did not involve primary data collection from individual patients, institutional review board approval was not needed.

Cost-effectiveness Analysis

We used standard cost-effectiveness analytic methods as recommended by the Panel on Cost-Effectiveness in Health and Medicine (21) by using a computer simulation model to project health outcomes and costs from a societal perspective over a lifetime horizon. Screening strategies were compared in an incremental cost-effectiveness analysis. The strategies were ranked in order of increasing effectiveness and then in order of increasing cost. Dividing the difference in cost (incremental cost) by the difference in health outcome (incremental effectiveness, measured in quality-adjusted life-years [QALYs]) provides the incremental cost-effectiveness ratio (ICER), which describes the cost required to obtain one additional QALY by using the next more effective strategy. Lifetime costs were measured in 2007 U.S. dollars. A 3% annual discount rate was applied to both costs and QALYs.

Implications for Patient Care

- The results of this analysis suggest that breast cancer screening outcomes for women with *BRCA1* gene mutations can be improved through annual combined screening with screen-film mammography and MR imaging.
- Compared with annual mammography alone, annual combined screening for *BRCA1* gene mutation carriers is likely cost-effective when the value placed on gaining an additional quality-adjusted life-year is in the range of $50 000–$100 000.

Screening Strategies Evaluated

Details of the model have previously been reported (22), and an overview is provided in Appendix E1 (online). Three annual screening strategies were evaluated relative to a strategy of clinical surveillance without imaging, as follows: *(a)* screen-film mammography, *(b)* MR imaging, and *(c)* combined mammography and MR imaging (hereafter called combined screening). All screening strategies began at age 25 years, on the basis of the recommendations of the Cancer Genetics Studies Consortium (23) and the National Comprehensive Cancer Network (24). For women undergoing combined screening, we assumed that both tests were performed contemporaneously.

Published online
10.1148/radiol.09091086

Radiology 2010; 254:793–800

Abbreviations:
ICER = incremental cost-effectiveness ratio
QALY = quality-adjusted life-year

Author contributions:
Guarantor of integrity of entire study, J.M.L.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, J.M.L.; experimental studies, P.M.M., C.Y.K., G.S.G.; statistical analysis, J.M.L., C.Y.K., E.F.H., G.S.G.; and manuscript editing, J.M.L., P.M.M., C.Y.K., D.B.K., P.D.R., E.F.H., G.S.G.

Funding:
This research was supported by the National Cancer Institute (grant K07CA128816) and the Breast Cancer Surveillance Consortium (grants U01CA63740, U01CA86082, U01CA63736, U01CA70013, U01CA69976, U01CA63731, U01CA70040).

Authors stated no financial relationship to disclose.

Reflecting current clinical practice, a positive result with either mammography or MR imaging was considered a positive combined screening result.

The diagnosis of cancer included a three-stage testing sequence of screening, diagnostic work-up, and biopsy. Women with positive screening results underwent further diagnostic work-up, which consisted of additional mammographic views, with or without breast ultrasonography. Women whose diagnostic work-up results were negative or benign were tracked as having had false-positive screening examination results. Women whose diagnostic work-up results were suspicious for malignancy subsequently underwent biopsy to establish a final diagnosis of malignant or benign disease. We assumed that women with cancer who had a true-positive screening result also had positive diagnostic work-up findings, leading to a recommendation for biopsy. Among women without cancer, the probability of a biopsy recommendation after diagnostic work-up was assumed to be conditionally independent of the initial screening test results. If the biopsy results demonstrated benign disease, the woman was tracked as having had both a false-positive screening examination and a false-positive biopsy. Women with negative screening results underwent no further intervention until the next screening event. If a cancer was missed on a screening test (false-negative result), cancer progression continued until the next screening event or until the cancer manifested clinically as an interval cancer.

Model Input Parameters

Input parameters were identified through a critical review of the medical literature and publicly available databases (25–27). Many key model parameters have been previously reported (22). As part of the ongoing model refinement process, the model was recalibrated by using a simulated annealing algorithm (28) to identify values for several natural history parameters (Appendix E1, Tables E1, E2 [online]). The sensitivity of screen-film mammography, MR imaging, and combined screening (Table E3 [online]), stratified according to cancer invasiveness and size, as well as the specificity of each screening modality (Table E4 [online]), were obtained from a multicenter trial of women at increased familial risk for breast cancer (13). Costs related to screening and diagnosis were derived from 2007 Medicare reimbursement rates (26). Additional costs of care, patient time costs, and quality-of-life weights were derived from the medical literature (Tables E5, E6 [online]). Costs from years prior to 2007 were adjusted to 2007 U.S. dollars by using the medical care component of the consumer price index (29). In the base case, quality-of-life weights for women with breast cancer were applied for 5 years, at which time their quality-of-life weight reverted to that of a healthy, cancer-free woman of the same age. In the base case, no short-term quality-of-life decreases related to breast cancer screening or false-positive test results were incorporated.

Outcomes

Primary outcomes projected were: *(a)* lifetime costs, *(b)* QALYs, and *(c)* ICERs for each screening strategy. Additional long-term health outcomes projected were as follows: absolute life expectancy gain and breast cancer mortality reduction obtained with each screening strategy. Intermediate health outcomes evaluated included the following: mean age at diagnosis, mean diameter of invasive cancers, and stage distribution of cancers detected with each screening strategy. The diagnostic consequences of screening that we evaluated were the percentage of women with one or more false-positive screening test results in their lifetimes, the percentage of women with one or more false-positive biopsy results, and the frequency distribution of false-positive test results. The relationship between false-positive screening test results and breast cancer mortality reduction was examined by calculating the number of additional false-positive screening test results required to prevent a breast cancer death.

Sensitivity Analysis

We analyzed the model as a Markov Monte Carlo simulation to examine first-order uncertainty, which characterizes the random variability in individual outcomes conditional on underlying parameter values. We examined the effect of second-order uncertainty, which characterizes the imprecision of knowledge in regard to parameter values, by performing univariate threshold-level sensitivity analysis to identify parameters that had values that could cause the ICER for annual combined screening either to decrease below $50 000 per QALY or to increase above $100 000 per QALY. Parameters examined over a plausible clinical range included mutation penetrance, diagnostic test performance of screening, costs of screening and diagnosis, annual discount rate, and quality-of-life weights for women with breast cancer.

Sensitivity analyses also were used to evaluate diagnostic test performance. In multivariate sensitivity analyses, paired sensitivity and specificity values for annual combined screening were obtained from published trials of multimodality screening in women at increased genetic risk (15,17). We also used points along a breast MR imaging summary receiver operating characteristic curve (30) as a plausible lower bound for sensitivity and specificity values of the annual combined strategy. Although Leach et al (13) reported no increase in specificity between initial and subsequent screening examinations, other investigators (15,31) have reported such an increase. We, therefore, performed additional sensitivity analyses, assuming a 5% increase in specificity for subsequent screening for each modality.

To examine the potential effect of risk-reducing prophylactic oophorectomy (32,33), we performed sensitivity analyses in which the risk of breast cancer was reduced by 50%, following prophylactic oophorectomy at ages 35, 40, or 45 years. Accordingly, the mortality risk from ovarian cancer was subsequently subtracted from a woman's age-specific nonbreast cancer mortality risk. Because transient quality-of-life effects have been shown to affect the results of cost-effectiveness analyses of breast cancer screening (34–36) and quality-of-life weights for breast biopsy have been identified (37), these short-term quality-of-life effects were included in the sensitivity analysis (Table E7 [online]).

Results

Health Outcomes

Model projections indicated that all annual screening strategies helped improve intermediate outcomes, with identification of more cancers at an earlier age and smaller size (Table 1). Of the three screening strategies evaluated, annual combined screening was best at depicting early-stage cancers. With this strategy, the median invasive cancer diameter was 1.1 cm, and approximately 80% of diagnosed cancers were in situ or node negative in stage. Long-term outcomes also improved with screening. Average cohort life expectancy increased with screening, with the greatest gain seen with annual combined screening. At every age, screening helped reduce breast cancer mortality (Fig 1), with the greatest relative mortality reduction (22.3%) achieved with annual combined screening.

Screening with MR imaging also was associated with a high rate of false-positive test results (Table 2). With MR imaging screening, most of the women undergoing screening had one or more false-positive screening examination results during their lives (MR imaging alone, 87.9%; combined screening, 90.5%). Of these women, approximately one-half were recalled for further evaluation four or more times during their lives (MR imaging alone, 46.1%; combined screening, 54.5%). In addition, more than 33% of women who underwent MR imaging screening also underwent biopsies with benign results.

Table 3 presents the relationship between false-positive test results and breast cancer mortality reduction. With annual mammographic screening, 37 false-positive screening examination results occurred for every breast cancer death averted. When annual MR imaging was added to annual mammographic screening, 137 additional false-positive screening examination results occurred for each additional life saved.

Cost-effectiveness Analysis

In cost-effectiveness analysis, screening strategies were ranked in order of increasing QALYs and then cost (Table 4). Annual combined screening was the most effective, producing 44.624 QALYs, and also had the highest lifetime cost ($110973). ICERs were calculated to determine the cost required to gain one additional QALY by using the next more effective strategy. Because the ICER for annual MR imaging screening was higher than that of the next more effective screening strategy (annual combined screening), it was eliminated from consideration by extended dominance (21). The ICERs for the remaining strategies were then recalculated. The ICER for annual mammographic screening versus clinical surveillance alone was $16751 per additional QALY gained. The cost of annual combined screening versus annual mammographic screening was $69125 per QALY.

Sensitivity Analyses

Univariate sensitivity analysis results indicated that the ICER for annual

Table 1

Screening Strategy Outcomes

Outcome	Clinical Surveillance	Annual Screen-Film Mammography	Annual MR Imaging	Annual Combined Screening
Total life expectancy (y)	72.33	73.45	73.63	74.17
Cumulative incidence (%)	66.5	71.6	71.5	71.6
Mean age at diagnosis (y)	45.8	45.4	45.3	45.1
Median invasive tumor size (cm)	2.7	2.0	1.4	1.1
Invasive cancers ≤2 cm in diameter (%)	32.2	49.7	65.3	74.9
Stage at diagnosis (%)				
Ductal carcinoma in situ	4.7	17.6	15.6	18.3
Local (node negative)	50.5	51.4	59.1	61.6
Regional (node positive)	40.1	28.7	23.2	18.7
Distant	4.7	2.4	2.1	1.4
Breast cancer mortality per 1000 women diagnosed with breast cancer	533	446	438	415
Breast cancer mortality benefit compared with clinical surveillance (%)	...	16.4	17.8	22.3

Figure 1

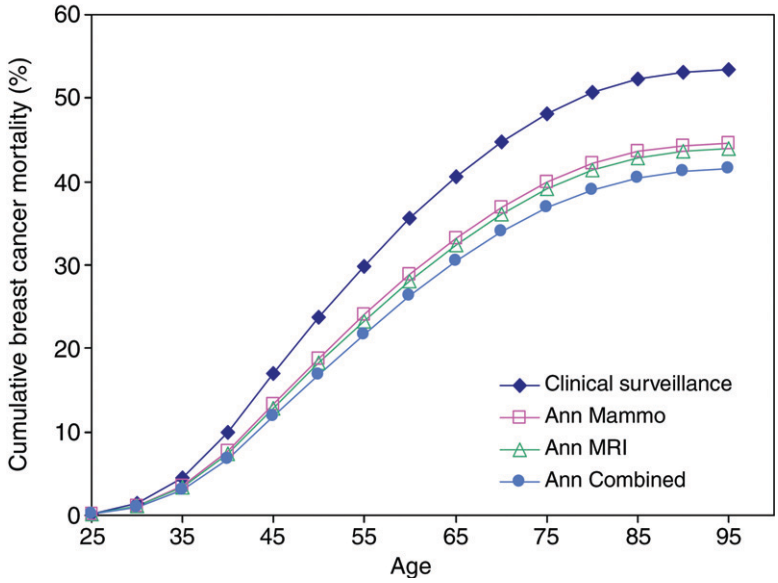

Figure 1: Cumulative breast cancer mortality according to screening strategy. *Ann Mammo* = annual screen-film mammography, *Ann MRI* = annual MR imaging, *Ann Combined* = annual combined screening.

Table 2

False-Positive Results according to Screening Strategy

Result	Annual Screen-Film Mammography	Annual MR Imaging	Annual Combined Screening
Women with ≥1 false-positive screening test results	63.9	87.9	90.5
No. of false-positive screening examinations			
Women with 1	45.8	18.1	14.0
Women with 2	26.7	19.0	16.0
Women with 3	13.8	16.8	15.5
Women with ≥4	13.7	46.1	54.5
Women with >1 false-positive biopsy results	14.6	33.1	37.9
No. of biopsies			
Women with 1	88.7	73.4	69.6
Women with 2	10.0	19.8	21.6
Women with ≥3	1.3	6.8	8.8

Note.—Data are percentages.

Table 3

Relationship between False-Positive Screening Results and Mortality Reduction

Strategy per 100 000 Women	Breast Cancer Deaths	Additional Lives Saved	False-Positive Screening Examinations	Additional False-Positive Examinations	Additional False-Positive Screenings per Additional Life Saved
No. with clinical surveillance	35 549	...	...	...	...
No. with annual screen-film mammography	31 961	3588	133 443	133 443	37
No. with annual combined screening	29 713	2248	440 651	307 208	137

Table 4

Cost-effectiveness of Screening

Strategy	Cost ($)	Incremental Cost ($)	QALYs	Incremental QALYs	ICER (Δ$/ ΔQALY)
Clinical surveillance	96 042	...	44.21	...	...
Annual screen-film mammography	100 336	4294	44.46	0.25	16 751
Annual MR imaging	108 641	8305	44.50	0.04	Eliminated*
Annual combined screening	110 973	2332	44.624	0.12	69 125†

* Compared with annual screen-film mammography, $206 384 per QALY.

† Compared with annual screen-film mammography.

combined screening was influenced by assumptions in regard to breast MR imaging cost and mutation penetrance (Table 5). Varying the cost for breast MR imaging caused the ICER for annual combined screening to vary over the widest range. As this cost decreased from the base-case value of $577 to the threshold value of $433, the ICER for annual combined screening decreased to, and then decreased below, $50 000 per QALY. As the cost for screening breast MR imaging increased to the threshold value of $960, the ICER for annual combined screening increased and then exceeded $100 000 per QALY.

Annual combined screening also became more cost-effective as breast cancer risk increased and became less cost-effective as risk decreased. The ICER of annual combined screening decreased to less than $50 000 per QALY when mutation penetrance increased from 65% to 71% and exceeded $100 000 per QALY when mutation penetrance decreased below 48%. Results of sensitivity analyses for evaluation of the potential effect of risk-reducing prophylactic oophorectomy at varying ages demonstrated a similar effect. When prophylactic oophorectomy was performed at age 45 years for all women in the cohort, the subsequent decrease in both risk and competing mortality caused the ICER for annual combined screening to increase from the base-case value of $69 125 to $95 643 per QALY. With prophylactic oophorectomy at age 40 years, the ICER for annual combined screening exceeded $100 000 per QALY and continued to increase with surgery at earlier ages.

The cost-effectiveness of annual combined screening was also influenced by estimates of diagnostic test performance. For most sensitivity-specificity pairs evaluated, the ICER for annual combined screening remained between $50 000 and $100 000 per QALY (Fig 2). It was only at an extreme portion of the receiver operating characteristic curve, where the sensitivity of combined screening decreased below 76%, that the ICER exceeded $100 000 per QALY. The ICER also remained between $50 000 and $100 000 per QALY when the specificity for each modality during incident screening rounds was increased by 5%. Additional sensitivity analyses of costs, annual discount rate, quality-of-life weights, and natural history parameter values were performed, all of which yielded ICER values less than $100 000 per QALY (Appendix E1 [online]).

Discussion

The results of this analysis suggest that breast cancer screening outcomes

Table 5

Threshold-level Sensitivity Analysis Results

Parameter	Base-Case Value	Range	Threshold Level for ICER <$50 000 per QALY	Threshold Level for ICER >$100 000 per QALY
Cost of breast MR imaging ($)	577	288–1731*	433	960
Mutation penetrance (%)	65	40–75	71	58
Age at prophylactic oophorectomy (y)	Not included	45, 40, 35	...	40

* Cost is 50%–300% times the base-case value.

Figure 2

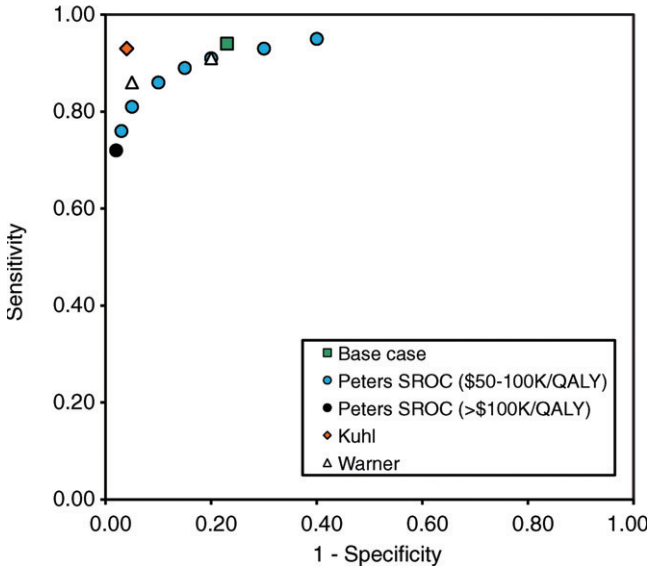

Figure 2: Sensitivity analysis of diagnostic test performance. ICER for annual combined screening remained within range of $50 000–$100 000 per QALY for most sensitivity and specificity pairs examined, until the sensitivity of combined mammography and MR imaging screening declined below 76%. Base case = Leach et al (13), *Peters* = Peters et al (30), *Kuhl* = Kuhl et al (17), *Warner* = Warner et al (15).

for women with *BRCA1* gene mutations can be improved through annual combined screening with screen-film mammography and MR imaging. When we compared three annual screening strategies, breast cancers were identified at smaller sizes and earlier stages and the greatest breast cancer mortality reduction was provided with combined screening. These results also highlight an important trade-off related to screening with MR imaging: an increased rate of false-positive test results. Our study provides a quantitative point estimate and frequency range of false-positive screening results, as well as their relationship to breast cancer mortality reduction. When annual MR imaging was added to annual mammographic screening, model projections of the number of additional false-positive screening test results incurred to avert a death from breast cancer increased from 37 to 137. These findings can be placed in the context of a survey by Schwartz et al (38) of women's preferences in regard to mammographic screening. In the study of Schwartz et al, 63% of women aged 18–97 years with no personal history of breast cancer indicated that they would accept 500 or more false-positive screening test results to avert a death from breast cancer. Thus, for women with *BRCA1* gene mutations, whose risk of breast cancer is much higher than that of the general population, the benefits of intensive surveillance for breast cancer are likely to outweigh the effects of false-positive screening results projected by our model.

When cost-effectiveness analysis was used to compare screening strategies, the most effective strategy, annual combined screening, was also the most costly. In the base-case analysis, the cost to gain an additional QALY through annual combined screening when compared with annual mammography alone was $69 125 per QALY. Annual MR imaging was more cost-effective when added as an adjunct to annual mammography rather than as a replacement. These findings suggest that the current screening recommendations for women at increased genetic risk of breast cancer from the American Cancer Society (20) are likely cost-effective.

Cost-effectiveness analysis provides a method for comparing the relative value of alternative interventions to improve health outcomes. Although no current consensus exists on a single dollar-per-QALY threshold value for defining whether an intervention can be considered cost-effective in the United States, commonly identified threshold values range from $50 000 to $100 000 per QALY (39,40). Applying this range to our base-case results, annual combined screening would likely be considered cost-effective (at $69 125 per QALY).

Another frequently applied approach to evaluating the potential cost-effectiveness of an intervention involves comparison with other accepted clinical practices. A cost-effectiveness analysis (36) of mammographic screening for women aged 40 years and older, on the basis of actual U.S. screening patterns, yielded an estimated ICER of $37 058 per QALY in 2000 U.S. dollars compared with no mammographic screening, which is equivalent to an ICER of $49 883 in 2007 U.S. dollars, after adjusting for inflation. Cost-effectiveness analyses of breast cancer screening focusing on subgroups within the general population have demonstrated higher ICERs (less cost-effective). A cost-effectiveness analysis (41) of adding annual mammographic screening for women aged 40–49 years to annual screening for women aged 50–69 years yielded an ICER of $168 400 per QALY in 1995 U.S. dollars ($268 107 in 2007 U.S. dollars). Kerlikowske et al (42) estimated that the ICER for annual mammographic screening for women up to age 79 years was $73 855

per year of life saved in 1998 U.S. dollars ($107 092 in 2007 U.S. dollars).

In the closest direct comparison with our results, Plevritis et al (35) estimated that the ICER for adding annual MR imaging to annual mammographic screening for women with *BRCA1* mutations aged 25–69 years is $88 705 per QALY ($96 422 per QALY in 2007 U.S. dollars), compared with our result of $69 125 per QALY. The incremental benefit in our analysis is more conservative than that of Plevritis et al, which is probably related to differing structural assumptions in the model, particularly those related to the natural history of ductal carcinoma in situ. The incremental costs in our analysis are also lower, probably related to differences in the sources for treatment costs and in how these costs were applied. Given the differences in model structure and underlying assumptions, the ICER estimates from our study and the study of Plevritis et al are roughly comparable. Because a definitive randomized controlled trial is unlikely to be performed, results such as these from different models may be valuable contributions to the developing consensus in regard to the long-term clinical effectiveness and cost-effectiveness of breast cancer screening with MR imaging.

The projected cost-effectiveness of annual combined screening is strongly dependent on the cost of an MR imaging examination and the underlying breast cancer risk in the women being screened. Variations in MR imaging cost could shift the ICER for annual combined screening from less than $50 000 per QALY to more than $100 000 per QALY. Similarly, annual combined screening was more cost-effective with increasing risk and less so with decreasing risk, because of either variation in mutation penetrance or prophylactic oophrectomy. It is important to note that the decision to undergo risk-reducing prophylactic oophorectomy is an individual one, which is based on a woman's personal preferences, goals, and level of risk tolerance. Even after prophylactic oophorectomy, our model projected that screening with annual combined mammography and MR imaging resulted in increased life expectancy and quality-adjusted life expectancy beyond that attainable with annual mammography alone.

Although the diagnostic test performance of the annual combined screening also had the potential to affect its cost-effectiveness, sensitivity for combined screening would have to be less than 76% (at the extreme end of the range of clinically plausible values) to increase the ICER beyond $100 000 per QALY.

Two potential limitations of our study were based on our choices for input parameter values. For some model parameter values, we extrapolated data from the general population to the *BRCA1* mutation carrier population. Whenever possible, parameter estimates specific to *BRCA1* mutation carriers were used. However, in some instances we based input parameter estimates on sources with larger sample sizes in the general population (25,27,43). We also used Medicare reimbursement (26) as a proxy for diagnostic costs, even though many women with *BRCA1* mutations undergoing screening are younger than 65 years, because Medicare estimates are the most generalizable among those of major health care payers (21).

For the combined screening strategy in this analysis, the two tests were assumed to be performed contemporaneously on an annual basis, as performed in multimodality screening trials (13–17). Consideration of screening with MR imaging and mammography at alternating 6-month intervals also has been advocated (44). Although not included in this analysis, modeling efforts to evaluate the comparative effectiveness of alternating and annual combined screening with MR imaging and mammography are under way.

In summary, annual combined screening for *BRCA1* mutation carriers provides the greatest life expectancy gain and is likely cost-effective, when the value placed on gaining an additional QALY is in the range of $50 000–$100 000. The benefits of screening with increased intensity for these women are likely to outweigh the effects of false-positive screening results.

Acknowledgment: We thank the Breast Cancer Surveillance Consortium for providing deidentified data used during model calibration and as model input parameters.

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