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Benefits, Harms, and Cost-Effectiveness of Supplemental Ultrasonography Screening for Women With Dense Breasts

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Background: Many states have laws requiring mammography facilities to tell women with dense breasts and negative results on screening mammography to discuss supplemental screening tests with their providers. The most readily available supplemental screening method is ultrasonography, but little is known about its effectiveness.

Objective: To evaluate the benefits, harms, and cost-effectiveness of supplemental ultrasonography screening for women with dense breasts.

Design: Comparative modeling with 3 validated simulation models.

Data Sources: Surveillance, Epidemiology, and End Results Program; Breast Cancer Surveillance Consortium; and medical literature.

Target Population: Contemporary cohort of women eligible for routine screening.

Time Horizon: Lifetime.

Perspective: Payer.

Intervention: Supplemental ultrasonography screening for women with dense breasts after a negative screening mammography result.

Outcome Measures: Breast cancer deaths averted, quality-adjusted life-years (QALYs) gained, biopsies recommended after a false-positive ultrasonography result, and costs.

Results of Base-Case Analysis: Supplemental ultrasonography screening after a negative mammography result for women aged 50 to 74 years with heterogeneously or extremely dense breasts averted 0.36 additional breast cancer deaths (range across models, 0.14 to 0.75), gained 1.7 QALYs (range, 0.9 to 4.7), and resulted in 354 biopsy recommendations after a false-positive ultrasonography result (range, 345 to 421) per 1000 women with dense breasts compared with biennial screening by mammography alone. The cost-effectiveness ratio was $325 000 per QALY gained (range, $112 000 to $766 000). Supplemental ultrasonography screening for only women with extremely dense breasts cost $246 000 per QALY gained (range, $74 000 to $535 000).

Results of Sensitivity Analysis: The conclusions were not sensitive to ultrasonography performance characteristics, screening frequency, or starting age.

Limitation: Provider costs for coordinating supplemental ultrasonography were not considered.

Conclusion: Supplemental ultrasonography screening for women with dense breasts would substantially increase costs while producing relatively small benefits.

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Mammographic breast density is a risk factor for breast cancer (1, 2). It also affects mammography performance (3–6). The false-negative rate of screening mammography varies as much as 10-fold from the lowest to the highest categories of breast density (5). Because breast density affects cancer risk and the false-negative rate of screening, at least 19 states have enacted legislation requiring that women with dense breasts be told about their breast density after screening mammography and that they should discuss supplemental screening tests, such as ultrasonography, with their providers (7, 8). Similar legislation is under consideration at the national level (9).

Breast density notification laws have an uncertain effect on health but could affect millions of women. More than 40% of women aged 40 to 74 years have dense breasts (10), defined in the laws as heterogeneously or extremely dense breast tissue by the American College of Radiology's Breast Imaging Reporting and Data System (BI-RADS) (9, 11). However, the American College of Radiology and other organizations have cautioned legislators, health policymakers, and health care providers to carefully consider the unintended consequences of legislation about breast density notification, including the uncertain harms and benefits of supplemental screening (8, 12–15). These concerns are amplified because of the subjective nature of the BI-RADS breast density assessment and the challenges that providers face in accurately assessing and communicating breast cancer risk to their patients.

Ultrasonography is often suggested for supplemental screening of women with dense breasts because it is widely available and has relatively low direct medical costs (16–18). Shortly after Connecticut became the first state to enact a law about breast density notification, as many as 30% of women with dense breasts at some practices within the state were having supplemental ultrasonography screening (19–21). Limited data from clinical trials and observational studies suggest that the addition of handheld ultrasonography

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EDITORS' NOTES

Context

Many states have enacted laws that require mammography facilities to advise women with dense breasts and a negative mammography to consider supplemental testing with their providers.

Contribution

Three validated microsimulation models compared breast cancer outcomes, quality-adjusted life-years gained, and costs for mammography alone versus supplemental ultrasonography after a negative mammography result for women with dense breasts aged 50 to 74 years.

Caution

Other imaging methods, such as digital breast tomosynthesis, were not assessed.

Implication

Supplemental ultrasonography screening for women with dense breasts would result in limited health gains and substantially increase costs.

screening to mammography for women with dense breasts increases cancer detection rates at the expense of increased biopsies for women without cancer (16, 19–22). Moreover, the effect of supplemental ultrasonography screening on long-term outcomes, such as breast cancer mortality and its cost-effectiveness at a population level, are unknown (8).

We assessed the potential benefits, harms, and cost-effectiveness of supplemental screening ultrasonography for women with dense breasts using 3 established Cancer Intervention and Surveillance Modeling Network breast cancer models (23). The models incorporate evidence from clinical trials and observational studies to estimate the effect of various screening scenarios on breast cancer outcomes, including breast cancer mortality, quality-adjusted life-years (QALYs), and costs (24, 25). The results provide evidence for policymakers considering legislation about breast density notification and for women and providers evaluating screening options for women with dense breasts.

METHODS

We used 3 microsimulation models developed independently within the National Cancer Institute–funded Cancer Intervention and Surveillance Modeling Network consortium (www.cisnet.cancer.gov): Model E (Erasmus University Medical Center, Rotterdam, the Netherlands), model G-E (Georgetown University Medical Center, Washington, DC, and Albert Einstein College of Medicine, Bronx, New York), and model W (University of Wisconsin, Madison, Wisconsin, and Harvard Medical School, Boston, Massachusetts). These modeling groups collaborate in the program project grant that supported this study and are described at http://cisnet.cancer.gov/breast/profiles.html and elsewhere (26–28). **Appendix Table 1** (available at www.annals.org) outlines the main model differences and assumptions. Our analyses used a lifetime horizon and federal payer perspective. In brief, the models simulated life histories of women who were at risk for breast cancer, had screening, were treated for breast cancer diagnosed by screening or clinical detection, and were at risk for dying of breast cancer and other causes. The models had independent approaches and modeling structures (23) but used common inputs, including incidence in the absence of screening, mammography performance, treatment effectiveness, and competing causes of death (29). The models approximately replicated U.S. breast cancer incidence and mortality trends (26–28, 30) (**Appendix Figure**, available at www.annals.org). For this analysis, we used simulated cohorts of women born in 1960, as described elsewhere (24, 25).

Model Variables

At age 40 years, women in the simulated model cohorts were assigned an initial breast density on the basis of the distribution of BI-RADS density categories for premenopausal women in the Breast Cancer Surveillance Consortium (BCSC) (**Table 1**) (31). At age 50 years, women were assigned to the same breast density category or the next lower category so the prevalence of breast density categories matched the BCSC observed prevalence for postmenopausal women (31). Sensitivity analyses were conducted with model W to examine the effect of reassigning density at both ages 50 and 65 years, on the basis of the BCSC data on the prevalence of breast density for women aged 50 to 64 years (44% with dense breasts) and 65 years or older (33% with dense breasts). In all scenarios, a woman's

Table 1. Key Common Input Used by the 3 Simulation Models: BI-RADS Breast Density

BI-RADS Breast Density	Prevalence, %*		Relative Risk for Breast Cancer†	
	Age <50 y	Age ≥50 y	Age <50 y	Age ≥50 y
Almost entirely fat	4.3	10.2	0.49	0.59
Scattered fibroglandular densities	34.3	49.0	1.00 (reference)	1.00 (reference)
Heterogeneously dense	47.0	35.5	1.55	1.46
Extremely dense	14.4	5.3	2.00	1.77

BI-RADS = Breast Imaging Reporting and Data System.
* Density prevalence is based on Breast Cancer Surveillance Consortium data for premenopausal vs. postmenopausal women having screening mammography (31).
† Unpublished data from the Breast Cancer Surveillance Consortium.

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modeled risk for breast cancer depended on her age and breast density, on the basis of BCSC data (Table 1).

Sensitivity and specificity of digital mammography were determined as a function of age, breast density, and screening interval using BCSC data (Appendix Table 2, available at www.annals.org) (32). To our knowledge, the American College of Radiology Imaging Network Protocol 6666 study, a randomized trial of using handheld ultrasonography to screen women with at least 1 risk factor for breast cancer, was the only controlled study of ultrasonography test performance (33). On the basis of this study, experts estimated screening ultrasonography performance after a negative mammography result for average-risk women. We used a screening ultrasonography sensitivity of 55% for women with dense breasts after a negative mammography result. We used a specificity of 94%, with positive examination results defined as those recommended for biopsy. Models were calibrated so 94% of ultrasonography screen–detected cancer cases were invasive and 6% were in situ, as seen in published studies (16, 22). Sensitivity analyses evaluated a range of performance characteristics (Table 2).

Health-related quality-of-life utilities were a function of age (34) and decremented for breast cancer diagnosis and stage-specific treatment (35). Sensitivity analyses included short-term reductions in quality of life for a screening examination (0.6% for 1 week per screening examination) or a positive screening result (10.5% for 5 weeks) (36).

The cost of a digital mammography screen was $138 based on the 2013 Medicare reimbursement rate. Screening ultrasonography does not currently have a specific reimbursement rate, so we used the reimbursement rate for diagnostic breast ultrasonography, which is $100. Sensitivity analyses were also conducted using higher potential reimbursement rates for screening ultrasonography because of its increased work intensity compared with diagnostic ultrasonography. Diagnostic costs for additional imaging and biopsy after a positive screening mammography result and costs for cancer treatment were based on Medicare reimbursement rates, utilization patterns seen in the BCSC, and estimates from the literature (32, 37). Diagnostic costs after a positive ultrasonography result were assumed to be equal to the biopsy-related costs of diagnostic work-up after a positive mammography result. All costs were in 2013 U.S. dollars.

Screening Strategies

Primary analysis compared 3 strategies for women aged 50 to 74 years receiving biennial mammography screening: mammography alone, mammography plus screening ultrasonography after a negative mammography result for women with extremely dense breasts, and mammography plus handheld screening ultrasonography after a negative mammography result for women with heterogeneously or extremely dense breasts (base case). Secondary analyses evaluated the 3 strategies as an annual screening regimen for women aged 40 to 74 years. All strategies were compared with "no screening." All scenarios assumed 100% adherence to the screening regimen and adjuvant treatment guidelines.

Table 2. Key Common Input Used by the 3 Simulation Models: Screening Ultrasonography Performance

Screening Ultrasonography Performance	Base-Case Value (Range in Sensitivity Analyses)
Sensitivity, %	55 (45–85)
Specificity, %	94 (90–98)
Cost of screening ultrasonography, $	100 (100–138)

Statistical Analysis

For each strategy, the models estimated breast cancer mortality rates, life-years, QALYs, false-positive examination results, and costs across the lifetimes of each simulated woman beginning at age 40 years. Costs, life-years, and QALYs were discounted at 3% annually (38). Within-model cost-effectiveness ratios were calculated for each ultrasonography strategy relative to its similar mammography-alone strategy by dividing the difference in total costs by the difference in QALYs. All results are presented as median and range from the 3 simulation models.

Role of the Funding Source

This work was funded by the National Cancer Institute. The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; or the decision to submit the manuscript for publication.

RESULTS

The 3 models yielded similar results for the estimated benefits and harms of the screening strategies (Figure 1 and Appendix Tables 3 and 4, available at www.annals.org). In the absence of screening, the models estimated 25.4 breast cancer deaths (range, 21.4 to 27.5 deaths) per 1000 women. Strategies with mammography screening alone reduced breast cancer deaths to 19.7 (range, 14.7 to 20.3 deaths) and 15.2 (range, 10.3 to 17.5 deaths) per 1000 women for biennial mammography screening for those aged 50 to 74 years and annual mammography screening for those aged 40 to 74 years, respectively. Relative to "no screening," these gains came at an increase in total costs of approximately $1 million per 1000 women for biennial mammography screening for those aged 50 to 74 years and $3 million per 1000 women for annual mammography screening for those aged 40 to 74 years.

For women aged 50 to 74 years having biennial screening, the models estimated that supplemental ultrasonography would result in 504 ultrasonography

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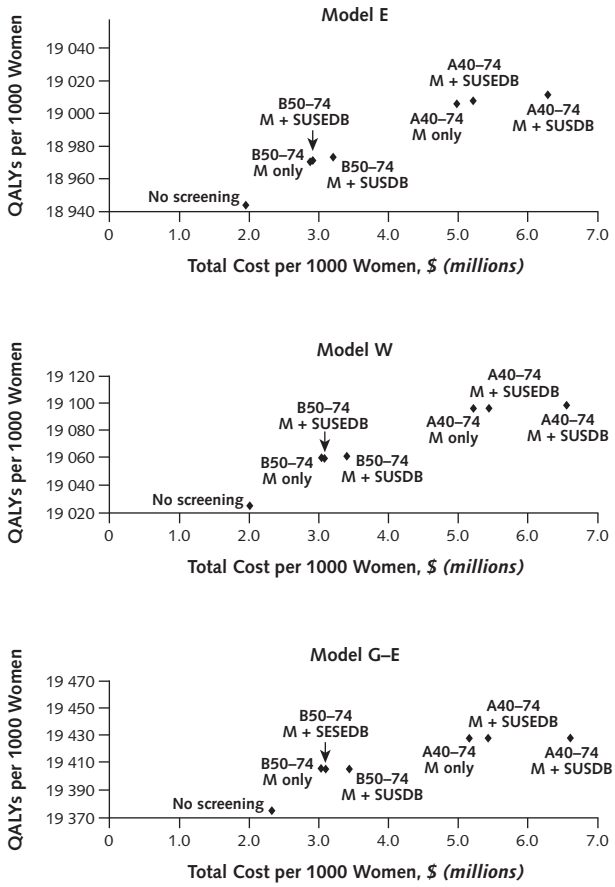
Figure 1. Discounted QALYs versus costs by model and screening strategy.



A40–74 = annual screening for women aged 40–74 y; B50–74 = biennial screening for women aged 50–74 y; M = mammography; model E = Erasmus University Medical Center, Rotterdam, the Netherlands; model G-E = Georgetown University Medical Center, Washington, DC, and Albert Einstein College of Medicine, Bronx, New York; model W = University of Wisconsin, Madison, Wisconsin, and Harvard Medical School, Boston, Massachusetts. QALY = quality-adjusted life-year; SUSDB = supplemental ultrasonography screening for women with dense breasts (heterogeneously or extremely dense); SUSEDB = supplemental ultrasonography screening for women with extremely dense breasts.

screening examinations (range, 361 to 584 examinations) per 1000 women if targeted to women with extremely dense breasts and 3827 ultrasonography screening examinations (range, 3417 to 4048 examinations) per 1000 women if targeted to women with heterogeneously or extremely dense breasts (Table 3).

Compared with biennial mammography screening alone for women aged 50 to 74 years, supplemental screening ultrasonography for women with extremely dense breasts averted 0.30 additional breast cancer deaths (range, 0.14 to 0.75 deaths) and produced 1.1 additional QALYs per 1000 women with extremely dense breasts (range, 0.8 to 3.9 QALYs) (Table 4). The median 1.1 QALYs gained per 1000 women is equal to 9.6 hours per woman. These gains came at the cost of 189 biopsies recommended after a false-positive ultrasonography result (range, 173 to 259 recommendations) and $287 000 per 1000 women with extremely dense breasts (range, $271 000 to $411 000). These findings produced a cost-effectiveness ratio of $246 000 per QALY gained (range, $74 000 to $535 000 per QALY gained) for supplemental ultrasonography relative to digital mammography screening alone. Supplemental ultrasonography screening for women with heterogeneously or extremely dense breasts averted 0.36 additional breast cancer deaths (range, 0.17 to 0.93 deaths) and produced 1.7 additional QALYs (range, 0.9 to 4.7 QALYs), at a cost of 354 biopsy recommendations after a false-positive ultrasonography result and $560 000 per 1000 women with heterogeneously or extremely dense breasts (range, $529 000 to $625 000). These findings produced a cost-effectiveness ratio of $325 000 per QALY gained (range, $112 000 to $766 000 per QALY gained) for supplemental ultrasonography relative to mammography screening alone (Table 4).

For an annual screening regimen for women aged 40 to 74 years, the benefits, harms, and costs of supplemental ultrasonography screening were substantially amplified (Tables 3 and 4). Supplemental ultrasonography screening for women with heterogeneously or extremely dense breasts averted 0.43

Table 3. Outcomes per 1000 Women Across the 3 Simulation Models, by Screening Strategy*

Screening Strategy	Mammography Screening Examinations, *n*†	Ultrasonography Screening Examinations, *n*
No screening	0	0
Biennial mammography in women aged 50–74 y		
Alone	11 014 (10 754–11 207)	0
Plus ultrasonography for extremely dense breasts‡	11 013 (10 753–11 207)	504 (361–584)
Plus ultrasonography for heterogeneously or extremely dense breasts‡	11 009 (10 746–11 207)	3827 (3417–4048)
Annual mammography in women aged 40–74 y		
Alone	30 172 (30 159–31 287)	0
Plus ultrasonography for extremely dense breasts‡	30 165 (30 155–31 287)	2151 (1837–2293)
Plus ultrasonography for heterogeneously or extremely dense breasts‡	30 145 (30 142–31 286)	12 397 (11 776–12 802)

QALY = quality-adjusted life-year.
* Numbers are medians, and numbers in parentheses are ranges. All outcomes computed from age 40 y until death. Life-years, QALYs, and total costs were discounted at 3% per year.
† <13 000 biennial mammography screenings were done in women aged 50–74 y and <35 000 annual mammography screenings were done in women aged 40–74 y because women in the cohort who died of other causes or were already diagnosed with breast cancer were not screened.
‡ Screening ultrasonography after a negative digital screening mammography result.

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additional breast cancer deaths (range, 0.08 to 1.28 deaths) and produced 3.0 additional QALYs (range, 0.7 to 9.4 QALYs) per 1000 women with heterogeneously or extremely dense breasts compared with mammography screening alone. These findings yielded a cost-effectiveness ratio of $728 000 per QALY gained (range, $223 000 to $3 509 000 per QALY gained) for supplemental ultrasonography relative to mammography screening alone (Table 4).

The incremental cost-effectiveness ratio of expanding supplemental ultrasonography screening from women with extremely dense breasts to women with either heterogeneously or extremely dense breasts was $338 000 per QALY gained (range, $121 000 to $562 000 per QALY gained) in the biennial screening scenario for women aged 50 to 74 years and $776 000 per QALY gained (range, $259 000 to $3 583 000 per QALY gained) for the annual screening scenario for women aged 40 to 74 years (data not shown).

Close examination of the model results revealed that differences in model estimates of the benefits of supplemental ultrasonography screening were largely due to variation in the estimated ultrasonography screening cancer detection rates among women with dense breasts after a negative mammography result (Table 5).

For biennial screening of women aged 50 to 74 years, the cost-effectiveness ratio of supplemental ultrasonography screening of women with heterogeneously or extremely dense breasts compared with mammography alone improved to $127 000 per QALY gained (range, $60 000 to $353 000 per QALY gained) when using elevated screening ultrasonography sensitivity (0.85) and specificity (0.98) (Figure 2). Increasing the cost of a screening ultrasonography examination to equal screening mammography had a modest effect on cost-effectiveness ratio (median, $396 000 per QALY gained), whereas the inclusion of short-term utility decrements for screening tests and diagnostic work-up substantially reduced the cost-effectiveness (median, $703 000 per QALY gained) of supplemental ultrasonography. The reassignment of breast density at both age 50 and 65 years (vs. at age 50 years only) had a small effect on the results for model W ($347 000 vs. $325 000 per QALY gained for the base-case scenario).

DISCUSSION

Our models predicted that supplemental ultrasonography screening for women with dense breasts would result in limited health gains and substantially increased expenses. The 3 models estimated that supplemental screening of women with heterogeneously or extremely dense breasts and a negative mammography result would cost more than $100 000 per QALY gained for either biennial screening of women aged 50 to 74 years or annual screening of women aged 40 to 74 years. The models consistently showed that targeting supplemental ultrasonography screening to women with extremely dense breasts having biennial mammography would be more efficient than targeting women with either heterogeneously or extremely dense breasts, although even this strategy was not cost-effective by most standards. The results also demonstrated that if supplemental ultrasonography screening was used, it would be more cost-effective for biennial screening of women aged 50 to 74 years than annual screening of women aged 40 to 74 years.

Although estimates of the breast cancer deaths averted and QALYs gained with supplemental ultrasonography screening varied across models, all models found a small effect of supplemental ultrasonography screening on breast cancer mortality rates and QALYs, particularly compared with the effect of screening mammography alone, which has a comparatively high sensitivity for detecting breast cancer. Consistent with previous work (25), our models estimated that biennial mammography alone for women aged 50 to 74 years averted approximately 6 breast cancer deaths per 1000 women compared with no screening. Supplemental ultrasonography screening of all women with heterogeneously or extremely dense breasts was estimated to

Table 3–Continued

Deaths Due to Breast Cancer, *n*	Life-Years	QALYs	Cost, *$ (millions)*
25.4 (21.4–27.5)	23 065.5 (22 947.7–23 510.0)	19 024.9 (18 943.8–19 374.4)	2.02 (1.96–2.31)
19.7 (14.7–20.3)	23 108.5 (22 981.0–23 548.7)	19 059.8 (18 970.4–19 405.4)	3.02 (2.87–3.05)
19.6 (14.7–20.3)	23 108.7 (22 981.6–23 548.9)	19 059.9 (18 970.9–19 405.5)	3.08 (2.91–3.08)
19.1 (14.5–20.2)	23 109.8 (22 984.4–23 549.4)	19 060.8 (18 973.3–19 405.9)	3.39 (3.20–3.42)
15.2 (10.3–17.5)	23 151.5 (23 025.4–23 575.4)	19 096.5 (19 005.9–19 427.5)	5.15 (4.99–5.22)
15.0 (10.3–17.5)	23 152.0 (23 027.4–23 575.5)	19 096.9 (19 007.6–19 427.6)	5.42 (5.22–5.45)
14.4 (10.1–17.4)	23 153.8 (23 032.3–23 575.9)	19 098.4 (19 011.7–19 427.9)	6.58 (6.28–6.60)

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Table 4. Benefits and Harms in Women With Dense Breasts From 3 Simulation Models for Supplemental Ultrasonography Screening Relative to Digital Mammography Alone*

Supplemental Screening Strategy†	Deaths Due to Breast Cancer Averted, *n*	Life-Years Gained	QALYs Gained
Biennial screening in women aged 50–74 y			
Supplemental ultrasonography for extremely dense breasts§	0.30 (0.14–0.75)	1.2 (0.9–4.5)	1.1 (0.8–3.9)
Supplemental ultrasonography for heterogeneously or extremely dense breasts‖	0.36 (0.17–0.93)	2.1 (1.0–5.6)	1.7 (0.9–4.7)
Annual screening in women aged 40–74 y			
Supplemental ultrasonography for extremely dense breasts§	0.35 (0.04–1.40)	3.6 (0.6–14.0)	3.1 (0.6–11.8)
Supplemental ultrasonography for heterogeneously or extremely dense breasts‖	0.43 (0.08–1.28)	3.7 (0.8–11.3)	3.0 (0.7–9.4)

QALY = quality-adjusted life-years.
* Numbers are medians, and numbers in parentheses are ranges.
† Supplemental ultrasonography indicates screening ultrasonography after a negative digital screening mammography result.
‡ For supplemental ultrasonography screening for women with heterogeneously or extremely dense breasts compared with that for women with extremely dense breasts.
§ Outcomes per 1000 women with extremely dense breasts.
‖ Outcomes per 1000 women with heterogeneously or extremely dense breasts.

reduce the breast cancer death rate by 0.36 deaths per 1000 women with dense breasts compared with mammography screening alone. The models were consistent in finding that supplemental ultrasonography screening for women with heterogeneously or extremely dense breasts would cost more than $100 000 per QALY gained relative to mammography screening alone. Thus, despite improved screening sensitivity with the addition of supplemental ultrasonography, each model projected a limited effect on breast cancer mortality rates and QALYs gained because of relatively low cancer detection rates for screening ultrasonography among women at average risk who have regular mammography screening.

Although breast density legislation typically defines dense breasts as heterogeneously or extremely dense, we found that scenarios in which supplemental ultrasonography screening was limited to women with extremely dense breasts were relatively more efficient. For biennial screening of women aged 50 to 74 years, the models estimated improved cost-effectiveness for supplemental ultrasonography screening when targeted to women with extremely dense breasts; 1 model estimated $74 000 per QALY gained relative to mammography alone. All models generated unfavorable cost-effectiveness ratios for supplemental ultrasonography screening of women with extremely dense breasts for annual screening of women aged 40 to 74 years, reinforcing the effect of screening frequency on results.

Conclusions were generally consistent across models and robust in sensitivity analyses. Model estimates of costs and false-positive ultrasonography screening results for each screening strategy were in close agreement. The models showed more substantial variation in estimates of the benefits of supplemental screening, although all models reported small benefits. Cost-effectiveness ratios used measures of benefit in the denominator; thus, the ratios were sensitive to small differences.

The range in model-estimated supplemental screening benefits reflects uncertainty about breast cancer natural history in the absence of screening. The models used independent approaches to simulate the natural history of breast cancer with different assumptions for unobservable variables, such as duration of the preclinical screen-detectable phase of cancer and the proportion of cancer that does not ultimately lead to breast cancer death. Sensitivity analyses also indicated considerable variation in cost-effectiveness according to the ultrasonography screening sensitivity and specificity variables. No randomized, controlled studies are available on the use of adjunct ultrasonography for screening in women with dense breasts but at otherwise average risk for breast cancer (33). Data are needed on ultrasonography screening performance in community settings directly relevant to breast density legislation (that is, among women with dense breasts, a negative mammography result, and various risks for breast cancer). Variation in comparative effectiveness estimates could be reduced with high-quality data on ultrasonography screening, including cancer detection rate, stage distribution, and false-negative rate after a negative mammography result among women with dense breasts at various ages and levels of breast cancer risk. Such data would be particularly useful in evaluating alternative ultrasonography screening strategies that target women on the basis of factors beyond breast density alone, including breast cancer risk or likelihood of a false-negative mammography result.

Estimates of the benefits of supplemental ultrasonography screening were substantially affected by considering short-term utility decrements that may result from screening examinations and diagnostic workup. In sensitivity analyses that assigned short-term utility decrements for mammography and ultrasonography examinations, the median cost per QALY gained from supplemental ultrasonography screening increased from $325 000 to $703 000. These results suggest that the benefit-to-harm balance of supplemental ultrasonography could vary substantially depending on a woman's tolerance for false-positive results and screening-related anxiety. Recent findings from the Digital Mammographic Imaging Screening Trial (39)

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Table 4–Continued

Biopsies Recommended After a False-Positive Ultrasonography Result, *n*	Additional Cost, $	Cost per QALY Gained Relative to Mammography Alone, $	Incremental Cost per QALY Gained, $‡
189 (173–259)	287 000 (271 000–411 000)	246 000 (74 000–535 000)	
354 (345–421)	560 000 (529 000–652 000)	325 000 (112 000–766 000)	338 000 (121 000–562 000)
879 (865–1018)	1 693 000 (1 596 000–1 889 000)	553 000 (135 000–3 221 000)	
1219 (1174–1333)	2 210 000 (2 103 000–2 363 000)	728 000 (223 000–3 509 000)	776 000 (259 000–3 583 000)

suggest that although anxiety is increased after a false-positive mammography result, health utility scores, as measured by the EuroQol-5D questionnaire, do not differ from women with a negative mammography result. Further research is needed to examine the short-term effects of supplemental ultrasonography screening on health utility scores, particularly because of the frequency of biopsy after an abnormal screening ultrasonography examination.

Our cost-effectiveness analysis was from the payer perspective and did not include societal costs, such as patient time or facility costs for coordinating ultrasonography screening; these factors would further increase the costs of supplemental screening. We assumed 100% screening and treatment adherence in evaluating the screening strategies and did not evaluate supplemental screening strategies for women who did not have routine mammography. We considered only false-positive ultrasonography recommendations for biopsy because only a small fraction of women with suspicious screening ultrasonography findings but a negative mammography result are referred for additional imaging (19–21). However, a substantial fraction of ultrasonography screening examinations resulted in recommended short-interval follow-up (19–21). We did not model short-interval follow-up, which would further increase costs and likely reduce the cost-effectiveness of supplemental ultrasonography screening. Thus, the implications and optimal management of women receiving short-interval follow-up recommendations after ultrasonography screening is an area for further research.

Our findings indicated that supplemental ultrasonography screening of women with dense breasts would substantially increase costs while producing small benefits in breast cancer deaths averted and QALYs gained. To further improve our understanding of these harms and benefits, we need research that provides high-quality estimates of the performance of supplemental ultrasonography screening in women at various levels of breast cancer risk. This includes both handheld ultrasonography screening and automated whole breast ultrasonography, which is an emerging technology with the potential to increase the standardization of ultrasonography screening while reducing user skill and time constraints (40, 41). We also need estimates of the utility decrements associated with supplemental screening.

The widespread replacement of film mammography by digital mammography in the United States has reduced but not eliminated the disparity in screening

Table 5. Sample Histories From 3 Simulation Models of Annual Screening With Digital Mammography Plus Ultrasonography for Women Aged 40 to 74 y With Heterogeneously or Extremely Dense Breasts*

Variable	Model E	Model W	Model G-E
Screening mammograms, *n*†	9652	9583	9694
True-positive screening mammography results, *n*	27	38	26
Mammography cancer detection rate‡	2.8	4.0	2.7
Negative mammography results, *n*	8811	8669	8684
Ultrasonography screening examinations, *n*§	3497	3090	3435
True-positive screening ultrasonography results, *n*	2.8	1.8	0.3
False-negative screening ultrasonography results, *n*	2.3	1.1	0.2
Biopsies recommended after a false-positive screening ultrasonography result, *n*	206	198	219
Ultrasonography cancer detection rate‡‖	0.8	0.6	0.1
Ultrasonography sensitivity, %¶	55	62	57
Ultrasonography specificity, %	94	94	94
Invasive ultrasonography-detected cancer, %**	94	94	96

Model E = Erasmus University Medical Center, Rotterdam, the Netherlands; model G-E = Georgetown University Medical Center, Washington, DC, and Albert Einstein College of Medicine, Bronx, New York; model W = University of Wisconsin, Madison, Wisconsin, and Harvard Medical School, Boston, Massachusetts.

* Screening outcomes per 10 000 women are shown for a single calendar year corresponding to age 52 y.

† Women previously diagnosed with breast cancer were not screened.

‡ Per 1000 examinations.

§ Supplemental ultrasonography screening occurred in women with heterogeneously or extremely dense breasts after a negative mammography result.

‖ Cases of cancer detected among women with a negative screening mammography result.

¶ Although the overall sensitivity target for screening ultrasonography was 55% in each model, the models used different techniques to calibrate detection probability curves that can vary on the basis of patient age, tumor size, and other factors, thereby resulting in modest differences in sensitivity across models for the observed sensitivity for a given age group (in this case, age 52 y).

** Versus in situ cancer.

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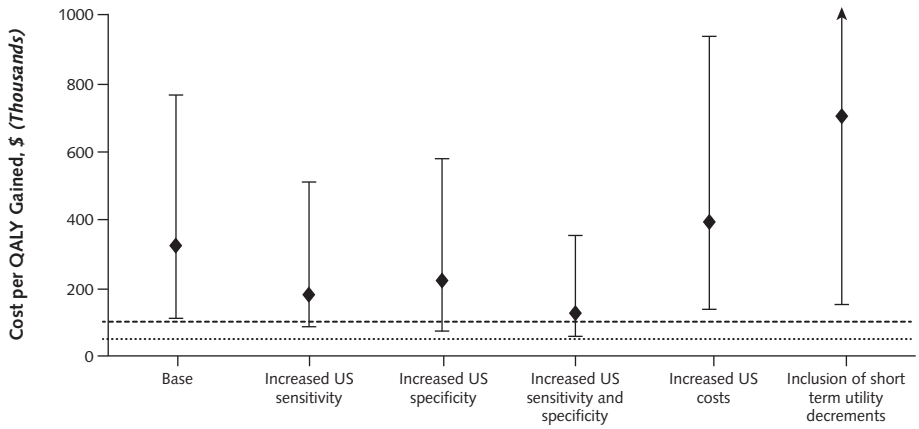
Figure 2. Sensitivity analyses comparing costs per QALY gained for biennial mammography alone with mammography plus supplemental US for women aged 50 to 74 y with heterogeneously or extremely dense breasts.



The *x*-axis shows key variables that were changed. Diamonds show the median from the 3 simulation models. Error bars show the range across models. Dashed and dotted lines indicate $100 000 and $50 000 per QALY gained, respectively. The values explored for each variable are described in the Methods section and **Tables 1** and **2**. QALY = quality-adjusted life-year; US = ultrasonography.

mammography sensitivity according to breast density (42). Targeted supplemental screening strategies are also motivated by the elevated breast cancer risk for women with dense breasts. Although our results demonstrate that, even under optimistic assumptions, supplementary handheld ultrasonography screening in women with dense breasts but otherwise average risk is not cost-effective, it remains possible that a better-performing technology with targeted application to women with dense breasts or to women at higher-than-average risk may be useful. We particularly need studies evaluating the potential role of additional imaging methods, such as magnetic resonance imaging and digital breast tomosynthesis, in screening for women with dense breasts.

Our results are directly applicable to breast density legislation. The value of breast density notification is complex and must be evaluated from various perspectives. We hope our results inform discussions about pending national legislation and provide health care providers and women with information to guide decisions about screening strategies.

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Appendix Table 1. Key Assumptions and Features in the 3 Simulation Models*

Variable	Model E	Model W	Model G-E
Breast cancer natural history			
Model structure	Continuous-time tumor growth model beginning in preclinical in situ disease; subset does not progress from in situ to invasive disease	Continuous-time tumor growth model beginning in preclinical in situ disease; subset does not progress from early invasive disease and may regress if undetected	State transition model beginning in preclinical in situ disease; subset does not progress from in situ to invasive disease
Parameter estimation	Calibrated to U.S. stage-specific breast cancer incidence between 1975 and 2000	Calibrated to U.S. stage-specific breast cancer incidence and mortality between 1975 and 2000	Calibrated to U.S. stage-specific breast cancer incidence between 1975 and 2000
Screening and treatment			
Implementation of screening benefits	Tumor size	Tumor size; age shifts	Stage; age shifts
Implementation of treatment benefits	Cure fraction	Cure faction	Hazard reduction
Factors affecting treatment benefits	ER and HER2 status; age; calendar year	ER status; age; calendar year; stage at diagnosis	ER and HER2 status; age; calendar year; stage at diagnosis
Software			
Programming language	Delphi	C++	C++

ER = estrogen receptor; HER2 = human epidermal growth factor receptor-2; model E = Erasmus University Medical Center, Rotterdam, the Netherlands; model G-E = Georgetown University Medical Center, Washington, DC, and Albert Einstein College of Medicine, Bronx, New York; model W = University of Wisconsin, Madison, Wisconsin, and Harvard Medical School, Boston, Massachusetts.
* Adapted from reference 32.

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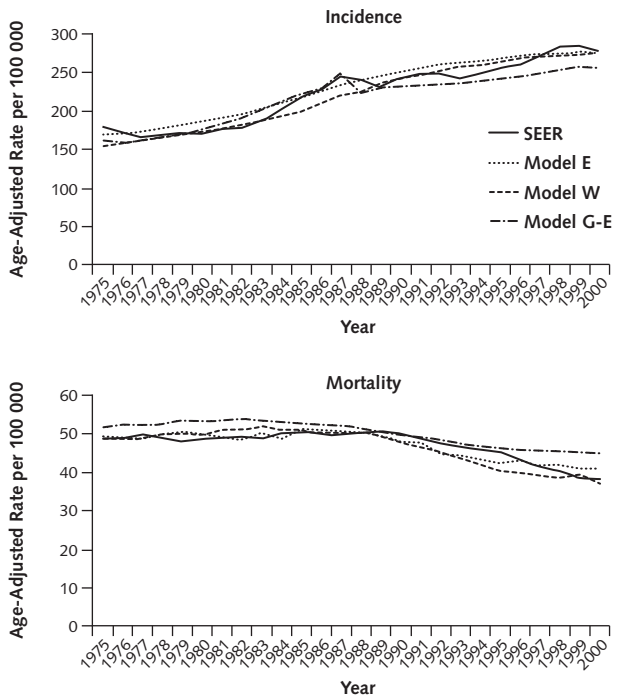
Appendix Figure. Model replication of U.S. incidence and mortality patterns for women aged 30 to 79 y during 1975–2000.



Model E = Erasmus University Medical Center, Rotterdam, the Netherlands; model G-E = Georgetown University Medical Center, Washington, DC, and Albert Einstein College of Medicine, Bronx, New York; model W = University of Wisconsin, Madison, Wisconsin, and Harvard Medical School, Boston, Massachusetts; SEER = Surveillance, Epidemiology, and End Results Program.

Appendix Table 2. Digital Mammography Sensitivity and Specificity, by Screening Interval, Age Group, and Breast Density*

BI-RADS Breast Density, by Age and Screening Interval	Sensitivity, %	Specificity, %
Almost entirely fat		
40–49 y		
First screening	84	90
Annual screening†	69	95
Biennial screening‡	76	94
50–74 y		
First screening	88	92
Annual screening	76	95
Biennial screening	82	95
Scattered fibroglandular densities		
40–49 y		
First screening	91	83
Annual screening	82	90
Biennial screening	87	89
50–74 y		
First screening	94	85
Annual screening	87	92
Biennial screening	90	90
Heterogeneously dense		
40–49 y		
First screening	86	78
Annual screening	74	87
Biennial screening	80	85
50–74 y		
First screening	90	81
Annual screening	80	89
Biennial screening	85	88
Extremely dense		
40–49 y		
First screening	87	82
Annual screening	74	90
Biennial screening	80	88
50–74 y		
First screening	90	85
Annual screening	80	92
Biennial screening	85	90

BI-RADS = Breast Imaging Reporting and Data System.
* From the Breast Cancer Surveillance Consortium, 2001–2008; adapted from reference 32. Sensitivity and specificity based on a 12-mo follow-up for defining interval cancer. Multivariable logistic regressions were used to estimate parameters. Covariates included age, screening frequency, and breast density.
† Screening examinations with a screening in the previous 9–18 mo included in the calculation.
‡ Screening examinations with a screening in the previous 19–30 mo included in the calculation.

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Appendix Table 3. Model-Specific Outcomes per 1000 Women Associated With Biennial Digital Mammography Screening in Women Aged 50 to 74 y, by Screening Strategy*

Screening Strategy	Mammography Screening Examinations, *n*	Ultrasonography Screening Examinations, *n*	Biopsies Recommended After a False-Positive Ultrasonography Result, *n*	Deaths Due to Breast Cancer, *n*	Life-Years	QALYs	Total Cost, $
Model E							
No screening	0	0	0	25.4	22 947.7	18 943.8	1 956 003
Biennial mammography							
Alone	11 014	0	0	19.7	22 981.0	18 970.4	2 872 768
Plus ultrasonography for extremely dense breasts†	11 013	504	27	19.6	22 981.6	18 970.9	2 914 062
Plus ultrasonography for heterogeneously or extremely dense breasts†	11 009	3827	212	19.1	22 984.4	18 973.3	3 197 490
Model W							
No screening	0	0	0	21.4	23 065.5	19 024.9	2 021 074
Biennial mammography							
Alone	10 754	0	0	14.7	23 108.5	19 059.8	3 048 791
Plus ultrasonography for extremely dense breasts†	10 753	361	23	14.7	23 108.7	19 059.9	3 084 855
Plus ultrasonography for heterogeneously or extremely dense breasts†	10 746	3417	218	14.5	23 109.8	19 060.8	3 393 578
Model G-E							
No screening	0	0	0	27.5	23 510.0	19 374.4	2 312 148
Biennial mammography							
Alone	11 207	0	0	20.3	23 548.7	19 405.4	3 018 824
Plus ultrasonography for extremely dense breasts†	11 207	584	37	20.3	23 548.9	19 405.5	3 078 048
Plus ultrasonography for heterogeneously or extremely dense breasts†	11 207	4048	258	20.2	23 549.4	19 405.9	3 418 949

Model E = Erasmus University Medical Center, Rotterdam, the Netherlands; model G-E = Georgetown University Medical Center, Washington, DC, and Albert Einstein College of Medicine, Bronx, New York; model W = University of Wisconsin, Madison, Wisconsin, and Harvard Medical School, Boston, Massachusetts; QALY = quality-adjusted life-year.

* All outcomes computed from age 40 y until death. Life-years, QALYs, and total costs were discounted at 3% per year.

† Screening ultrasonography after a negative screening mammography result.

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Appendix Table 4. Model-Specific Outcomes per 1000 Women Associated With Annual Digital Mammography Screening in Women Aged 40 to 74 y, by Screening Strategy*

Screening Strategy	Mammography Screening Examinations, *n*	Ultrasonography Screening Examinations, *n*	Biopsies Recommended After a False-Positive Ultrasonography Result, *n*	Deaths Due to Breast Cancer, *n*	Life-Years	QALYs	Total Cost, $
Model E							
No screening	0	0	0	25.4	22 947.7	18 943.8	1 956 003
Annual mammography							
Alone	30 159	0	0	15.2	23 025.4	19 005.9	4 989 653
Plus ultrasonography for extremely dense breasts†	30 155	2151	124	15.0	23 027.4	19 007.6	5 219 332
Plus ultrasonography for heterogeneously or extremely dense breasts†	30 142	12 397	721	14.4	23 032.3	19 011.7	6 280 442
Model W							
No screening	0	0	0	21.4	23 065.5	19 024.9	2 021 074
Annual mammography							
Alone	30 172	0	0	10.3	23 151.5	19 096.5	5 223 561
Plus ultrasonography for extremely dense breasts†	30 165	1837	117	10.3	23 152.0	19 096.9	5 448 521
Plus ultrasonography for heterogeneously or extremely dense breasts†	30 145	11 776	751	10.1	23 153.8	19 098.4	6 584 407
Model G-E							
No screening	0	0	0	27.5	23 510.0	19 374.4	2 312 148
Annual mammography							
Alone	31 287	0	0	17.5	23 575.4	19 427.5	5 147 210
Plus ultrasonography for extremely dense breasts†	31 287	2293	147	17.5	23 575.5	19 427.6	5 419 072
Plus ultrasonography for heterogeneously or extremely dense breasts†	31 286	12 802	818	17.4	23 575.9	19 427.9	6 598 051

Model E = Erasmus University Medical Center, Rotterdam, the Netherlands; model G-E = Georgetown University Medical Center, Washington, DC, and Albert Einstein College of Medicine, Bronx, New York; model W = University of Wisconsin, Madison, Wisconsin, and Harvard Medical School, Boston, Massachusetts; QALY = quality-adjusted life-year.

* All outcomes computed from age 40 y until death. Life-years, QALYs, and total costs were discounted at 3% per year.

† Screening ultrasonography after a negative screening mammography result.

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