


Cost-effectiveness of annual versus biennial screening mammography for women with high mammographic breast density

J Med Screen
2014, Vol. 21(4) 180–188
© The Author(s) 2014
Reprints and permissions:
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/0969141314549758
msc.sagepub.com


Reka Pataky^{1,2}, Zahra Ismail¹, Andrew J Coldman², Mark Elwood³, Karen Gelmon^{4,5}, Lindsay Hedden^{6,7}, Greg Hislop², Lisa Kan⁸, Bonnie McCoy⁹, Ivo A Olivetto¹⁰ and Stuart Peacock^{1,2,6}

Abstract

Objectives: The sensitivity of screening mammography is much lower among women who have dense breast tissue, compared with women who have largely fatty breasts, and they are also at much higher risk of developing the disease. Increasing mammography screening frequency from biennially to annually has been suggested as a policy option to address the elevated risk in this population. The purpose of this study was to assess the cost-effectiveness of annual versus biennial screening mammography among women aged 50–79 with dense breast tissue.

Methods: A Markov model was constructed based on screening, diagnostic, and treatment pathways for the population-based screening and cancer care programme in British Columbia, Canada. Model probabilities and screening costs were calculated from screening programme data. Costs for breast cancer treatment were calculated from treatment data, and utility values were obtained from the literature. Incremental cost-effectiveness was expressed as cost per quality adjusted life year (QALY), and probabilistic sensitivity analysis was conducted.

Results: Compared with biennial screening, annual screening generated an additional 0.0014 QALYs (95% CI: –0.0480–0.0359) at a cost of \$819 (\$ = Canadian dollars) per patient (95% CI: 506–1185), resulting in an incremental cost effectiveness ratio of \$565,912/QALY. Annual screening had a 37.5% probability of being cost-effective at a willingness-to-pay threshold of \$100,000/QALY.

Conclusion: There is considerable uncertainty about the incremental cost-effectiveness of annual mammography. Further research on the comparative effectiveness of screening strategies for women with high mammographic breast density is warranted, particularly as digital mammography and density measurement become more widespread, before cost-effectiveness can be reevaluated.

Keywords

screening mammography, cost-effectiveness, breast density, health economics

Date received: 17 February 2014; accepted: 12 August 2014

Introduction

Breast density – a measure of the relative amount of epithelial and connective tissue to fat – is a strong risk factor for breast cancer,^{1,2} and dense breast tissue may mask tumours on mammograms, reducing the effectiveness of regular screening.³ Women with breast density of over 75% as measured on mammograms are at least four times more likely to develop breast cancer than women with very low (<10%) breast density.^{4–7} The sensitivity of mammography screening has been reported to be as low as 62% in women with extremely dense breasts, compared with 88% in women with almost entirely fatty breasts.⁸ Consequently, women with dense breasts are significantly more likely to be diagnosed with interval cancers

¹Canadian Centre for Applied Research in Cancer Control, Vancouver, Canada

²Cancer Control Research, BC Cancer Agency, Vancouver, Canada

³School of Population Health, University of Auckland, Auckland, New Zealand

⁴Medical Oncology, BC Cancer Agency, Vancouver, Canada

⁵Department of Medicine, University of British Columbia, Vancouver, Canada

⁶School of Population and Public Health, University of British Columbia, Vancouver, Canada

⁷Canadian Health Human Resources Network, Ottawa, Canada

⁸Screening Mammography Program of British Columbia, Vancouver, Canada

⁹Breast Cancer Prevention & Risk Assessment Clinic, University of British Columbia, Vancouver, Canada

¹⁰Division of Radiation Oncology, Tom Baker Cancer Centre, and University of Calgary, Calgary, Canada

Corresponding author:

Stuart Peacock, 675 West 10th Avenue, Vancouver, BC, V5Z 1L3 Canada.
Email: speacock@bccrc.ca

(vs. screen-detected cancers) than women with non-dense breasts.^{3,9,10}

There is continued debate in the literature regarding the effect of breast density on breast cancer outcomes. Survival for interval cancer is worse than for screen-detected cancer.^{11,12} Women with dense breasts are reportedly more likely to be diagnosed with larger tumours,^{13–16} but findings for nodal involvement and other prognostic factors are mixed, with some studies reporting an association between breast density and higher risk disease,^{13,14} and others reporting no effect.^{15,16} Breast density alone does not appear to be an independent predictor of survival; controlling for patient and disease characteristics, including stage and method of detection, breast cancer survival among women with dense breasts is no different from that among women without dense breasts.¹⁷ In one study, the case fatality ratio among women with dense breasts was found to be lower than that among women with fatty breasts;¹⁸ however, women with dense breasts remained at significantly higher risk of breast cancer mortality, due to their elevated risk of developing the disease.¹⁸

More frequent mammography screening has been proposed as a way to improve the early detection of cancers in women with dense breasts. Studies comparing the outcomes at different breast cancer screening intervals for women with dense breasts have reported mixed results. A model by van Gils et al. found that screening women with $\geq 75\%$ breast density annually instead of biennially could result in a 36% reduction in interval cancers in that subpopulation.¹⁹ Similarly, by simulating mean sojourn time for cancers in dense and non-dense breasts, Chiu *et al.* suggested that reducing the screening interval from three years to one could halve the proportion of interval cancers in women with dense breasts, from 44% to 22%.⁹ However, White et al. report from observational data that, among women with dense breasts, those who undergo biennial screening are no more likely to have late stage cancers, larger tumours, or higher grade cancers than women screened annually.²⁰ There is also the potential for overdiagnosis of breast cancer due to higher frequency screening; however, overdiagnosis rates reported in the literature vary widely,²¹ and there are no data on the effect of breast density on risk of overdiagnosis.

With the high risk of developing breast cancer, and a potential reduction in interval cancers, increasing the frequency of mammography screening from every two years to annually for women with dense breasts may be an attractive policy option, but there is significant uncertainty around the cost-effectiveness of this intervention. Screening women over age 50 with dense breast tissue every two years has been found to be cost-effective at a US\$50,000/QALY threshold, compared with screening every 3–4 years.²² For annual screening, however, the incremental cost-effectiveness is over US\$340,000/QALY.²²

Until a recent policy change,²³ women in British Columbia (BC) with dense breasts were offered annual

screening from ages 40 to 49, and biennial screening from ages 50–79. The purpose of this study was to assess the incremental cost-effectiveness of annual screening mammography from ages 50–79 for women with $\geq 75\%$ mammographic breast density.

Methods

Model

We constructed a Markov model to estimate the benefits and costs, from the health system perspective, associated with annual versus biennial screening mammography for women with high breast density. The model structure was based on screening, diagnosis, and care pathways for the Screening Mammography Program of BC (SMPBC), a population-based screening programme, and the BC Cancer Agency (BCCA). An advisory panel of clinicians and decision-makers, including a radiologist, oncologists, epidemiologists, and the director of screening operations, led the development of the model structure (Figure 1). The model simulates a hypothetical population of 50 year-old women with dense breasts participating in the SMPBC, with screening annually or biennially to age 79, assuming full participation. The model was constructed with a six month cycle length and a lifetime time horizon. The model structure, costs and utilities were the same in the annual and biennial arms of the model; only the transition probabilities differed.

Probabilities

Transition probabilities, summarized in Table 1, were calculated using SMPBC and BC Cancer Registry data. The SMPBC database includes participant characteristics, the

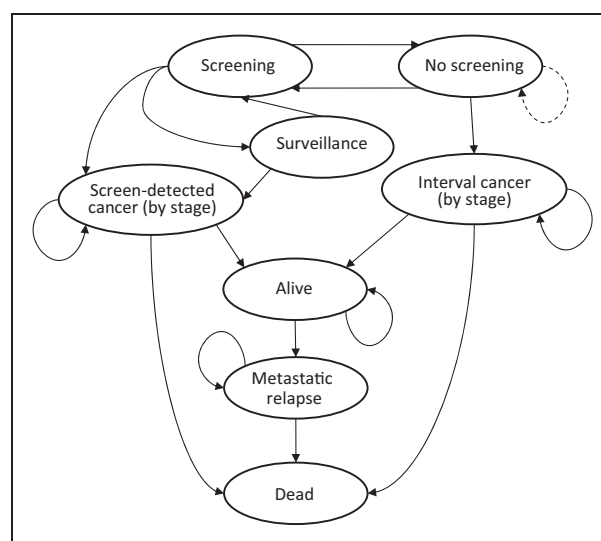


Figure 1. Model Structure. In the annual screening arm, women alternate between 'screening' and 'no screening' states every cycle (6 months); in the biennial arm, women spend three cycles in the 'no screening' state (indicated by dashed line).

Table 1. Transition probabilities for model.

Probability*		Annual screening		Biennial screening	
		Mean	95% CI	Mean	95% CI
Abnormal screen	50–59 years	0.070	0.061–0.079	0.082	0.069–0.094
	60–69 years	0.051	0.046–0.056	0.060	0.053–0.066
	70–79 years	0.037	0.034–0.039	0.043	0.040–0.047
Cancer diagnosis following abnormal screen	50–59 years	0.079	0.065–0.093	0.084	0.069–0.099
	60–69 years	0.156	0.107–0.205	0.163	0.109–0.217
	70–79 years	0.209	0.122–0.297	0.251	0.128–0.374
Interval cancer diagnosis†	50–59 years	0.0013	0.0011–0.0015	0.0015	0.0013–0.0017
	60–69 years	0.0017	0.0014–0.0021	0.0020	0.0017–0.0024
	70–79 years	0.0021	0.0014–0.0028	0.0025	0.0017–0.0032
Cancer diagnosis from surveillance	50–59 years	0.037	0.019–0.054	0.031	0.016–0.046
	60–69 years	0.073	0.037–0.109	0.062	0.032–0.092
	70–79 years	0.122	0.062–0.182	0.103	0.053–0.154
<u>Stage distribution‡</u>		Screen-detected		Interval cancers	
		Mean	95% CI	Mean	95% CI
Stage distribution	In Situ	0.237	0.214–0.266	0.089	0.073–0.108
	Stage I	0.500	0.468–0.531	0.343	0.313–0.372
	Stage II	0.234	0.208–0.260	0.476	0.446–0.508
	Stage III	0.027	0.018–0.038	0.090	0.073–0.107
	Stage IV	0.002	0.0002–0.006	0.002	0.0002–0.006
<u>10-year survival§</u>		Screen-detected		Interval cancers	
		Mean	95% CI	Mean	95% CI
Stage I		0.953	0.938–0.964	0.941	0.910–0.961
Stage II	50–69 years	0.803	0.772–0.828	0.744	0.732–0.755
	≥ 70 years	0.781	0.693–0.848	0.585	0.545–0.624
Stage III	50–69 years	0.503	0.253–0.687	0.580	0.494–0.657
	≥ 70 years	0.310	0.035–0.577	0.422	0.201–0.627
Stage IV	50–69 years	0.102	0.073–0.131	0.102	0.073–0.131
	≥ 70 years	0.046	0.022–0.074	0.046	0.022–0.074

*transition probabilities for abnormal screen and cancer diagnosis are specific to women with extremely dense breasts ($\geq 75\%$ density); beta distributions were fit to probability estimates for probabilistic sensitivity analysis.

†interval cancer risk expressed per 6-month model cycle.

‡Stage distributions by detection method were fit to Dirichlet distributions for probabilistic sensitivity analysis.

§Survival by stage and detection method was modeled with Weibull functions; parameters were fit to multinormal distributions for probabilistic sensitivity analysis.

date and result of screening mammograms, and records of follow-up procedures and diagnosis after an abnormal screen, since 1988. The Registry includes demographic, diagnosis, and mortality information for all cancer cases in BC since 1969.

The probability of a woman having an abnormal screen and undergoing diagnostic workup was calculated by analyzing SMPBC screening results from 2005 to 2007. The subset of screening centres reporting Breast Imaging, Reporting and Data System (BI-RADS) density was used to calculate the distribution of breast density $\geq 75\%$ (BI-RADS category 4) and screen positivity

rates. Cancer incidence for women with dense breasts was estimated by applying the density distribution and relative rates by density category⁶ to rates calculated for all SMPBC participants from 2005 to 2007. Age-specific incidence for screen-detected and interval cancers were calculated separately for participants who had been screened annually (defined as <16 months since preceding screen) or biennially (18–30 months since preceding screen). Observed screen positivity rates and incidence by screening frequency were used directly; no assumptions regarding sensitivity and specificity were required. SMPBC data from 2003 were analyzed to determine the

probability of a woman undergoing additional surveillance after receiving a false positive screening result.

Stage distribution of screen-detected and interval cancers and survival by stage were assumed to be no different for women with dense breasts than for the general breast cancer population, and were calculated from the BC Cancer Registry. Breast cancer survival rates by stage were calculated by fitting a series of Weibull models to Registry data. All-cause mortality was from Statistics Canada life tables.²⁴

Utility

Quality of life adjustments were made using utility values abstracted from the literature. Studies with relevant utility values were identified.^{25–27} Utility weights used in the model are summarized in Table 2. For two health states, diagnostic work-up following an abnormal screen and remission following initial treatment, the best available utility values had been measured using a visual analog scale;²⁵ these values were scaled up to approximate standard gamble values.²⁸ Women participating in a screening programme are generally healthy members of the population. We assumed their utility value would be that of full health. An abnormal screen and subsequent diagnostic workup is accompanied by anxiety and potential pain and discomfort, and utility during this time is slightly reduced.²⁵ Utilities for breast cancer by stage at diagnosis were applied for the first year following diagnosis;²⁶ a value representing remission was applied to subsequent cycles.²⁵

Costs

Costs included: the mean cost of a mammogram, from operating costs of the SMPBC;²⁹ mean costs associated with diagnosis or surveillance following an abnormal screen, including diagnostic mammogram, ultrasound, consultations, core biopsy, or fine needle aspiration procedures; and the cost of treating breast cancer (Table 2).

The mean costs of diagnostic work-up and surveillance were calculated by combining patient-level resource use from the SMPBC data from 2003, and procedure costs estimated from the BC Medical Services Fee Schedule.³⁰ The cost of treating breast cancer was calculated using treatment records from breast cancer patients in their first year after diagnosis. For in situ disease and stage I–III breast cancer, the frequency of systemic therapy, radiation therapy, and surgical procedures were calculated from BCCA administrative data from 2002. The BCCA pharmacy provided the mean drug and delivery cost for systemic therapy protocols. The BCCA radiation therapy programme provided the average number of radiation fractions received by patients one year post diagnosis according to stage, and a mean cost per fraction estimated using the radiation therapy operating budget. The cost of surgery (mastectomy and lumpectomy) was estimated by combining professional costs from the BC Medical Services Fee Schedule, with local case cost and hospitalization costs. The cost of treating metastatic breast cancer was based on a study of BC women in 1995–1996.³¹ The cost of chemotherapy for metastatic breast cancer was

Table 2. Utility weights and cost inputs for model.

Health State	Utility weight		Unit Cost (per cycle)	
	Mean	95% CI*	Mean	95% CI†
Screening	1.00	–	\$62	\$35–\$99
Diagnostic Workup	0.994	0.986–1.00	\$177	\$101–\$261
Surveillance	0.994	0.986–1.00	\$108	\$62–\$167
Dead	0.000	–	\$0	–
Alive (full health)	1.00	–	\$0	–
	Utility weight‡		Total Cost (per case)	
	Mean	95% CI	Mean	95% CI
In Situ	0.965	0.440–1.00	\$4,408	\$4211–\$6789
Stage I	0.910	0.314–1.00	\$5,864	\$3436–\$8863
Stage II	0.750	0.320–0.983	\$9,546	\$5559–\$14,371
Stage III	0.510	0.272–0.745	\$11,705	\$6397–\$18,093
Stage IV§	0.450	0.203–0.557	\$23,262	\$18,086–\$29,188

*utility weights were fit to beta distributions for probabilistic sensitivity analysis; screening/full health (1.0) and dead (0) were not varied.

†where a confidence interval was not available, or possible to calculate, it was assumed that standard deviation was equal to one quarter of the point estimate; all costs were fit to gamma distributions for probabilistic sensitivity analysis.

‡for all cancer health states, utility weight was applied for the first year following diagnosis, after which a remission utility (0.965) was applied.

§utility and cost for metastatic relapse were assumed to be the same as for diagnosis with Stage IV disease.

updated using BCCA systemic therapy utilization data from 2002–2007, and the cost of hospitalization and radiotherapy was inflated to 2007 values.³² All costs in the model are expressed in 2007 Canadian dollars.

Analysis

The model was built and analyzed using TreeAge Pro 2013.³³ The cohort accumulates quality-adjusted life years (QALYs) and costs associated with each health state in every cycle. Costs and QALYs were discounted at 3% per annum. The changes in costs and quality-adjusted life expectancy for annual screening, relative to biennial screening, were used to calculate an incremental cost-effectiveness ratio (ICER) expressed as dollars per QALY gained.

Probabilistic sensitivity analysis was conducted using a Monte Carlo simulation with 1000 trials sampling from distributions for all parameters – probabilities, costs, and utilities. Beta distributions were used for utilities and probabilities, gamma distributions were used for costs, Dirichlet distributions were used for stage distributions, and multinormal distributions were used for parameters for survival curves. One-way sensitivity analysis was carried out on the cost of a screening mammogram, the cost of diagnostic work-up, utility adjustment, and discount rate.

Ethics approval was obtained from the University of British Columbia/British Columbia Cancer Agency Research Ethics Board.

Results

Annual screening compared with biennial screening generated an additional 0.0014 QALYs (95% CI:

–0.0480–0.0359) at an additional cost of \$819 (95% CI: 506–1,185), resulting in an ICER of \$565,912/QALY. Model projections of lifetime breast cancer incidence were slightly higher in the annual screening arm compared with the biennial screening arm, with a higher proportion of cancers detected through screening, a higher proportion of in situ and stage I cancers, and slightly reduced breast cancer mortality (Table 3).

A scatter plot of the incremental cost and QALYs from 1000 replications (Figure 2) shows the simulations clustered around the y-axis. In 43.4% of simulations, annual screening resulted in a loss of QALYs relative to biennial screening. The cost-effectiveness acceptability curve (Figure 3) indicates that annual screening mammography has only a 23.5% probability of being cost-effective at a willingness to pay of \$50,000/QALY, and a 37.5% probability of being cost-effective at a willingness to pay of \$100,000/QALY.

One-way sensitivity analysis indicates that the results were sensitive to the cost of a screening mammogram, with an ICER range of \$412,423/QALY–\$776,748/QALY as cost was varied from \$35 to \$99; results were far less sensitive to the cost of diagnostic work-up, which resulted in an ICER range of \$546,448/QALY–\$588,817/QALY as cost was varied from \$101 to \$261. Adjusting for utility had a large impact on cost effectiveness estimates: without applying utility weights, annual screening resulted in a mean gain in life expectancy of 0.0042 years (95% CI: –0.0201–0.0287), for an ICER of \$194,281/life-year gained. Discounting assumptions also had a large effect. Without discounting, annual screening cost \$82,387/QALY, while at a discount rate of 5%, annual screening was dominated by biennial screening, with a loss of 0.0013 QALYs at an additional cost of \$666.

Table 3. Model results and results of cost-effectiveness analysis for annual vs. biennial screening in women with dense breasts.

	Annual screening		Biennial screening			
	Mean	95% CI	Mean	95% CI		
Incidence (%)	26.6	23.4–30	23.2	20.7–26.0		
Screen-detection (%)	64.0	57.3–69.9	49.4	42.9–55.8		
Stage distribution (%)						
In situ	19.9	17.9–22.1	17.2	15.4–19.1		
Stage I	46	43.3–48.4	43	40.4–45.3		
Stage II	29.6	27.1–32	34.1	31.6–36.7		
Stage III	4.3	3.4–5.3	5.5	4.5–6.7		
Stage IV	0.20	0.05–0.47	0.20	0.05–0.43		
Breast cancer mortality (%)	2.85	2.48–3.30	2.99	2.63–3.42		
	Annual screening		Biennial screening		Increment	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
Cost (\$)	2,747	2,152–3,454	1,928	1,515–2,386	819	506–1,185
QALY	21.000	20.437–21.075	20.998	20.359–21.067	0.0014	–0.0480–0.0359
Cost-utility (\$/QALY)	131	102–164	92	72–114	565,912	–

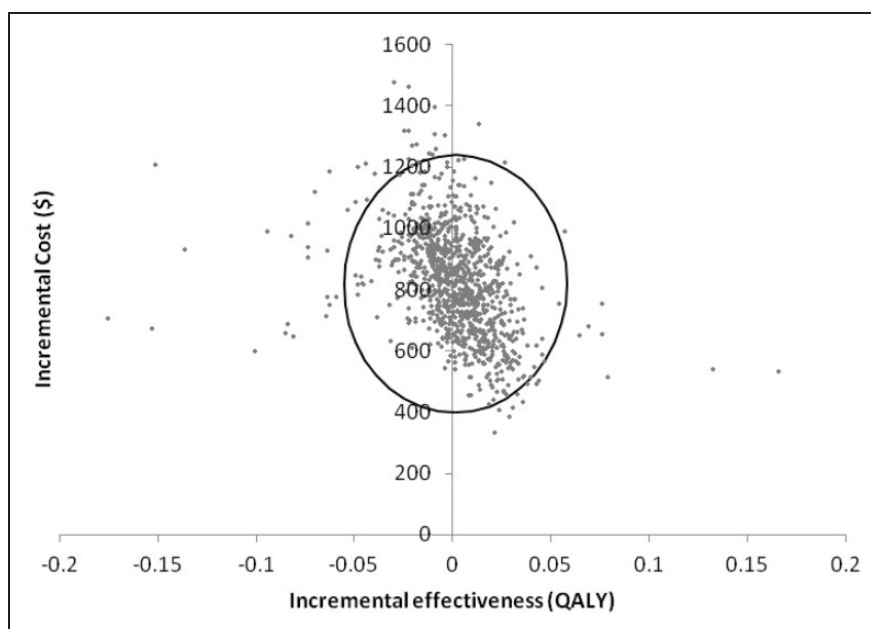


Figure 2. Scatter plot of incremental cost and effectiveness for 1000 simulations. Ellipse indicates 95% of confidence limit. Abbreviations: QALY, quality-adjusted life year.

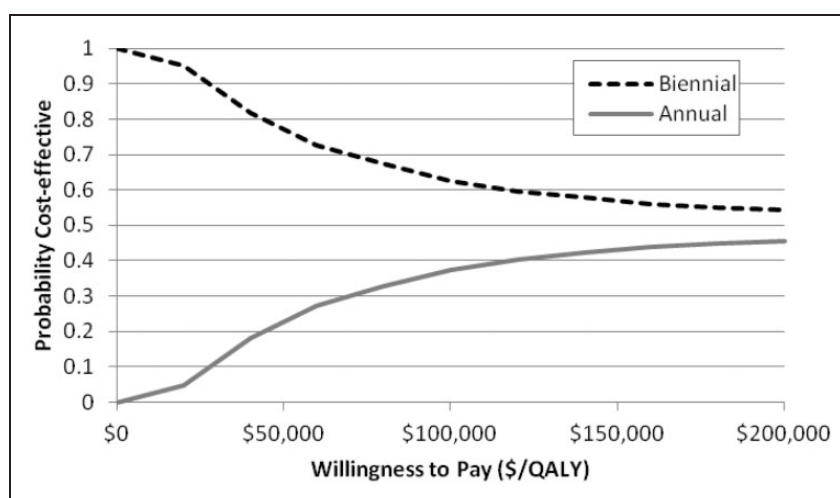


Figure 3. Cost-effectiveness acceptability curve for annual vs. biennial screening. Abbreviations: QALY, quality-adjusted life year.

Discussion

Our model predicted that there is a small mean incremental benefit to women with dense breasts who undergo annual screening mammography from ages 50 to 79, compared with biennial screening; however, there is considerable uncertainty around that result, with 43% of simulations resulting in a loss of QALYs. The model also predicted a positive incremental cost in all simulations.

Annual screening mammography for women with dense breasts has only a 38% probability of being cost-effective at a willingness-to-pay threshold of \$100,000/

QALY, with a mean ICER of over \$500,000/QALY. This value far exceeds the commonly cited cost-effectiveness thresholds of £20,000–£30,000/QALY (approximately \$30,000–\$45,000/QALY)³⁴ or \$50,000/QALY.³⁵ A retrospective analysis of the cost-effectiveness on various screening mammography strategies found that the cost-effectiveness varied widely depending on screening interval and age at first and last screen.³⁶ The study did not evaluate the cost-effectiveness of annual screening mammography for women with high mammographic breast density, but the results show that frequency of screening mammography has a large impact of the cost-effectiveness of the intervention. For women with dense

breast tissue, Schousboe et al. reported that biennial screening, relative to screening every 3–4 years, is cost-effective at a threshold of US\$50,000/QALY in women over the age of 50.²² The authors also found that targeting higher frequency screening at women with other risk factors – a family history of breast cancer, or a prior breast biopsy – improved cost-effectiveness.²² However, they report that the ICERs for annual screening vs. biennial screening, for all age groups and categories of breast density, were over US\$340,000/QALY. Our results indicate that there is little additional benefit from annual screening in all women with dense breasts, but further personalization of screening frequency may improve these outcomes.

The uncertainty around the benefit of annual screening mammography for women with dense breasts is consistent with the literature. The clinical impact of biennial versus annual screening has not been clearly demonstrated. While models have predicted a reduction in interval cancers between 36% and 50%,^{9,19} there is little trial or observational data on the potential stage shift and mortality reduction associated with higher frequency screening in this population. We found a trend towards reduced breast cancer mortality with annual screening, and a small but significant increase in breast cancer incidence. This difference in incidence probably represents overdiagnosis attributable to annual screening. Overdiagnosis was not explicitly built into the model; this difference arose from the observed cancer incidence in women screened annually versus biennially in the SMPBC. Estimated overdiagnosis rates vary widely²¹ and there is little information on the effect of screening frequency. Compared with annual screening, biennial³⁷ or triennial³⁸ screening strategies reportedly decrease overdiagnosis by less than half. Screening women aged 70–79 in the model was also a contributor, as overdiagnosis increases with age.³⁹

Effectiveness estimates in the model are very finely balanced, with many simulations resulting in a net loss of QALYs. The sensitivity to utility weights also illustrates this result. Reductions in utility from overdiagnosis of breast cancer and false positive screening results largely offset the small gains in life expectancy from reduced breast cancer mortality. Discounting highlights the differential timing of these effects. The potential harms of screening (false positives and overdiagnosis) occur well before the potential benefits (reduced breast cancer mortality and extended life expectancy), and when these future benefits are discounted at 5%/year, annual screening results in a net loss of QALYs.

Transition probabilities for screening were calculated using SMPBC data from 2005–2007, and a limitation of the study is that during those years screening was conducted largely with film mammography. As reported by the Digital Mammography Imaging Screening Trial, digital mammography is more accurate than film in younger women and in women with dense breasts.⁴⁰ In BC, screening sites are currently being converted to digital mammography. The film mammography data probably

underestimates the effectiveness of current digital screening practice, but because both the intervention and comparator arms of the current model would be affected, it is difficult to infer the impact on cost-effectiveness. Using data for film mammography also underestimates screening cost; however, digital mammography is potentially cost-effective in this population of high-risk women.⁴¹ Screening with tomosynthesis, ultrasound, or magnetic resonance imaging has also been proposed in this population. Digital breast tomosynthesis, which uses a series of images to produce three-dimensional data, has been found to have significantly higher sensitivity and specificity than digital mammography.⁴² Breast MRI has been recommended for women with a lifetime risk of breast cancer over 20–25%,⁴³ but there is little data on its effectiveness as a screening tool in women for whom breast density is their only risk factor. The addition of ultrasound to mammography for women with high breast density has been found to significantly increase the sensitivity of screening, but with an increase in the risk of false positive results.⁴⁴ Recently-adopted legislation in some American jurisdictions now requires radiologists to inform women of their breast density and recommend additional screening with ultrasound; however, more long-term clinical effectiveness and cost-effectiveness evidence is required to better understand the impact of these recommendations⁴⁵ and to inform future screening policy.

A limitation of this model is that it considered costs and outcomes in a defined population of women with dense breasts. The cost of assessing breast density among all screening participants, the accuracy of density assessment, or changes in women's breast density over time were not considered.

Furthermore, current definitions of breast density, measured as the relative area of the breast made up of fibroglandular tissue, do not reflect the three-dimensional distribution of breast tissue. Methods to model volumetric breast density from two-dimensional mammography images or from three-dimensional tomosynthesis are being validated against area-based measurements.⁴⁶ The clinical significance of volumetric breast density as a predictor for breast cancer risk or screening effectiveness is not yet known.

The model relied heavily on routinely collected observational data from the SMPBC and the BC Cancer Registry. The data are representative of local experience, but also present some limitations, as observational data may suffer from unadjusted confounding in a way that screening effectiveness estimates from randomized controlled trials do not.

This study is the first to evaluate the cost-effectiveness of annual screening mammography for women who have high mammographic breast density. The results indicate that there is considerable uncertainty about the incremental effectiveness of the intervention, but also suggest that annual screening for women aged 50–79 is not cost-effective, with a mean ICER of over \$500,000/QALY.

Further research on the comparative effectiveness of screening strategies for women with high mammographic breast density is warranted, as are subsequent economic evaluations exploring the value-for-money implications of these strategies.

Acknowledgements

The authors thank Dr. Paula Gordon, Medical Director of the Sadie Diamond Breast Program at BC Women's Hospital, for her contributions to the study and comments on the manuscript. The authors also thank members of the Screening Mammography Program of British Columbia, the British Columbia Breast Tumour Group, and participants in the provincial screening mammography programme.

Funding

This study was funded by Canadian Institutes of Health Research grant no. 162964 as part of a programme of research into setting priorities for cancer control. The Canadian Centre for Applied Research in Cancer Control is funded by the Canadian Cancer Society.

Conflict of interest

The authors have no conflicts of interest to declare.

References

1. Barlow WE, White E, Ballard-Barbash R, et al. Prospective Breast Cancer Risk Prediction Model for Women Undergoing Screening Mammography. *Journal of the National Cancer Institute* 2006;**98**:1204–14.
2. Tice JA, Cummings SR, Smith-Bindman R, Ichikawa L, Barlow WE, Kerlikowske K. Using clinical factors and mammographic breast density to estimate breast cancer risk: development and validation of a new predictive model. *Annals of Internal Medicine* 2008;**148**:337–47.
3. Mandelson MT, Oestreicher N, Porter PL, et al. Breast Density as a Predictor of Mammographic Detection: Comparison of Interval- and Screen-Detected Cancers. *Journal of the National Cancer Institute* 2000;**92**:1081–7.
4. McCormack VA, dos Santos Silva I. Breast Density and Parenchymal Patterns as Markers of Breast Cancer Risk: A Meta-analysis. *Cancer Epidemiology Biomarkers & Prevention* 2006;**15**:1159–69.
5. Boyd NF, Byng JW, Jong RA, et al. Quantitative Classification of Mammographic Densities and Breast Cancer Risk: Results From the Canadian National Breast Screening Study. *Journal of the National Cancer Institute* 1995;**87**:670–5.
6. Boyd NF, Guo H, Martin LJ, et al. Mammographic Density and the Risk and Detection of Breast Cancer. *New England Journal of Medicine* 2007;**356**:227–36.
7. van Gils C, Otten JM, Verbeek AM, Hendriks JCL. Mammographic breast density and risk of breast cancer: Masking bias or causality? *Eur J Epidemiol* 1998;**14**:315–20.
8. Carney PA, Miglioretti DL, Yankaskas BC, et al. Individual and Combined Effects of Age, Breast Density, and Hormone Replacement Therapy Use on the Accuracy of Screening Mammography. *Annals of Internal Medicine* 2003;**138**:168–75.
9. Chiu SY-H, Duffy S, Yen AM-F, Tabár L, Smith RA, Chen H-H. Effect of Baseline Breast Density on Breast Cancer Incidence, Stage, Mortality, and Screening Parameters: 25-Year Follow-up of a Swedish Mammographic Screening. *Cancer Epidemiology Biomarkers & Prevention* 2010;**19**:1219–28.
10. Ciatto S, Visioli C, Paci E, Zappa M. Breast density as a determinant of interval cancer at mammographic screening. *Br J Cancer* 2004;**90**:393–6.
11. Eriksson L, Czene K, Rosenberg L, Tornberg S, Humphreys K, Hall P. Mammographic density and survival in interval breast cancers. *Breast Cancer Research* 2013;**15**:R48.
12. Shen Y, Yang Y, Inoue LYT, Munsell MF, Miller AB, Berry DA. Role of Detection Method in Predicting Breast Cancer Survival: Analysis of Randomized Screening Trials. *Journal of the National Cancer Institute* 2005;**97**:1195–203.
13. Aiello EJ, Buist DSM, White E, Porter PL. Association between Mammographic Breast Density and Breast Cancer Tumor Characteristics. *Cancer Epidemiology Biomarkers & Prevention* 2005;**14**:662–8.
14. Roubidoux MA, Bailey JE, Wray LA, Helvie MA. Invasive Cancers Detected after Breast Cancer Screening Yielded a Negative Result: Relationship of Mammographic Density to Tumor Prognostic Factors. *Radiology* 2004;**230**:42–8.
15. Porter GJR, Evans AJ, Cornford EJ, et al. Influence of Mammographic Parenchymal Pattern in Screening-Detected and Interval Invasive Breast Cancers on Pathologic Features, Mammographic Features, and Patient Survival. *American Journal of Roentgenology* 2007;**188**:676–83.
16. Eriksson L, Czene K, Rosenberg L, Humphreys K, Hall P. The influence of mammographic density on breast tumor characteristics. *Breast Cancer Research and Treatment* 2012;**134**:859–66.
17. Gierach GL, Ichikawa L, Kerlikowske K, et al. Relationship Between Mammographic Density and Breast Cancer Death in the Breast Cancer Surveillance Consortium. *Journal of the National Cancer Institute* 2012;**104**:1218–27.
18. Olsen AH, Bihrmann K, Jensen MB, Vejborg I, Lynge E. Breast density and outcome of mammography screening: a cohort study. *Br J Cancer* 2009;**100**:1205–8.
19. van Gils CH, Otten JDM, Hendriks JHCL, Holland R, Straatman H, Verbeek ALM. High mammographic breast density and its implications for the early detection of breast cancer. *J Med Screen* 1999;**6**:200–4.
20. White E, Miglioretti DL, Yankaskas BC, et al. Biennial Versus Annual Mammography and the Risk of Late-Stage Breast Cancer. *Journal of the National Cancer Institute* 2004;**96**:1832–9.
21. Moss S. Overdiagnosis and overtreatment of breast cancer: Overdiagnosis in randomised controlled trials of breast cancer screening. *Breast Cancer Research* 2005;**7**:230–4.
22. Schousboe JT, Kerlikowske K, Loh A, Cummings SR. Personalizing Mammography by Breast Density and Other Risk Factors for Breast Cancer: Analysis of Health Benefits and Cost-Effectiveness. *Annals of Internal Medicine* 2011;**155**:10–20.
23. BC Cancer Agency. Breast Screening Policy.
24. Life Tables, Canada, Provinces and Territories, 2005 to 2007. No. 001 ed.: Statistics Canada, 2012.
25. Bonomi AE, Boudreau DM, Fishman PA, et al. Quality of life valuations of mammography screening. *Quality of Life Research* 2008;**17**:801–14.

26. Schleinitz MD, DePalo D, Blume J, Stein M. Can differences in breast cancer utilities explain disparities in breast cancer care? *J Gen Intern Med* 2006;**21**:1253–60.
27. Earle CC, Chapman RH, Baker CS, et al. Systematic overview of cost-utility assessments in oncology. *J Clin Oncol* 2000;**18**:3302–17.
28. Torrance GW, Feeny DH, Furlong WJ, Barr RD, Zhang YM, Wang QN. Multiattribute utility function for a comprehensive health status classification system-Health Utilities Index Mark 2. *Med Care* 1996;**34**:702–22.
29. Screening Mammography Program: 2010 Annual Report. Vancouver, BC: BC Cancer Agency, 2010.
30. BC Medical Services Commission. Payment Schedule. Ministry of Health Services, 2007.
31. Wai ES, Trevisan CH, Malfair Taylor SC, Mates D, Jackson JS, Olivotto IA. Health System Costs of Metastatic Breast Cancer. *Breast Cancer Research and Treatment* 2001;**65**:233–40.
32. Table 326-0002: Consumer Price Index (CPI), 2001 basket content. *Health and Personal Care*. Ottawa: Statistics Canada, 2007.
33. TreeAge Software. *TreeAge Pro 2013*. Williamstown, MA: TreeAge Software, Inc, 2013.
34. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the economic evaluation of health care programmes*. 3rd ed. Oxford: Oxford University Press, 2005.
35. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *Canadian Medical Association Journal* 1992;**146**:473–81.
36. Stout NK, Rosenberg MA, Trentham-Dietz A, Smith MA, Robinson SM, Fryback DG. Retrospective Cost-effectiveness Analysis of Screening Mammography. *Journal of the National Cancer Institute* 2006;**98**:774–82.
37. Mandelblatt JS, Cronin KA, Bailey S, et al. Effects of Mammography Screening Under Different Screening Schedules: Model Estimates of Potential Benefits and Harms. *Annals of Internal Medicine* 2009;**151**:738–47.
38. Gunsoy NB, Garcia-Closas M, Moss SM. Estimating breast cancer mortality reduction and overdiagnosis due to screening for different strategies in the United Kingdom. *Br J Cancer* 2014;**110**:2412–9.
39. Coldman A, Phillips N. Incidence of breast cancer and estimates of overdiagnosis after the initiation of a population-based mammography screening program. *Canadian Medical Association Journal* 2013;**185**:E492–E8.
40. 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**:1773–83.
41. Tosteson ANA, Stout NK, Fryback DG, et al. Cost-Effectiveness of Digital Mammography Breast Cancer Screening. *Annals of Internal Medicine* 2008;**148**:1–10.
42. Michell MJ, Iqbal A, Wasan RK, et al. A comparison of the accuracy of film-screen mammography, full-field digital mammography, and digital breast tomosynthesis. *Clinical Radiology* 2012;**67**:976–81.
43. Saslow D. American cancer society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin* 2007;**57**:75–89.
44. Berg WA, Blume JD, Cormack JB, et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. *JAMA* 2008;**299**:2151–63.
45. Hooley RJ, Greenberg KL, Stackhouse RM, Geisel JL, Butler RS, Philpotts LE. Screening US in Patients with Mammographically Dense Breasts: Initial Experience with Connecticut Public Act 09-41. *Radiology* 2012;**265**:59–69.
46. Yaffe M. Mammographic density. Measurement of mammographic density. *Breast Cancer Research* 2008;**10**:209.