

*Short Communication***A Model-Based Comparison of Breast Cancer Screening Strategies: Mammograms and Clinical Breast Examinations**Yu Shen¹ and Giovanni Parmigiani²¹Department of Biostatistics and Applied Mathematics, M.D. Anderson Cancer Center University of Texas, Houston, Texas and ²Departments of Oncology, Biostatistics, and Pathology, Johns Hopkins University, Baltimore, Maryland**Abstract**

In screening for secondary prevention of breast cancer, clinical breast examination (CBE) combined with mammography may improve overall screening sensitivity compared with mammography alone. A systematic evaluation of the relative expenses and projected benefit of combining these two screening modalities is not presently available. We addressed this issue using a microsimulation model incorporating age-specific preclinical duration of the disease, age-specific sensitivities of the two modalities, age-specific incidence of the disease, screening strategy, and competing causes of mortality. We examined a total of 48 screening strategies, depending on the age range, the examination interval, and whether mammography or CBE is given at every one or two exam. Our results indicate that a biennial mammography can be cost-effective if coupled with annual

CBE. For each screening interval and starting age, giving mammography every two exams and CBE at every exam has the lowest marginal cost per year of quality-adjusted life saved, whereas giving both at every exam has the highest. Comparing annual mammography and CBE to biennial mammography and annual CBE from 50 to 79, the total cost was reduced by 35%, whereas the marginal quality-adjusted life years only decreased by 12%. Similar reductions are observed for other starting ages. It is cost-effective to have a biennial mammography if coupled with an annual CBE. Annual mammography combined with CBE every 6 months will lead to a 41% increase in the quality-adjusted life years compared with annual mammography and CBE from 50 to 79, whereas the total cost increases by 30%. (Cancer Epidemiol Biomarkers Prev 2005;14(2):529–32)

Introduction

Breast cancer remains a major public health concern among North American women. Screening for breast cancer is a common and valuable approach to secondary prevention (1, 2). Despite broad utilization, there is variability on the specific implementation of screening policy. Differences involve frequency, starting age, examination modality, and other aspects. Some controversy still exists on the most appropriate implementation. For example, American Cancer Society and American College of Radiology recommend annual mammography screening for women ages ≥ 40 years, whereas National Cancer Institute recommends screening every 1 to 2 years (3, 4).

In selecting optimal screening approaches, benefits of early detection in terms of morbidity and mortality need to be carefully balanced against the burden to women and cost to the health care system. Although extensive literature exists on the costs and benefits of mammography screening versus not screening, and on alternative starting ages and frequencies of the examination (5–20), insufficient attention has been given to a potentially critical factor: The impact of combining mammography and clinical breast examination as done in randomized breast cancer screening trials, such as Health Insurance Plan of

New York Study (21), Canadian National Breast Cancer Screening Study (22), and the Edinburgh trial (23). Recent studies suggest that mammography combined with CBE may improve the overall screening sensitivity compared with mammography alone (24–28). CBE is generally easier to administer as part of a routine physical examination and is less expensive than mammography. Adding routine CBE to mammography can be particularly valuable among younger women for whom the sensitivity of mammography alone is lower (29).

This study provides the first comprehensive investigation of screening strategies, including both mammography and CBE, in terms of mortality reduction and costs. Its long-term goal is to promote more efficient early detection programs. The benefits of screening depend on complex interactions among several factors: age-specific preclinical duration of the disease, age-specific sensitivities of the individual screening modalities, relationship among those modalities, age-specific incidence of the disease, and competing causes of mortality (30). To address these factors, we generalize an existing comprehensive simulation-based decision model of early breast cancer (31, 32) to evaluate alternative screening strategies, including potentially the use of CBE. The primary interest of this investigation is to compare the effects of various breast cancer screening policies and the costs directly associated to these policies. The health effect of interest is the expected gain in quality-adjusted survival relative to the typical health history of a woman not receiving screening exams.

Materials and Methods

Statistical Models and Data Sources. Our approach is a decision analysis based on a microsimulation model.

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The model was developed using data from several sources, including population-level data, randomized breast cancer screening trials data, and data from large clinical trials to evaluate standard treatments of breast cancer. Using this information, we generate the complete health history of birth cohort of women undergoing various screening strategies. We evaluate a total of 48 screening strategies, each determined by the combination of an age range (40-79, 45-79, and 50-79 years), an interval between examinations (0.5, 1, 1.5, and 2 years), and whether mammography and CBE are given at every exam or at every two exams. Outcomes of interest are the expected gain in quality-adjusted life years (QALYS) and expected total costs of examinations. Marginal cost is defined as the difference in total costs between the screened and unscreened cohorts. We do not explicitly consider the costs of false-positive exams, possible overdiagnosis, and the downstream financial consequences of early detection (33, 34). We consider two cost scenarios: CBE at \$100, mammography at \$200 or \$150. The cost ratio of mammography and CBE is a critical component in the comparisons of different screening strategies. Here, two cost ratios (1.5 and 2) between mammography and CBE are investigated. The marginal effectiveness for each screening strategy is the difference between the expected QALYS in the screened and unscreened cohorts. The ratio of cost to QALYS is then the marginal cost per year of quality-adjusted life saved. All costs are expressed in U.S. dollars, and are rounded to the nearest \$100.

For each strategy, we generate a birth cohort of 100,000 women by Monte Carlo simulation. For all women who develop breast cancer during their lifetime, we simulate their natural histories, which include the age at onset of the preclinical disease, the preclinical durations (via tumor growth rates), the age at onset of the clinical disease, and the subsequent survival time depending on age and tumor characteristics at detection, which in turn depend on the mode of detection. Therefore, breast cancer mortality associated with a screening strategy is an output of the model rather than an input, and no specific mortality reduction is assumed *a priori*. We take a public health perspective and average outcomes over individual histories for each of the screening strategies being evaluated. Because of space limitations, we refer the reader to the references for general methodologic approach (32), survival model (35), quality adjustments (35), and specific extensions made for this analysis (36). We give a brief summary here.

We simulate breast cancer events following age-specific incidences of preclinical disease and mortality from other causes. For women with breast cancer, we simulate a natural

history from the onset of detectable preclinical disease, through tumor growth, to clinical disease, and death. The age-specific incidence of preclinical disease cannot be directly observed but can be derived using a deconvolution approach (37), given the age-specific incidence of clinical breast cancer and the distribution of preclinical duration. The age-specific incidence of clinical breast cancer is well-documented in cancer registries. The age cohort-specific breast cancer incidences developed in ref. 38 is used for this purpose. Based on current literature, we generalize a commonly used exponential distribution for preclinical duration to incorporate age effect and uncertainties (39). The resulted distribution function is a smoothed exponential mixture, where the mean of sojourn time depends on the age of onset of preclinical disease. In a sensitivity analysis, we also explore two alternative models for preclinical duration distribution, which are based on the log-normal distribution (40, 41). We used data from the Canadian National Breast Screening Study trials (23) and the Nijmegen trial (41) to estimate the sojourn time distribution used in the models above.

In each simulated history, cancer may be detected early by screening or diagnosed clinically depending on the strategy and a woman's natural history. We simulate age-specific sensitivities of mammography and CBE while incorporating uncertainty based on several early detection trials (27, 42, 43). The sensitivity of each screening modality is assumed to depend on tumor size and age at the time of test via a logit model. Random variation within the cohort is incorporated by a beta distribution (36). The screening sensitivity is not a fixed value for any given tumor size and age, but a random value where the uncertainty is modeled via a beta prior distribution. The screening sensitivities generated from simulations show a reasonable range of variations, consistent with data from breast cancer screening trials (27). The overall sensitivity of a screening policy using both mammography and CBE is estimated under the assumption that the two modalities are independent (28).

After diagnosis of breast cancer, the length of a woman's survival and her quality-adjusted survival after detection are predicted by the model from her age and tumor characteristics at the diagnosis, and from the treatment that she receives following diagnosis. The tumor characteristics at detection determine the treatment received thereafter, according to the guidelines established by the NIH Consensus Conference on Early Breast Cancer in 1991. The predictive survival distribution given the risk factors at detection was established based on data from four Cancer and Leukemia Group B trials (32, 44-46). The women may die from breast cancer or other competing

Table 1. Summary of evaluation of alternative breast cancer screening as we vary the interval between examinations and the combination of screening modalities used

Age at start of program	Interval between examinations (y)	Combination of modalities	Marginal cost of examinations	Marginal benefit	MCQYLS
40	1/2	MM/1, CBE/1	19,700	0.221	89,200
		MM/1, CBE/2	16,400	0.198	82,800
		MM/2, CBE/1	13,100	0.195	67,200
40	1	MM/1, CBE/1	10,000	0.135	73,600
		MM/1, CBE/2	8,300	0.121	68,600
		MM/2, CBE/1	6,600	0.117	56,900
40	2	MM/1, CBE/1	5,100	0.076	66,600
		MM/1, CBE/2	4,200	0.069	61,500
		MM/2, CBE/1	3,400	0.069	49,500
50	1/2	MM/1, CBE/1	14,000	0.152	92,100
		MM/1, CBE/2	11,700	0.142	82,100
		MM/2, CBE/1	9,300	0.141	66,400
50	1	MM/1, CBE/1	7,100	0.099	72,100
		MM/1, CBE/2	5,900	0.092	64,300
		MM/2, CBE/1	4,700	0.087	54,500
50	2	MM/1, CBE/1	3,700	0.055	66,900
		MM/1, CBE/2	3,100	0.047	64,400
		MM/2, CBE/1	2,400	0.050	48,600

NOTE: Results correspond to a cost ratio of 2 between mammography and CBE. Abbreviations: MM, mammography; MCQYLS, marginal cost per year of life gained.

causes depending on the actuarial tables using a 1960 birth cohort from the census database. Therefore, the mortality reduction for each screening strategy is an output of the simulation model, indirectly determined from high-quality data on treatment efficacy and current guidelines.

Results

Figure 1 shows the trade-off plots for the 48 strategies in both cost scenarios. Table 1 also gives the cost-effectiveness ratios for two starting ages and three screening intervals. Figure 1 (left) corresponds to a cost ratio of 1.5 between mammography and CBE, and Fig. 1 (right) to a ratio of 2. The three rows correspond to starting ages of 40, 45, and 50 for regular screening programs. For each screening interval and starting age, giving mammography every two exams and CBE at every exam has the lowest marginal cost per year of quality-adjusted life saved; therefore, it is the most cost-effective strategy among the four combinations of modalities. In contrast, giving both mammography and CBE at every exam has the highest marginal cost per year of quality-adjusted life saved. Screening every 6 months with both mammography and CBE has the highest marginal effectiveness and the highest costs. In the cost scenario with a cost ratio of

mammography and CBE of 2, comparing annual mammography and CBE to biennial mammography and annual CBE from ages 50 to 79, the total cost is reduced by 35%, whereas the marginal QALYS only decreases by 12%. Similar reductions are observed for the starting age of 40. More frequent screening with annual mammography combined with CBE every 6 months leads to a substantial increase (44% for the starting age 40; 41% for the starting age 50) in the marginal QALYS compared with the commonly used strategy of annual mammography and CBE, whereas the total cost increases by 31%. Giving mammography every two exams and CBE at every exam has similar marginal QALYS as giving mammography at every exam and CBE every two exams. However, the expected cost of the former is ~20% lower than the latter (Table 1).

With screening intervals of 1.5 and 2 years, marginal effectiveness is low, especially if mammography and CBE are given every two exams. With mammography at every exam, differences in QALYS gains between CBE every one and two exams are not substantial across all intervals. In contrast, differences in QALYS are larger if mammography is given every two exams, especially for screening intervals of 6 months and 1 year. Overall, strategies with either mammography or CBE given every year are more effective than the alternatives. We perform sensitivity analyses using the three

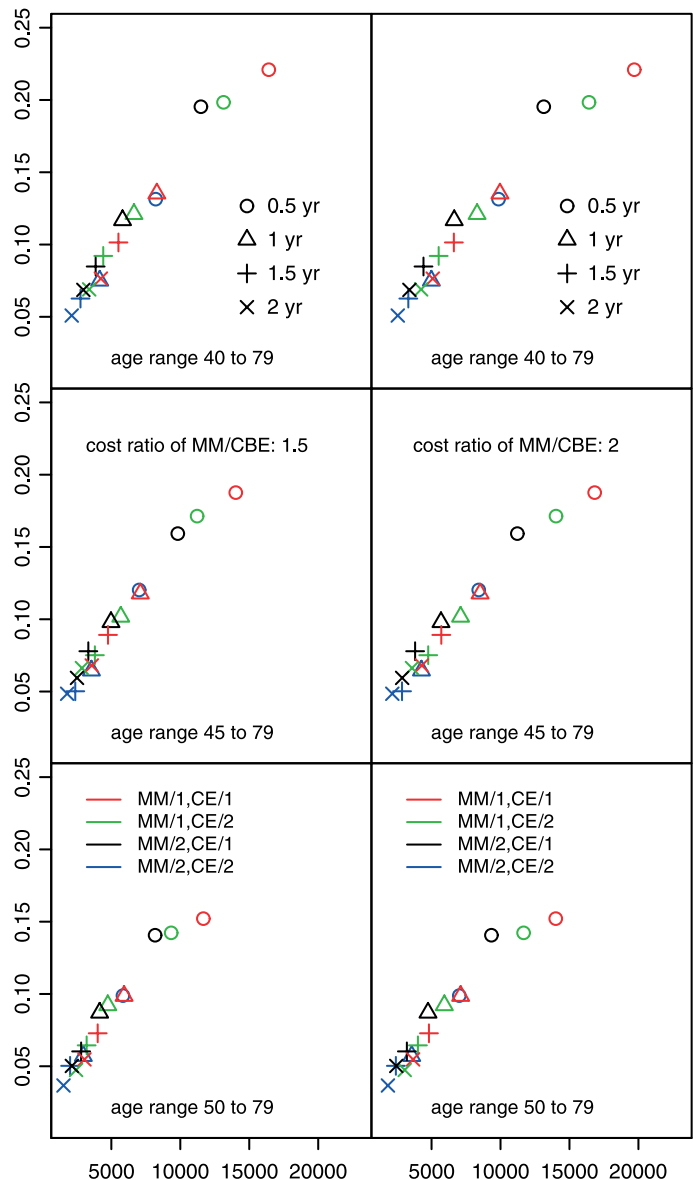


Figure 1. Trade-off plots: X axis, total cost in U.S. dollars rounded to the nearest \$100; Y axis, QALYS. Points, strategies. Different colors, combinations of examination modality; different dot shapes, screening intervals.

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different age-specific preclinical duration distributions. Results are similar across scenarios, although marginal QALYs are slightly higher (~1-2%) for the log-normal models. With the two cost ratios under investigation, there is an increase in an overall cost for each strategy, especially the strategies with relatively short screening intervals. However, this does not change the relative cost-effectiveness of the policies.

Discussion

In summary, this analysis is the first to evaluate the costs and utility of the combined use of mammography with CBE in early detection of breast cancer. Our conclusions are based on a microsimulation model that uses the best available evidence to simulate health histories of women at risk of breast cancer under various screening strategies. We do not make any preset assumptions on the efficacy of either mammography or clinical breast exam in terms of mortality reduction. The mortality reduction for each screening strategy is an output from the Monte Carlo simulation.

Compared to actual breast cancer early detection trials, the mortality reductions estimated in this study are generally higher for a given screening strategies. A possible reason for this is that in early detection trials, regular screening examinations including mammography or/and clinical breast examination were only offered three to five times with either 1 or 2 years interval, and the compliance of women in various trials were much lower than 100%. In our analysis, women in the cohort take regular screening examination over a period of at least 30 years with 100% compliance if they do not die of competing risks.

Evidence from randomized clinical trials suggests that clinical breast examination, combined with regular mammography, will enhance the overall sensitivity of a screening plan. Our results suggests that adding CBE to biennial or annual mammography can be cost-effective, whereas CBE alone cannot replace regular mammography in screening practice. A common practice in Europe for women ages >50 years is to have a mammography every other year. A clinical breast examination would be helpful during the year in which they do not have their regular mammography.

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