Evaluation of Breast Cancer Risk Assessment Techniques: A Cost-effectiveness Analysis

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Abstract

Objective: **Assess the effectiveness and cost-effectiveness of using biomarkers and risk assessment tools to stratify women for breast cancer preventive interventions.**
Methods: **A Markov model was developed to compare risk management strategies for high-risk women considering chemoprevention. Annual screening is compared to the use of chemoprevention for all women and the use of risk assessment technologies to stratify patients for chemoprevention. The biomarker atypia was used to stratify women by risk. Random fine-needle aspiration (rFNA) and ductal lavage (DL) were evaluated and compared as the risk assessment tools used to discover atypia. Sensitivity analyses explore assumptions regarding the prognostic and predictive characteristics of atypia, both the relative breast cancer risk and benefit from chemoprevention women with atypia incur.**
Results: **Risk assessment strategies using rFNA or DL in combination with chemoprevention are found to be cost-effective (<$50,000 per life year saved) in high-risk groups under most scenarios. Both strategies were more effective and less costly in younger cohorts. Effectiveness of the risk assessment strategies increased when higher risk and increased benefit from chemoprevention were associated with atypia. Within the scenarios tested, rFNA is less costly than DL.**
Conclusion: **rFNA and DL appear to be cost-effective in high-risk women, assuming women with detected atypia choose tamoxifen. The tools are largely effective for women who are not motivated to take tamoxifen but would be if atypia were found. As biomarker risk assessment tools better predict the risk of breast cancer and or benefit of interventions, their cost-effectiveness increases.** (Cancer Epidemiol Biomarkers Prev 2004;13(12):2043–52)

Introduction

As new technologies are developed to detect biomarkers that predict breast cancer risk, it is important to understand the clinical value of these tests. This becomes particularly important in the setting of breast cancer care, where public demand for procedures often precedes long-term outcome data on biomarkers and interventions. Predictive modeling can generate insight for both the application and development of prevention strategies that incorporate the use of biomarker detection in decision making.

The National Surgical Adjuvant Breast and Bowel Project P01 Breast Cancer Prevention Trial (BCPT) data show that the use of tamoxifen, a chemopreventive agent, can decrease a woman's risk of breast cancer. The average relative risk reduction seen in the BCPT due to tamoxifen use was 49%, yet the absolute risk reduction was low; the annual absolute risk reduction of invasive breast cancer was 0.33% (1). Several analyses have shown tamoxifen to be a cost-effective preventive intervention and suggest that young women gain the most from the intervention (2, 3). A recent article by Freedman et al. (4) estimates that more than 10 million women in the United States are eligible for tamoxifen use. However, physicians are reluctant to recommend tamoxifen for high-risk women (5), and patients are reluctant to take tamoxifen regardless of educational interventions, citing fear of side effects as the most common deterrent (6). Studies have found that as few as 5% of eligible women choose tamoxifen therapy and <25% of women eligible for chemoprevention trials have elected to enroll (6, 7). One study by Tchou et al. (5) found that breast cancer risk as determined by the presence of atypical hyperplasia or lobular carcinoma *in situ* was predictive of tamoxifen acceptance by high-risk women, as compared with other common risk factors. This indicates that common risk assessment models used to define women as being at ''high risk'' for breast cancer are not sufficiently compelling for most patients or that the value of the intervention does not seem to warrant therapy. The clinical utility of defining women at highest risk of breast cancer and those most likely to benefit from chemoprevention becomes increasingly important in this setting.

The use of biomarkers to predict both risk of disease and response to chemoprevention are being proposed as a useful strategy for women who are reluctant to start and stay on tamoxifen therapy. Atypia is one of

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the known risk factors for breast cancer. A variety of methods are available to sample the breast to discover the presence of ductal atypia, including nipple aspirate fluid (NAF), random fine-needle aspiration (rFNA), and ductal lavage (DL). Clinical management of women with atypia has not been well established, due in part to limited information about long-term outcomes for women with atypia found through these discovery methods. However, guidelines for the management of high-risk women addressing the issue of biological markers of risk have recently been published (8). The level of risk women with atypia experience, although clearly elevated in relation to women without atypia, remains uncertain. Wrensch et al. (9) have shown that cytologic atypia found through NAF represents an ~2-fold increase in risk as compared to women in whom NAF was not expressed. Fabian et al. (10) have found that histologic atypia found on rFNA carries a 5-fold risk. Follow-up studies of women with atypia found through DL have not been reported. From available data, it is likely that atypical ductal cells hold a relative risk of breast cancer between 2- and 5-fold, regardless of the method used to detect it (11). The impact of atypia on risk seems to be greater when it is found in the context of other risk factors (9, 10). These data are consistent with data on histologic atypia (which is also a form of breast sampling), which has been found to confer a 2- to 10-fold risk of developing breast cancer, increasing with the presence of family history (1, 12, 13).

In addition to being a prognostic marker, atypia also appears to be a predictive marker. Women with atypical hyperplasia found through biopsy showed an increased response to tamoxifen as a preventive intervention in the BCPT (1). However, women with atypia found through the emerging risk assessment techniques have not been studied to determine the potential risk reduction tamoxifen lends them. It remains uncertain if women with a finding of atypical ductal cells using cytologic techniques can expect an increased benefit from tamoxifen. However, the BCPT data suggest it is likely.

Methods to screen women for atypia in the outpatient setting would augment current risk assessment methods, enabling physicians to identify women at increased risk for breast cancer and those who are likely to benefit from intervention, allowing physicians to tailor chemoprevention recommendations based on specific biological features. Fine-needle aspiration has long been a technique used to target areas in the breast for evaluation. It has been adapted to the prevention setting by Fabian et al. as a method to cytologically sample all quadrants of the breast. It is a minimally invasive and inexpensive technique shown to be reproducible in chemoprevention trials that can be done on all women (10).

NAF, although simple to obtain, does not yield sufficient cells to identify atypia for most women. DL, a method for cannulating the nipple duct orifices, has been shown to increase the chances of obtaining cellular samples for analysis. A recent multicenter study showed that DL is a safe and minimally invasive technique of obtaining a large number of ductal cells with a 3-fold increase in the ability to detect atypical cellular changes within the breast (14). A prospective study of 507 high-risk women showed that DL is feasible even in nulliparous and postmenopausal women. Seventy-three percent of the women in this study had inadequate specimens for analysis on NAF, as compared to 22% with the DL procedure. However, ductal lavage could only be done in women in whom NAF was obtained. In the Dooley et al. (14) study, 84% of the subjects had at least one NAF-yielding duct. The development of DL has provided clinicians and clinical researchers with a minimally invasive and potentially more successful and accurate method for obtaining cells to look for the presence of premalignant cellular changes.

We asked if the use of these tools could impact the cost-effectiveness of chemoprevention with tamoxifen. The goal of our analysis was twofold. In specific, we wanted to determine whether screening high-risk women using available risk assessment techniques could be considered a cost-effective clinical procedure by determining what assumptions about the cost, the prognostic and predictive power of these technologies are necessary. In general, we wanted to create a platform to evaluate and understand the strategic impact of a test using biological markers for breast cancer prevention. Our analysis compared four management strategies for a hypothetical cohort of women at high-risk for breast cancer. Sensitivity analysis was used to identify the critical variables that affect cost-effectiveness and survival to bring insight to the development of future prevention strategies.

Methods

Model Design. We developed a Markov model using DATA Professional software (TreeAge Software, Inc., Cambridge, MA) to simulate the outcomes of survival, quality-adjusted survival, and medical costs for hypothetical cohorts of high-risk women. The model assessed the value of risk assessment technologies to identify atypia in the breast cancer prevention setting. The following strategies were evaluated for a hypothetical cohort of high-risk women similar to those enrolled in the BCPT (5-year Gail risk of $\geq$1.67%):

1. Screening strategy: routine screening with mammography for all women
2. Tamoxifen strategy: tamoxifen therapy for all women
3. Ductal lavage strategy: attempt of DL for all women; tamoxifen use only by women with atypia
4. rFNA strategy: rFNA for all women; tamoxifen use only by women with atypia

Three different age groups, ages 40, 50, and 60 years, were examined in the analysis. The model is based on the results of the BCPT. Women transition through the following health states until age 110 or death: healthy, healthy while taking tamoxifen, noninvasive breast cancer, invasive breast cancer, metastatic breast cancer, endometrial cancer, pulmonary embolism, cataracts, and death (Fig. 1). Other health outcomes that are associated with tamoxifen use such as stroke and fractures were not included because they did not reach statistical significance in the BCPT (1).

Model Inputs. Model inputs are shown in Table 1. They are discussed by categories of breast cancer rates, breast cancer health state parameters, biomarker parameters, adverse event rates and assumptions.

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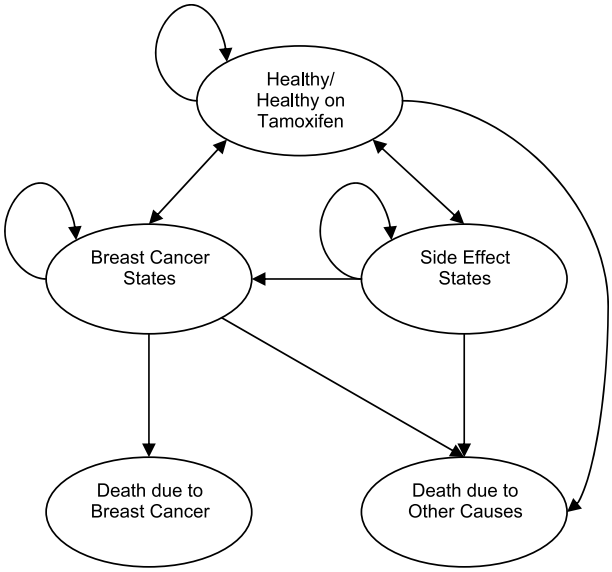

Figure 1. Markov model. A simplified representation of the clinical health states modeled.

Breast Cancer Rates and Health State Parameters. Average annual breast cancer rates by age were taken from the BCPT data for the reference model (1). Additional rates were obtained from other literature sources. Women enter both the noninvasive and invasive breast cancer states from the non–breast cancer states and travel back into healthy or side effect states, die due to age-specific mortality, or advance to metastatic breast cancer. The time until women are presumed to no longer incur risk of recurrence after breast cancer treatment is 15 years for noninvasive and invasive breast cancer based on a weighted average of both high-grade and low-grade cancers (15).

Biomarker Parameters. Biomarker data were taken from various sources. The model assumes that rFNA can be done on all women and atypia is found in a fraction (24%) of those women (10). Ductal lavage is performed only in women for whom NAF is obtained, and the majority (92%) of these ducts are cannulable, allowing for a successful lavage procedure (16, 17). Based on data from Fabian et al. (16), 65% of women with atypia on rFNA and 55% of women without atypia on rFNA were modeled to produce NAF. Similar to the rFNA procedure, atypia is found in only a fraction (23%) of women who undergo successful lavages (17). Research suggests that presence of atypia is found in small numbers of NAF samples, possibly due to insufficient number of cells collected for analysis (9, 17). Because this number has been found to be so small ($\sim$2%), this outcome was not modeled.

Adverse Events. Annual incidence rates of adverse events associated with tamoxifen were obtained from the BCPT data. Differences in rates between the placebo and tamoxifen groups in the BCPT reached statistical significance for cataracts, endometrial cancers, and pulmonary emboli. Because the increased rates of endometrial cancers and pulmonary emboli in women younger than 50 years on tamoxifen therapy were not statistically significant, risk of these events was modeled only in women age 50 years and older. The mortality rate of endometrial cancer was adapted from Cancer Facts and Figures (18). This mortality was experienced for 5 years before women returned to the other health states. Mortality for pulmonary emboli was incurred for 1 year only (19). We chose to model only the rate of cataract surgery seen in the BCPT, which had no additional mortality over the general age-specific mortality.

Assumptions. Where possible, estimates for parameters used in the model were obtained from the BCPT data and a review of current literature. Data on breast cancer risk for women with a presence of atypia were modeled after data from Wrensch et al. and Fabian et al., respectively. Wrensch et al. have 20-year follow-up data on the risk associated with atypia on NAF in the setting of additional risk factors such as biopsy or family history, factors simulated by the Gail model. The relative risk associated with atypia ranged from 2.4 to 4.9 across the populations targeted in their studies (9, 20).

Fabian et al. followed women after rFNA to determine the risk of breast cancer associated with atypia on rFNA. Women with a high, 10-year Gail risk estimate of $\leq$4% did not develop breast cancer over a 3-year period. Those with a 10-year Gail risk of $\geq$4% were found to have significantly higher rates of breast cancer, particularly if atypia was found. The 3-year incidence of breast cancer in the women with elevated Gail risk was 4% and 15% in the absence or presence of findings of cytologic atypia, respectively (10). These data suggest a 5-fold risk factor for atypia. However, these women had a baseline risk that was higher than the average woman in the BCPT. Some women in this study had a previous diagnosis of breast cancer and a good proportion fell into a risk category consistent with that of BRCA mutation carriers. The risk for women with atypia on rFNA was modeled as a 3-fold risk factor, accounting for discrepancies in these populations. This assumption was explored in sensitivity analysis.

Data on breast cancer risk in women who have undergone DL are not available. To estimate the risk of breast cancer for this different group, we used data from Wrensch et al. (9) and Fabian et al. (10) as a range for the value associated with atypia found through DL and explored the impact of this assumption in sensitivity analysis. The reference model assumed atypia on DL conferred a similar risk to that of atypia found through rFNA. The risk of breast cancer for women with atypia is modeled using these risk factors relative to women with no atypia. However, the rates of breast cancer for all women were normalized to maintain the overall expected number of breast cancer occurrences to be the same across all strategies.

The rate of noninvasive breast cancer is taken from the results of the BCPT for the average high-risk woman. For women in specific risk groups in which there are no data on the rates of noninvasive breast cancer, this rate is modeled as 40% of the invasive breast cancer rate to mimic the results of the BCPT for noninvasive breast cancer rates and sensitivities were run on this value. Additionally, women incur age-specific mortality each year and in each health state (21).

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Table 1. Inputs

Variable	Reference case	Range	Reference
Annual breast cancer rates			
Invasive breast cancer			
Age 40-49 y	0.00670	±25%	1
Age 50-59 y	0.00628	±25%	1
Age 60+ y	0.00733	±25%	1
Breast cancer parameters			
Stage of invasive disease at diagnosis			
Node negative (%)	70	50-90	15
Node positive (%)	30	10-50	15
Yearly progression rate from noninvasive to invasive breast cancer	0.01	0.005-0.05	1, 15
Yearly progression rate from invasive to metastatic breast cancer			
Node negative	0.04	0.01-0.1	15
Node positive	0.1	0.05-0.2	15
Biomarker parameters			
Probability of obtaining atypia on rFNA (%)	24	10-40	10
Probability of obtaining NAF if atypia found on rFNA (%)	65	50-80	16
Probability of obtaining NAF if no atypia found on rFNA (%)	55	40-70	16
Probability a NAF yielding duct is cannulable (%)	92	75-100	17
Probability of finding atypia in a cannulable duct (%)	23	10-40	17
Annual rates in general population			
Cataract surgery	0.0030	0.001-0.01	1
Endometrial cancer (over 50)	0.00076	0.0001-0.005	1
Pulmonary embolism (over 50)	0.00031	0.0001-0.001	1
Annual rates on tamoxifen			
Cataract surgery	0.00472	0.001-0.01	1
Endometrial cancer (over 50)	0.00305	0.001-0.01	1
Pulmonary embolism (over 50)	0.001	0.0001-0.005	1
Yearly mortality rate incurred in addition to age-specific mortality by Health State			
Metastatic breast cancer	0.6 per year	0.3-0.9	15
Endometrial cancer	0.008 per year	0.002-0.05	18
Pulmonary embolism	0.03 for one year	0.001-0.05	19
Assumptions			
Relative risk for biomarker			
Atypia found on rFNA	3	2-4	10
Atypia found on lavage	3	2-4	
Rate of noninvasive breast cancer (modeled as a fraction of the invasive breast cancer rate) (%)	40	25-55	1
Tamoxifen risk reduction			
Invasive breast cancer (%)			
All women	49	35-86	1
Women with atypia	86	49-86	1
Noninvasive breast cancer (%)			
All women	50	30-70	1

Risk reduction due to tamoxifen use is modeled in accordance with the BCPT results. For the average high-risk population in the trial, the risk reduction from tamoxifen was 49% for invasive cancers and 50% for noninvasive cancers. Women in the BCPT with previous atypical hyperplasia experienced an average of an 86% risk reduction for invasive cancers. The model uses these data points for a range of possible risk reduction for women with findings of atypia and was explored in sensitivity analyses. Due to conflicting results in chemoprevention trials, a lower rate of risk reduction from tamoxifen use was also explored in sensitivity analyses (22, 23).

Cost Parameters. Using data from the Group Health Cooperative of Puget Sound, we obtained cost data as shown in Table 2 for breast cancer care by stage and adjusted them to 2003 dollars using the Consumer Price Index (24-26). We used the attributable methodology to calculate the average costs of breast cancer care by age. Terminal cost for breast cancer in addition to costs estimates of cataract surgery, endometrial cancer, and pulmonary embolism were obtained from Hershman et al. (3). We used $900 as a yearly cost for tamoxifen based on typical prescribing data and looked at variations in this cost in sensitivity analyses. We collected data on the cost of NAF and DL from Cytyc Health Corporation.[3] rFNA costs were collected from University of California San Francisco and University of Kansas

[3] Cytyc, personal communication, 2002.

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Medical Center.[4,5]A large range for these values was explored in sensetivity analysis. The workup cost for atypical findings is not stardardized currently and is typically done only on those women with severe atypia, a small proportion of women with atypia. For these reasons, these costs were not modeled.

Comparisons or survival and quality-adjusted survival were done without discounting. A discount rate of 3% was used in the cost-effectiveness analyses. All outcomes were discounted in the cost-effectiveness analyses: survival, quality-adjusted survival, and costs.

Quality of Life Parameters. Quality of life adjustments were used in the analysis as shown in Table 2. The estimates used were based on a literature review of relevant sources(3, 27-36) The estimates of patient utility were derived using multiple methods including time tradeoff, standard gamble and rating scale methods. When a range for these utilities was found in the literature, a midrange value was used in the model and sensitivity analyses were performed around it.

Sensitivity Analysis. Sensitivity analyses were performed to determine the drivers of the model and threshold values for those parameters that change the optimal course of action. We looked specifically at the effect of changing specific parameters related to the high-risk population characteristics and tamoxifen variables in comparison with the reference model results. Because rFNA and DL are emerging technologies, data about breast cancer rates for women with atypia are limited or not available and much of our sensitivity analyses were focused on the assumptions made about these unknown parameters.

Results

Using the screening strategy as a reference, all prevention strategies extended survival, an effect that decreased with age. If it is assumed that all women identified as high risk will take tamoxifen, the tamoxifen strategy was the most effective and the DL strategy the least effective. The tamoxifen strategy extended expected survival by 160, 101, and 65 days for 40, 50, and 60-year-olds, respectively. The rFNA strategy extended expected survival by 79, 51, and 33 days and the DL strategy extended expected survival by 40, 26, and 17 days for the respective age groups as compared with the screening strategy. The quality-adjusted analyses showed similar results. The tamoxifen strategy extended expected quality-adjusted survival by 129, 66, and 34 days for 40, 50, and 60-year-olds, respectively. The rFNA strategy extended expected quality-adjusted survival by 76, 47, and 31 days and the DL strategy extended expected quality-adjusted survival by 36, 21, and 13 days, respectively. Both the life expectancy gains and the incremental cost-effectiveness ratios are shown in Fig. 2. The incremental cost-effectiveness ratios represent the incremental costs required per life year saved for each strategy compared with the screening strategy. The DL strategy is more costly and less effective in all age groups when compared with the rFNA strategy. Both the rFNA and DL strategies decrease below the widely accepted cost-effectiveness threshold of $50,000 per life year saved for all ages.

If we do not assume that all women at high risk will take tamoxifen, which is more reflective of current clinical practice, the relative cost-effectiveness of these strategies is quite different. If the proportion of women taking tamoxifen in the tamoxifen strategy is decreased, the cost-effectiveness of this strategy decreases. We varied the percentage of women willing to take tamoxifen and show the effect on the effectiveness of the risk assessment strategies (Fig. 3). The effectiveness of the tamoxifen strategy decreases and the value of the risk assessment strategies increases in comparison as women are less willing to take tamoxifen. When the percentage of women willing to take tamoxifen is modeled at ~50% and ~25% in all age groups, the tamoxifen strategy achieves equivalent expected gains to that of the rFNA strategy and the DL strategy, respectively. Figure 3 shows these threshold values. When the willingness to take tamoxifen in the tamoxifen strategy is below these thresholds, the corresponding strategies are more effective.

Further sensitivity analyses helped identify key variables and their impact on cost-effectiveness. If the relative risk associated with atypia is higher, the effectiveness of the risk assessment strategies increased, but the relative order of the strategies does not change. The effectiveness of

Table 2. Costs and utilities

Variable	Reference case	Range	Sources
Costs			
Noninvasive			
First year	$9,706	$8,000-15,000	24
Continuing years	$838	$500-1,500	24
Invasive			
First year	$14,264	$8,000-20,000	24
Continuing years	$2,029	$1,000-3,000	24
Metastatic			
Yearly	$10,851	$8,000-20,000	24
Cataract surgery	$3,505	$2,500-4,000	3
Endometrial cancer	$5,677	$3,000-10,000	3
Pulmonary embolism	$4,728	$3,000-10,000	3
Tamoxifen cost per year	$900	$600-1200	
DL costs			
Cost of NAF procedure	$100	$25-75	
Cost of rFNA procedure	$350	$175-525	
Cost of lavage procedure	$700	$350-1050	
Discount rate	3%	0%-5%	
Utilities			
Healthy	1	–	
Tamoxifen	0.97	0.5-1	3, 27
Noninvasive breast cancer	0.87	0.85-0.9	30, 34
Invasive breast cancer	0.68	0.65-0.95	3, 31, 33, 34
Metastatic breast cancer	0.38	0.3-0.6	3, 31, 33, 35
Endometrial cancer	0.74	0.6-0.8	3, 28
Pulmonary embolism	0.70	0.3-0.9	3, 29, 32
Cataracts	0.80	0.6-0.8	3, 36
Death	0	–	

[4] B.M. Ljung, personal communication, 2003.
[5] J.R. Klemp, personal communication, 2003.

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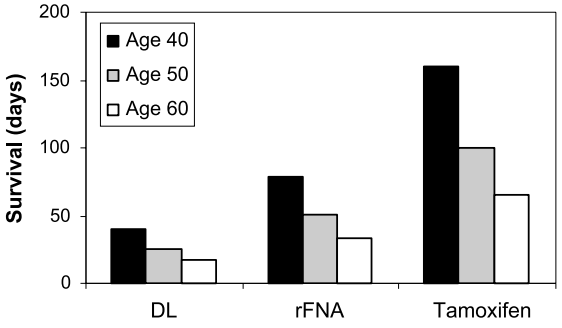

Reference Case Results

Strategy	Life Expectancy (yrs)	Incremental Life Expectancy (days)	Incremental Cost Effectiveness ($/LYS)
Age 40			
Screening	39.06	-	-
DL	39.16	40	$ 19,227
rFNA	39.27	79	$ 8,187
Tamoxifen	39.49	160	$ 16,531
Age 50			
Screening	30.33	-	-
DL	30.40	26	$ 28,473
rFNA	30.47	51	$ 13,147
Tamoxifen	30.61	101	$ 26,813
Age 60			
Screening	21.97	-	-
DL	22.02	17	$ 37,953
rFNA	22.06	33	$ 16,986
Tamoxifen	22.15	65	$ 35,275

Figure 2. Reference case results. Average incremental survival is represented graphically by age and strategy. Values of life expectancy, incremental life expectancy and cost-effectiveness compared with the screening strategy are shown in the table by age and strategy.

these strategies also increased if an increase in benefit from chemoprevention over the average benefit is associated with atypia. Less expensive prevention agents and risk assessment costs would also increase the cost-effectiveness of these strategies. Table 3 contains these sensitivity results. The scenarios in which the incremental cost-effectiveness ratios for the risk assessment strategies are higher than that of the tamoxifen strategy are boldface. In almost every scenario, the rFNA strategy is the most cost-effective strategy, followed by the tamoxifen strategy, and then the DL strategy. However, if the relative risk that the biomarker confers is high, then it becomes more effective to use DL than to offer tamoxifen in women older than 50 years. If the effectiveness of the intervention is similar for all women, the risk assessment procedures are not as cost-effective as the tamoxifen strategy. However, if the biomarkers confer both a higher risk and increased benefit from the intervention, the rFNA strategy is the most cost-effective strategy. In older women, the DL strategy is more effective than the tamoxifen strategy when there is a significant differential in the effectiveness of the intervention. Similarly, if the cost of the test for DL decreases, the DL strategy also becomes more cost-effective than the tamoxifen strategy. For expensive prevention interventions, the rFNA and DL also become more cost-effective.

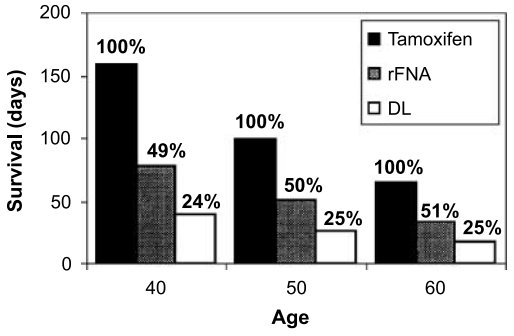

Figure 3. Threshold values for tamoxifen use by age. The threshold values for the percentage of women taking tamoxifen that make the tamoxifen strategy equivalent in terms of incremental survival to the DL (*open bar*) and the rFNA (*hatched bar*) strategies are graphed for each age group. When 24% (age 40 years) or 25% (ages 50 and 60 years) of women in the tamoxifen strategy take tamoxifen, this strategy becomes equivalent to the DL strategy. This threshold is 49% to 51% for the rFNA strategy.

Selected sensitivity analyses are shown graphically in Fig. 4. The effect of ranging the risk reduction due to tamoxifen therapy for women with atypia (Fig. 4A) and the cost of the risk assessment techniques (Fig. 4B) on the cost-effectiveness of the three strategies are graphed for a 40-year-old woman in relation to commonly accepted interventions (37-41). The examined strategies fall below $55,000 per life year saved, a lower bound estimate of the cost for hemodialysis, yet above the value for pap smear screening every 3 years that is estimated to be approximately $12,000 per life year saved. The value of mammography screening is higher than any of these strategies for women between ages 40 and 49 and is similar to these strategies for women 50 years of age and older, unless the biomarker tests are inexpensive, in which case screening mammography is relatively less cost-effective.

Discussion

Currently, the Gail risk assessment model is the clinical standard for breast cancer risk assessment in the

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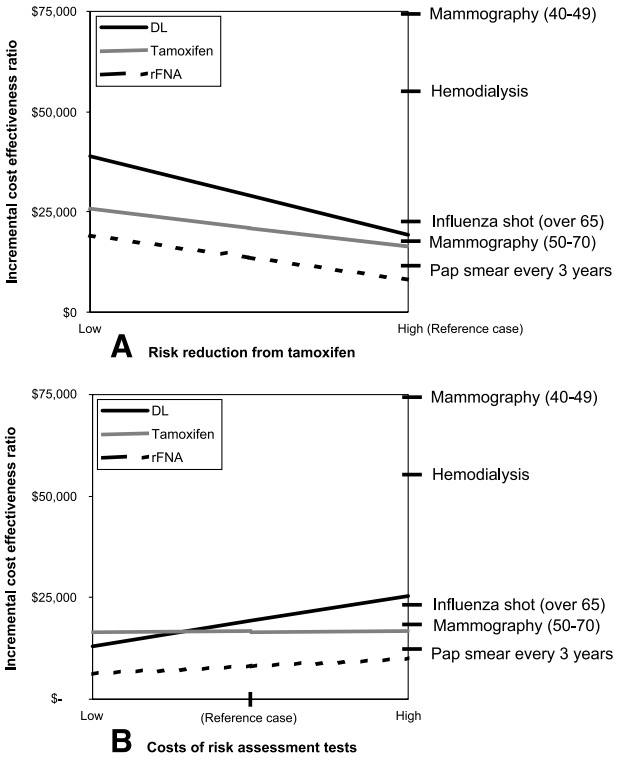

Figure 4. Sensitivity analyses. The impact of the risk reduction from tamoxifen (**A**) and the cost of the risk assessment tests (**B**) on the incremental cost effectiveness per life year saved. The cost-effectiveness values are compared with common procedures shown on the right axes. High, reference, and low values are shown in Table 3.

prevention setting. This model has been shown to be calibrated for a general population but not discriminatory for the individual patient. For a large group of women, the Gail model will successfully predict the expected number of breast cancers but cannot predict which specific women will get breast cancer with significant accuracy (42). For this reason, the Gail model is not an ideal clinical decision-making tool. Use of biomarkers as risk discriminators holds significant promise to improve current risk assessment methods. Our model clearly shows how, why, and for what age groups discriminatory risk assessment tools add value. If the presence of atypia is truly both a differentiator of breast cancer risk as well as a predictor of benefit from chemoprevention as preliminary evidence suggests, rFNA and DL would be particularly useful technologies to augment clinical risk assessment as shown by the sensitivity analysis in Table 3.

Although the tamoxifen strategy has the highest life expectancy gains, this strategy does not describe current practice with regard to tamoxifen (6, 7). Data suggest that only a small proportion of women offered tamoxifen choose to take it. Colleagues have observed that women eligible for the Study of Tamoxifen Against Raloxifene trial, only ~10% enroll (7). Port et al. (6) suggest this number is as low as 5%, a value well below the threshold in which both DL and rFNA are more cost-effective than tamoxifen for all women. A recent study by Tchou et al. (5) found that only 42% of eligible women who were offered tamoxifen chose it, a value that is below the threshold in which rFNA is more cost-effective than tamoxifen for all women. Noe et al. (3) and Hershman et al. (4) have shown that tamoxifen is highly cost-effective, more so in younger women. This result assumes that all women would be willing to take tamoxifen. However, if atypia were a discriminator of both risk and benefit, it is believable that women with atypia would be more willing to choose tamoxifen therapy with improved adherence, adding to the effectiveness of the risk assessment strategies. In fact, data from the BCPT and Study of Tamoxifen Against Raloxifene chemoprevention trials suggest that women with atypia are significantly more likely to choose tamoxifen therapy than those without (7).

This model is unique in that it helps us to guide risk assessment decision making at an individual level, something previous models do not do. Sensitivity analysis around willingness to take tamoxifen shows that if most patients are not willing to take tamoxifen based on risk assessment tools such as the Gail model, tools such as rFNA and DL would be cost-effective. In addition, the strategy of using these tools for women who do not feel that the Gail model or typical clinical risk assessment methods offer sufficient evidence for tamoxifen use is more cost-effective than the current situation in which a small number of women actually choose tamoxifen therapy (<25%). If a patient is motivated to take tamoxifen, further testing with rFNA or DL is not useful. However, for women who feel the presence of atypia would constitute sufficient evidence for tamoxifen use but her Gail score (or other risk assessment score) is not compelling enough to begin tamoxifen use, these tests would be an appropriate, cost-effective option to gather further information about a woman's risk of breast cancer.

The results of the model show that the ability to discriminate between women who have relatively low risk of breast cancer and those who are at relatively increased risk is critical to the effectiveness and cost-effectiveness of risk assessment technologies such as rFNA and DL. The model is highly sensitive to the annual relative risk of breast cancer for women who had findings of atypia. When the relative risk of breast cancer for women with atypia is twice that of women without atypia, the incremental effectiveness offered by the risk-refinement strategies does not significantly offset the additional costs of the procedures. The larger the difference in risk between the population with atypia and those without, the more cost-effective the risk-refinement strategies become. The smaller this gap in risk between the average women and those with atypia, the added cost of the risk-refinement procedures becomes less worthwhile. The analysis of the risk reduction of tamoxifen suggests that the value of the risk-refinement strategies dramatically increases if atypia identifies women who are not only at increased risk of breast cancer but also more likely to benefit from tamoxifen. The sensitivity results show that by treating a smaller group of women with increased risk of breast cancer and increased benefit from intervention is more cost-effective than treating the entire cohort of high-risk women. However, this strategy forgoes treating a large

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Table 3. Sensitivity analyses: incremental cost-effectiveness ratios as compared with the screening strategy by age

Age (y)	Strategy		Reference case	
*Relative risk of atypia**				
		Relative risk = 2	Relative risk = 3	Relative risk = 4
40	DL	**$24,077**	**$19,227**	**$16,808**
	rFNA	$10,954	$8,187	$6,812
	Tamoxifen	$17,388	$16,531	$16,803
50	DL	**$35,734**	**$28,473**	*$24,879*
	rFNA	$17,367	$13,147	$11,066
	Tamoxifen	$28,236	$26,813	$26,055
60	DL	**$47,950**	**$37,953**	*$33,032*
	rFNA	$22,739	$16,986	$14,159
	Tamoxifen	$37,263	$35,275	$34,200
Risk reduction from tamoxifen†				
		Women with atypia = 86% All other women = 35%	Women with atypia = 86% All other women = 49%	All women = 49%
40	DL	**$19,227**	**$19,227**	**$38,913**
	rFNA	$8,817	$8,187	$19,280
	Tamoxifen	$8,876	$16,531	$24,187
50	DL	$18,877	**$28,473**	**$57,411**
	rFNA	$13,147	$13,147	$29,770
	Tamoxifen	$30,552	$26,813	$42,268
60	DL	$37,953	**$37,953**	**$77,244**
	rFNA	$16,986	$16,986	$39,390
	Tamoxifen	$40,271	$35,275	$56,162
Cost of tests‡				
		Cost NAF = $25 Cost rFNA = $175 Cost lavage = $350	Cost NAF = $75 Cost rFNA = $350 Cost lavage = $700	Cost NAF = $100 Cost rFNA = $525 Cost lavage = $1050
40	DL	$12,956	**$19,227**	**$25,498**
	rFNA	$6,462	$8,187	$9,911
	Tamoxifen	$16,531	$16,531	$16,531
50	DL	$19,768	**$28,473**	**$37,178**
	rFNA	$10,753	$13,147	$15,540
	Tamoxifen	$26,813	$26,813	$26,813
60	DL	$26,045	**$37,953**	**$49,862**
	rFNA	$13,711	$16,986	$20,261
	Tamoxifen	$35,275	$35,275	$35,275
Cost of tamoxifen§				
		Cost Tamoxifen = $600	Cost Tamoxifen = $900	Cost Tamoxifen = $1200
40	DL	**$15,490**	**$19,227**	$22,964
	rFNA	$4,450	$8,187	$11,923
	Tamoxifen	$8,876	$16,531	$24,187
50	DL	**$23,386**	**$28,473**	$33,560
	rFNA	$8,060	$13,147	$18,233
	Tamoxifen	$16,050	$26,813	$37,577
60	DL	**$31,128**	**$37,953**	$44,778
	rFNA	$10,162	$16,986	$23,810
	Tamoxifen	$20,787	$35,275	$49,763

*Biomarker risk discrimination increases cost-effectiveness of DL and rFNA strategies.
†More effective intervention increases cost-effectiveness.
‡Inexpensive test offer highly cost-effective strategies.
§Inexpensive interventions offer highly cost-effective strategies.

group of women that will have some benefit, but have less risk of developing breast cancer and have a smaller level of risk reduction. This mirrors the clinical situation in which women are not motivated to take tamoxifen unless their benefit is high, emphasizing the importance of the discriminating biomarkers, in terms of both prediction of breast cancer risk and benefit from interventions.

As new technologies are developed to detect biomarkers that predict breast cancer risk, it is important to understand the potential value these tests hold, which determines their clinical feasibility. In the absence of long-term data, predictive modeling can provide insight in the application of risk assessment tools and in the design of prevention strategies. Although these are currently the most promising risk assessment tools

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available for breast cancer risk assessment, they are not without limitations. Both techniques are sampling techniques and hold the potential to miss atypia that is present. Only ducts that produce NAF can be lavaged, and it has been shown that atypia, as measured by rFNA, can be present in patients with ducts that do not produce NAF (16). Similarly, rFNA may miss atypia that is present within the breast. In addition, there are technical challenges regarding the interpretation of pathology results. These techniques require specially trained pathologists and standardized cytopathology assessments. The model helps us to understand what can be accomplished if the techniques work according to our assumptions, and the effect, through sensitivity analysis, of the tests performing less well.

The model helps us to guide decision making at both a policy level and an individual level and helps to focus future research. Our results support the prior findings that the use of tamoxifen as a chemopreventive is cost-effective (2, 3). However, in the clinical setting in which women are reluctant to use tamoxifen, risk assessment tools are cost-effective if the finding of atypia (in our example) would prompt a decision to take tamoxifen as a chemopreventive. Clearly, the discriminatory power of the biomarker and the interaction with chemopreventives are critical to this decision; further research on refining the significance of atypia and other biomarkers and the risk reduction associated with the chemopreventive agents is needed. These are the factors that drive the acceptance of breast cancer prevention strategies.

In thinking of how to develop and adapt therapies and tools used for the reduction of breast cancer risk, it is clear that inexpensive technologies that are highly discriminating are ideal. We showed our sensitivity results in the context of the cost-effectiveness of other well-known tests for the purpose of comparison. Sensitivity analyses on the cost of tamoxifen and the risk assessment tools show the important role costs play for emerging tools and therapies. These lessons will apply to other emerging biomarkers such as breast density and serum estradiol and their associated detection tools. The availability of inexpensive therapies and tools that are highly discriminating allows for cost-saving prevention strategies. However, more expensive therapies representing emerging therapeutics under fresh patents are not likely to be cost saving and would potentially be prohibitively expensive without the availability of tools for risk discrimination. Without the ability to discriminate those at highest risk, prevention therapies with similar characteristics as tamoxifen approach a questionably high level of cost per life year saved. However, it is remarkable to note that testing for a risk-stratifying biomarker such as atypia could be more cost-effective than screening mammography if the discovery costs are relatively inexpensive.

Reasonably priced tests that discriminate risks and increase adherence and willingness to take a known effective chemoprevention drug will be cost-effective. Based on available evidence, rFNA and DL seem to be such tools. Applying these results to individuals can identify patients likely to benefit from use of such tools. Prior to recommending a risk assessment procedure, it is important to consider whether women would change their decision about tamoxifen use if atypia were found. Patients already motivated to take tamoxifen will not benefit because their therapy decision is not likely to change based on risk-refinement results. Those at significant risk and unwilling to take tamoxifen will definitely benefit if they are willing to change their therapy decisions based on test results. Continued efforts to validate the implications of patient therapy decision are critical. Applying these results to the population, it is clear that such tests should be covered in the appropriate setting.

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