

Cost-effectiveness of Extended Adjuvant Letrozole Therapy After 5 Years of Adjuvant Tamoxifen Therapy in Postmenopausal Women With Early-stage Breast Cancer

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Objective: To estimate the cost-effectiveness of extended adjuvant letrozole in postmenopausal women with early breast cancer and estrogen or progesterone receptor-positive tumors who had completed 5 years of adjuvant tamoxifen.

Study Design: Cost-effectiveness analysis using a Markov model.

Methods: Using a Markov model, we estimated the incremental cost per quality-adjusted life-year (QALY) gained with extended adjuvant letrozole vs no extended adjuvant therapy. Probabilities of breast cancer recurrence or new contralateral tumor adverse effects and death were estimated using data from the MA.17 study and other secondary sources. Costs (in 2004 US dollars) and quality-of-life effects (utilities) of breast cancer events and adverse effects were derived from the literature.

Results: In base-case analyses, extended adjuvant letrozole vs no extended adjuvant therapy results in an expected gain of 0.34 QALYs per patient (13.62 vs 13.28 QALYs), at an additional lifetime cost of \$9699 per patient (\$55 254 vs \$45 555). The incremental cost per QALY gained with letrozole is \$28 728. Cost-effectiveness is sensitive to the assumed reduction in risk of breast cancer events with letrozole but is insensitive to the risks, costs, and quality-of-life effects of osteoporosis and hip fracture. Cost-effectiveness is less than \$100 000 per QALY for node-positive patients younger than 81 years and for node-negative patients younger than 73 years.

Conclusion: For postmenopausal women with early breast cancer who have completed 5 years of adjuvant tamoxifen, the cost-effectiveness of extended adjuvant letrozole is within the range of other generally accepted medical interventions in the United States.

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In women with estrogen receptor-positive early-stage breast cancer, 5 years of adjuvant tamoxifen citrate therapy has been shown to reduce the risk of recurrence by approximately 50% and mortality by approximately 25%.¹ However, tamoxifen therapy likely provides no additional benefit beyond 5 years and may result in reduced disease-free survival (DFS) and increased incidence of thromboembolism and endometrial cancer.² Because women with breast cancer, particularly those with hormone-dependent tumors, are at

elevated risk of recurrence for an indefinite period after initial diagnosis,³ there may be benefits from a safe and effective adjuvant therapy in women who have successfully completed 5 years of tamoxifen.

Letrozole is a third-generation aromatase inhibitor that has been shown to be superior to tamoxifen as first-line therapy for metastatic breast cancer.⁴ The National Cancer Institute of Canada Clinical Trials Group MA.17 study was a randomized double-blind placebo-controlled trial of a planned 5 years of extended adjuvant therapy with 2.5 mg/d of letrozole in 5187 postmenopausal women with early-stage breast cancer and estrogen or progesterone receptor-positive tumors who had successfully completed 4.5 to 6.0 years of postoperative adjuvant tamoxifen.^{5,6} The median age of study patients was 62 years. Approximately 45% of patients had positive axillary lymph node status, 45% had received adjuvant chemotherapy, and 58% had undergone lumpectomy or segmental mastectomy. In accord with predefined stopping criteria, the trial was

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Results of an evaluation of the cost-effectiveness of extended adjuvant letrozole therapy from the perspective of the United Kingdom National Health Service based on a model similar to the one used in this study (although different in several respects, including probabilities, cost, and utility estimates used) have been published elsewhere (Karnon J, Delea T, Johnston SR, et al. Cost-effectiveness of extended adjuvant letrozole in postmenopausal women after adjuvant tamoxifen therapy: the UK perspective. *Pharmacoeconomics.* 2006;24:237-250).

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unblinded after the first interim analysis (median follow-up, 2.4 years) because of a significant improvement in DFS (defined as the time from randomization to the recurrence of the primary disease or the development of a new primary breast cancer in the contralateral breast) with letrozole therapy.⁵ In the updated analysis of the MA.17 trial (median follow-up, 2.5 years), women in the letrozole group had significantly better DFS than those in the placebo group (94.4% vs 89.8% at 4 years; hazard rate, 0.57; $P < .001$).⁶ However, women in the letrozole group experienced a statistically significant increase in the risk of self-reported newly diagnosed osteoporosis compared with those taking placebo (8.1% vs 6.0%, median follow-up, 30 months; $P = .003$) and a statistically nonsignificant increase in the risk of bone fractures (5.3% vs 4.6%, $P = .25$).⁶

Although the MA.17 trial demonstrated that extended adjuvant therapy with letrozole reduces the risk of breast cancer events, policy decisions regarding the appropriate use of such therapy must weigh benefits against potential risks and costs to determine whether such therapy is cost-effective.⁷ The objective of this study was to evaluate the cost-effectiveness of extended adjuvant letrozole therapy vs no extended adjuvant therapy from the perspective of the US healthcare system.

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METHODS

Overview

We used a Markov model⁸ to evaluate the cost-effectiveness of up to 5 years of extended adjuvant letrozole therapy in postmenopausal women with early-stage breast cancer and receptor-positive tumors who had successfully completed approximately 5 years of postoperative adjuvant tamoxifen (Figure 1). A Markov model is an analytic framework that is useful for modeling disease progression during extended periods. In a Markov model, patients are assumed to be in one of a finite set of mutually exclusive health states (eg, alive and disease free, alive with recurrence, or dead) and to move among states as a consequence of events (eg, recurrence or death) that occur at regular intervals or cycles (eg, annually) based on transition probabilities associated with these events (eg, annual risk of recurrence or annual mortality). Values are assigned to each state to reflect the health benefit or cost associated with spending a cycle in that state, and expected values are calculated by multiplying the proportion of patients estimated to be in each state in each cycle by corresponding values and by summing first across states and then across cycles.

For each strategy, we used the Markov model to calculate the expected lifetime incidence of breast cancer and treatment-related adverse effects, costs, life

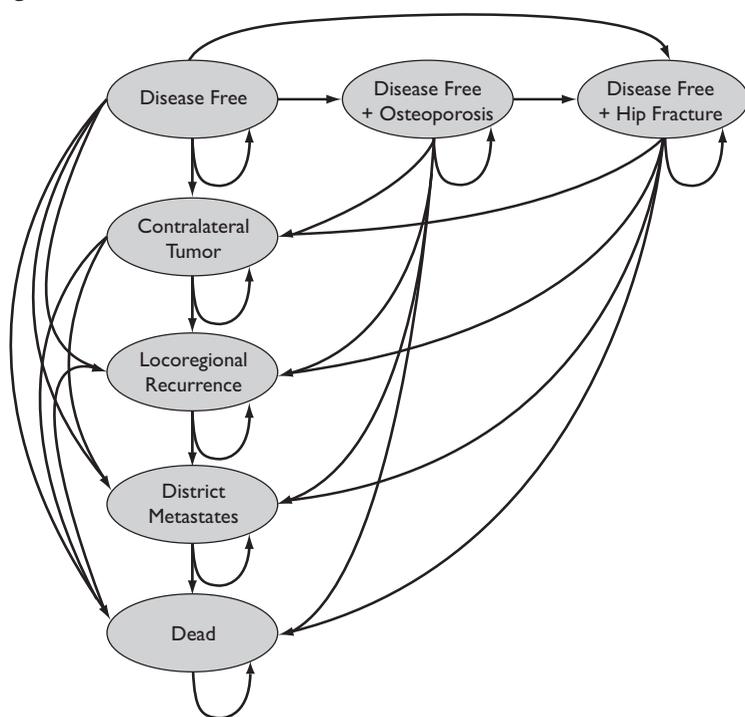
expectancy (or life-years [LYs]), disease-free LYs, and quality-adjusted LYs (QALYs). Quality-adjusted LYs are a measure of health outcome that adjust LYs for the quality of life during those years. Quality-adjusted LYs provide a common unit for comparison of health outcomes across different interventions or health problems and are calculated by multiplying LYs by utility values. Utility values are weights that represent patient preferences for different health states and range from 0.0 (death) to 1.0 (perfect health).

We calculated the incremental cost-effectiveness of extended adjuvant letrozole therapy vs no extended adjuvant therapy in terms of the ratio of the difference (letrozole vs no letrozole) in expected lifetime cost to the difference in LYs and in QALYs. All outcomes were evaluated during a 30-year time frame beginning with discontinuation of tamoxifen therapy (approximately 5 years after initial diagnosis of breast cancer). This time frame approximates a lifetime projection, consistent with recommended good research practices for modeling studies.⁹ In calculating cost-effectiveness, the LYs, QALYs, and costs were discounted at 3% annually.^{7,9} Our analysis was conducted from the perspective of the US healthcare system and considered only direct medical care costs. All estimated costs were adjusted to 2004 US dollars.¹⁰ We conducted deterministic sensitivity analyses to assess the robustness of our findings to changes in individual model inputs and assumptions. We also conducted probabilistic sensitivity analyses and constructed cost-effectiveness acceptability curves for each strategy.¹¹

Model Structure and Assumptions

Patients entering the model are assumed to be similar to those enrolled in the MA.17 trial (mean age of 62 years, 50% node positive, approximately 5 years after diagnosis, and disease free) and to receive letrozole for up to 5 years or no extended adjuvant therapy. In the model, disease-free patients are at risk of recurrence of primary disease or new primary tumor in the contralateral breast, development of osteoporosis, or hip fracture. We assumed that patients would discontinue letrozole after 5 years or on recurrence of the initial breast cancer, the occurrence of a new contralateral primary breast cancer, or a clinical hip fracture, whichever occurred first.

In the model, breast cancer recurrence is classified as locoregional recurrence or distant metastasis. Metastases are classified by site as follows: bone (bone or bone marrow), visceral (lung, liver, pleural effusion, or central nervous system), or soft tissue (all other sites). Patients with contralateral tumors are at risk of subsequent locoregional recurrence or distant metas-

Figure 1. Model Schematic

Distant metastases include soft tissue, bone, and visceral metastases. For simplicity, site-specific metastatic states are not shown.

tases, those with locoregional recurrence are at risk of distant metastases, and those with distant metastases are at risk of breast cancer death. Patients are at risk of recurrence for 15 years after initial diagnosis, contralateral tumor development, or locoregional recurrence. Patients without distant metastases are at risk of death from causes unrelated to breast cancer.

Consistent with results of the MA.17 trial,^{5,6} patients receiving letrozole are assumed to be at reduced risk of primary cancer recurrence or new contralateral tumor development but at increased risk of osteoporosis. In base-case analyses, we assumed that the distribution of breast cancer events by type would vary with extended adjuvant therapy received. Probabilities of breast cancer death were assumed to be dependent on metastatic site but otherwise to be independent of extended adjuvant therapy. Probabilities of breast cancer events and osteoporosis in patients who discontinue letrozole were assumed to be the same as the probabilities in those who had not received such therapy.

Although the difference in the incidence of bone fractures in the MA.17 trial⁶ between patients receiving letrozole vs placebo was not statistically significant, the use of aromatase inhibitors has been found to be associated with increased fracture risk compared with the use

of tamoxifen, and such effects would be consistent with the known antiestrogenic properties of aromatase inhibitors.¹² Therefore, we also assumed that letrozole therapy would be associated with an increased risk of hip fracture, consistent with the results of a prior study¹³ of the cost-effectiveness of adjuvant treatment with the aromatase inhibitor anastrozole. Risk of hip fracture was assumed to remain elevated following discontinuation of endocrine therapy, as effects on bone density might not be reversed with therapy discontinuation.

We assumed that patients with osteoporosis would receive lifelong treatment with a bisphosphonate¹⁴ and that patients with hip fracture would experience a lifelong increase in the risk of non-breast cancer death. We assumed that women with contralateral and locoregional recurrence would experience a temporary reduction in quality of life during the year of recurrence but that quality of life would return to prerecurrence levels in the absence of disease progression. Hip fracture and distant metastases were

assumed to result in permanent reductions in quality of life.

Model Estimation

We estimated model probabilities, costs, and health state utilities using a variety of published and unpublished sources.

Probabilities of Breast Cancer Events. For disease-free patients who do not receive extended adjuvant therapy, probabilities of breast cancer events in years 1 to 4 (after discontinuation of tamoxifen therapy) were based on Kaplan-Meier estimated DFS from the MA.17 trial updated analysis.⁶ Probabilities in years 5 to 10 were based on extrapolation of the estimated rate in year 4. For disease-free patients who are receiving letrozole during a given year, probabilities of breast cancer events were obtained by multiplying the corresponding values for patients not receiving letrozole by the estimated risk ratio (RR) of recurrence or contralateral tumor among patients receiving letrozole vs placebo in the MA.17 trial (RR, 0.58).^{5,6} We estimated the probabilities of different types of breast cancer events based on the treatment group-specific distributions of first events in the MA.17 trial using multinomial logit analysis.

The risk of recurrence following contralateral tumor was assumed to be equal to that immediately following

the original cancer diagnosis, which we estimated based on rates of recurrence (excluding contralateral tumors) for all control patients in the 1998 meta-analysis by the Early Breast Cancer Trialists' Collaborative Group¹ of randomized trials of adjuvant tamoxifen. Probabilities of distant metastases among patients with locoregional recurrence were estimated based on a weighted mean of annual survival probabilities from 8 studies¹⁵⁻²² that reported such data. We assumed that the relative frequencies of locoregional recurrence and distant metastases following contralateral tumor would be the same as that in disease-free patients. We estimated probabilities of breast cancer death by site of metastasis using survival data for patients with advanced disease who received first-line letrozole in the phase 3 study of the International Letrozole Breast Cancer Group.⁴

Probabilities of Treatment-related Adverse Effects.

The proportion of patients entering the model with osteoporosis, as well as the annual probabilities of developing new osteoporosis with letrozole therapy or with no extended adjuvant therapy, were estimated based on data on the proportion of patients with self-reported osteoporosis at baseline and at the end of follow-up in the MA.17 trial.^{5,6} We estimated the probabilities of hip fracture in women who do not receive letrozole based on age-specific incidence rates for fracture of the proximal femur among women residing in Rochester, Minn, from 1989 to 1991.²³ We adjusted these rates to reflect the effects of tamoxifen therapy on fracture risk using the RR of fracture for patients receiving tamoxifen vs placebo among women 50 years and older at entry in the National Surgical Adjuvant Breast and Bowel Project P-1 Study (RR, 0.79).²⁴ The RR of hip fracture among patients receiving letrozole vs no extended adjuvant therapy was estimated to be 1.15, based on the ratio of the incidence of bone fracture among patients receiving letrozole vs placebo in the updated analysis of the MA.17 trial.⁶ The RR of non-breast cancer death following hip fracture was based on results of a prospective study²⁵ of 7500 French women that used multivariate analysis to estimate the association between hip fracture and mortality, adjusting for age and baseline health status.

Probabilities of Non-Breast Cancer Death. Probabilities of non-breast cancer death were based on US vital statistics data.^{26,27}

Costs. The costs of contralateral tumor and locoregional recurrence were based on the difference in medical care charges in the year before vs the year after these events among women diagnosed as having breast cancer in a large midwestern healthcare system between 1996 and 2002.²⁸ Because charges are gener-

ally substantially greater than actual costs, charges reported in this study were adjusted downward using a cost-to-charge multiplier of 0.5.²⁹ The costs of distant metastases were based on results of a retrospective analysis of health insurance claims among 344 women enrolled in a variety of health plans of a large private health benefits company located principally in the southeastern and midwestern United States who were diagnosed as having metastatic breast cancer from 1993 to 1997.³⁰ Surveillance costs were based on estimates from a study³¹ of Medicare claims among women with breast cancer identified in the Surveillance, Epidemiology, and End Results cancer registries between 1990 and 1998. The costs of hip fracture were based on results of a retrospective study³² of Medicare claims data for women 65 years and older with early breast cancer who experienced fractures between 1997 and 1998. The costs of letrozole and bisphosphonate therapy (70 mg of alendronate sodium per week) for patients with osteoporosis were based on 2004 wholesale acquisition costs.³³ The cost of osteoporosis screening in patients receiving letrozole was based on the median 2004 Medicare reimbursement rate for dual-energy x-ray absorptiometry of the hip and spine (*Current Procedural Terminology* code 76075).³⁴

Utility Values. Utility values were based on results of a study³⁵ of preferences for disease states associated with breast cancer in 70 women aged 55 to 70 years from the United States and the United Kingdom who had early-stage breast cancer and received adjuvant therapy but had not experienced disease recurrence. In that study, utilities were assessed for hypothetical disease states using a chained standard gamble technique. Because utility values differed significantly for US patients vs UK patients, we used the values for US patients. To calculate the long-term decrement in utility with hip fracture, we assumed that 50% of those with hip fracture would experience severe long-term disability as a consequence.³⁵ Because utility values for osteoporosis were not assessed in this study,³⁵ we assumed that osteoporosis would have no material effects on quality of life in our base-case analyses and examined the effect of this assumption in sensitivity analyses.

Base-case estimates and data sources are summarized in **Table 1** and in **Table 2**.

Analyses

Base-case Analyses. For each strategy, we calculated the expected number of breast cancer events, new cases of osteoporosis, hip fractures, breast cancer and non-breast cancer deaths, disease-free LYs, overall LYs, and QALYs, as well as the costs of letrozole therapy,

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Table 1. Probability Estimates Used in Model*

Variable	Extended Adjuvant Letrozole	No Extended Adjuvant Therapy	Source
Recurrence or contralateral tumor disease free			
Year 1 after tamoxifen	.0122	.0210] Goss et al, ⁵ 2003; and Goss et al, ⁶ 2005
Year 2 after tamoxifen	.0148	.0255	
Year 3 after tamoxifen	.0195	.0335	
Year 4 after tamoxifen	.0151	.0260	
Year 5 after tamoxifen	.0151	.0260	
Years 6-10 after tamoxifen	.0260	.0260	
Type of first event recurrence or contralateral tumor			
Contralateral	.1806	.1848] Goss et al, ⁵ 2003; and Goss et al, ⁶ 2005
Locoregional recurrence	.2258	.1957	
Distant metastases			
Soft tissue	.0839	.0435	
Bone	.2774	.3152	
Visceral	.2323	.2609	
Recurrence contralateral tumor			
Years 1-5 postrecurrence	.0363	.0363] Early Breast Cancer Trialists' Collaborative Group, ¹ 1998
Years 6-15 postrecurrence	.0269	.0269	
Distant metastases locoregional recurrence			
Years 1-5 postrecurrence	.1236	.1236] Moran and Haffty, ¹⁵ 2002; Doyle et al, ¹⁶ 2001; Haylock et al, ¹⁷ 2000; Schmoor et al, ¹⁸ 2000; Kamby and Sengelov, ¹⁹ 1997; Borner et al, ²⁰ 1994; Toonkel et al, ²¹ 1983; and Koning and Hart, ²² 1998
Years 6-15 postrecurrence	.0752	.0752	
Breast cancer death distant metastases			
Soft tissue	.1573	.1573] Mouridsen et al, ⁴ 2001
Bone	.2674	.2674	
Visceral	.2562	.2562	
Osteoporosis			
Baseline	.1200	.1200] Goss et al, ⁵ 2003; and Goss et al, ⁶ 2005
Annual	.0371	.0274	
Age at hip fracture, y			
35-39	.00007	.00006] Melton et al, ²³ 1999; Fisher et al, ²⁴ 1998; and Goss et al, ⁶ 2005
40-44	.00021	.00018	
45-49	.00037	.00032	
50-54	.00076	.00066	
55-59	.00095	.00083	
60-64	.00190	.00165	
65-69	.00254	.00221	
70-74	.00316	.00275	
75-79	.00990	.00861	
80-84	.02114	.01838	
≥85	.02861	.02488	
Risk ratio non-breast cancer death hip fracture			
Year 1 postfracture	3.1	3.1] Empana et al, ²⁵ 2004
Year 2 postfracture	1.9	1.9	

*|/ indicates probability of event conditional on prior event.

other breast cancer care, and treatment of osteoporosis and hip fracture. We also calculated the incremental cost per LY and QALY gained with letrozole vs no extended adjuvant therapy.

Deterministic Sensitivity Analyses. Key model probabilities and costs were varied from 50% to 150% of base-case values unless otherwise specified. Because the median duration of follow-up in the MA.17 trial was only 2.5 years, we generated results assuming patients receiving letrozole would receive only 3 years of extended adjuvant therapy. Because there is evidence that the benefits of adjuvant hormonal therapy with tamoxifen and aromatase inhibitors may persist after discontinuation of therapy,^{37,38} we also conducted an analysis in which we assumed that the benefits of letrozole would persist for 5 years after therapy discontinuation. We also generated results assuming that the distribution of recurrences by type would be the same for letrozole vs no extended adjuvant therapy, that there are no carryover effects of endocrine therapy on risk of hip fracture, and that all patients receiving letrozole would receive prophylactic bisphosphonates and such prophylaxis would eliminate the excess risk of fractures observed in the MA.17 trial. Results were also generated for alternative model time frames of 5, 10, 20, and 40 years, as well as by age at initiation of letrozole therapy and by nodal status.

Probabilistic Sensitivity Analyses. We constructed 1000 sets of probability and cost estimates by simultane-

ously sampling from estimated probability distributions of key model parameters.¹³ Probabilities of model events were assumed to be distributed as β random variables, relative risks as log-normal random variables, and cost and disutilities as normal random variables. Proportions of breast cancer events by type were modeled using a multinomial logit model. Estimates for which distributional information was unavailable were assumed to have

Table 2. Cost and Utility Estimates Used in Model

Variable	Estimate	Source
Costs, \$		
Breast cancer care		
Disease free, no osteoporosis or hip fracture, per year	1700	Warren et al, ³¹ 2002
Contralateral tumor, per year		
Year 1 postrecurrence	24 483	Lamerato et al, ²⁸ 2004; and Centers for Medicare & Medicaid Services ²⁹
Year 2 postrecurrence	1700	Warren et al, ³¹ 2002
Locoregional recurrence per year		
Year 1 postrecurrence	19 500	Lamerato et al, ²⁸ 2004; and Centers for Medicare & Medicaid Services ²⁹
Years ≥ 2 postrecurrence	1700	Warren et al, ³¹ 2002
Distant metastases, per year		
Year 1 postrecurrence	42 300	Berkowitz et al, ³⁰ 2000
Years ≥ 2 postrecurrence	21 900	
Terminal care, per death	16 700	
Hip fracture, per year		
Year 1 postfracture	42 000	Zhou et al, ³² 2004
Years ≥ 2 postfracture	3900	
Letrozole, 2.5 mg/d	7.07	Red Book Update, ³³ 2005
Alendronate, 70 mg/wk	15.38	
Osteoporosis testing, per year	135	Centers for Medicare & Medicaid Services ³⁴
Utilities		
Disease free		
No hip fracture	0.97	Sorensen et al, ³⁵ 2004; and Leibson et al, ³⁶ 2002
Hip fracture		
Year 1 after hip fracture	0.67	
Years ≥ 2 after hip fracture	0.93	
Contralateral tumor		
Year 1 postrecurrence	0.77	
Years ≥ 2 postrecurrence	0.97	
Locoregional recurrence		
Year 1 postrecurrence	0.77	
Years ≥ 2 postrecurrence	0.97	
Distant metastases	0.65	

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lower and upper bounds of 95% confidence intervals equal to 50% to 150% of base-case values (distributional information for all model inputs is available in an appendix at ajmc.com). For each set of estimates, we calculated expected lifetime costs and QALYs for each strategy, along with the differences between strategies in costs and QALYs. The resulting estimates were then arrayed on a cost-effectiveness plane, and cost-effectiveness acceptability curves were constructed for each strategy.

Software. The model was programmed using TreeAge Data version 4.0 decision analysis software (TreeAge Software, Inc, Williamstown, Mass). Analyses were conducted using TreeAge Data Interactive and Microsoft Excel and Microsoft Visual Basic 6.0 (Redmond, Wash).

(Table 3). Disease-free survival is estimated to be increased by approximately 10 months per patient. Life-years and QALYs (undiscounted) are estimated to be increased by approximately 6 months per patient. On a discounted basis, extended adjuvant letrozole is projected to result in 0.32 additional LYs and in 0.34 additional QALYs. Expected costs of extended adjuvant letrozole (\$11 435 per patient) are partly offset by an expected \$2850 savings in other breast cancer care. The expected costs of treatment of osteoporosis and hip fracture are increased by \$397 and \$716, respectively, in patients receiving letrozole. Therefore, the total incremental cost of letrozole vs no extended adjuvant therapy is \$9699 per patient. Cost-effectiveness is \$30 270 per LY gained and \$28 728 per QALY gained.

RESULTS

Base-case Results

Extended adjuvant letrozole for 5 years is estimated to prevent 4 recurrences per 100 patients treated

Deterministic Sensitivity Analyses

Cost-effectiveness was most sensitive to changes in the relative risk of recurrence or contralateral tumor with letrozole therapy and in the baseline probability of

Table 3. Base-case Model Results

Expected Outcome	Extended Adjuvant Letrozole	No Extended Adjuvant Therapy	Difference
Events, %			
Recurrence or contralateral tumor			
Contralateral tumor	3.2	4.0	-0.8
Locoregional recurrence	3.9	4.9	-1.0
Metastases	14.5	18.2	-3.7
Total	17.6	22.0	-4.4
Breast cancer death	13.0	16.4	-3.4
Osteoporosis	33.5	29.7	3.8
Hip fracture	11.6	9.6	2.0
Hip fracture death	2.1	1.8	0.4
Nondiscounted disease-free life-years, per patient	17.98	17.16	0.82
Total life-years per patient			
Not discounted	19.23	18.74	0.48
Discounted	14.22	13.90	0.32
Quality-adjusted life-years			
Not discounted	18.40	17.90	0.50
Discounted	13.62	13.28	0.34
Discounted costs, \$ per patient			
Extended adjuvant letrozole	11 435	0	11 435
Breast cancer care	36 194	39 043	-2850
Osteoporosis treatment	3426	3029	397
Hip fracture	4199	3483	716
Total	55 254	45 555	9699

Table 4. One-way Deterministic Sensitivity Analyses on Selected Model Parameters

Variable	Difference, Letrozole vs No Extended Adjuvant Therapy		Cost per QALY, \$
	Costs	QALYs	
Base case	9699	0.338	28 728
Relative risk of recurrence contralateral tumor with letrozole			
0.43	8916	0.471	18 939
0.75	10 575	0.190	55 803
Relative risk of hip fracture with letrozole			
1.08	9467	0.350	27 061
1.15	9928	0.325	30 502
Probability of recurrence/contralateral tumor disease free			
0.5 × Base case	11 088	0.169	65 607
1.5 × Base case	8527	0.479	17 783
Probability of recurrence contralateral tumor			
0.5 × Base case	9775	0.330	29 658
1.5 × Base case	9638	0.344	27 990
Probability of distant metastases locoregional recurrence			
0.5 × Base case	9848	0.317	31 059
1.5 × Base case	9619	0.350	27 454
Probability of breast cancer death distant metastases			
0.5 × Base case	8030	0.287	27 979
1.5 × Base case	10 456	0.360	29 067
Probability of hip fracture			
0.5 × Base case	9422	0.354	26 631
1.5 × Base case	9938	0.323	30 767
Relative risk of death hip fracture			
0.5 × Base case	9753	0.346	28 213
1.5 × Base case	9654	0.331	29 167
Cost of recurrence/contralateral tumor			
0.5 × Base case	11 601	0.338	34 364
1.5 × Base case	7796	0.338	23 092

QALYs indicates quality-adjusted life-years; “|,” probability of event conditional on prior event.

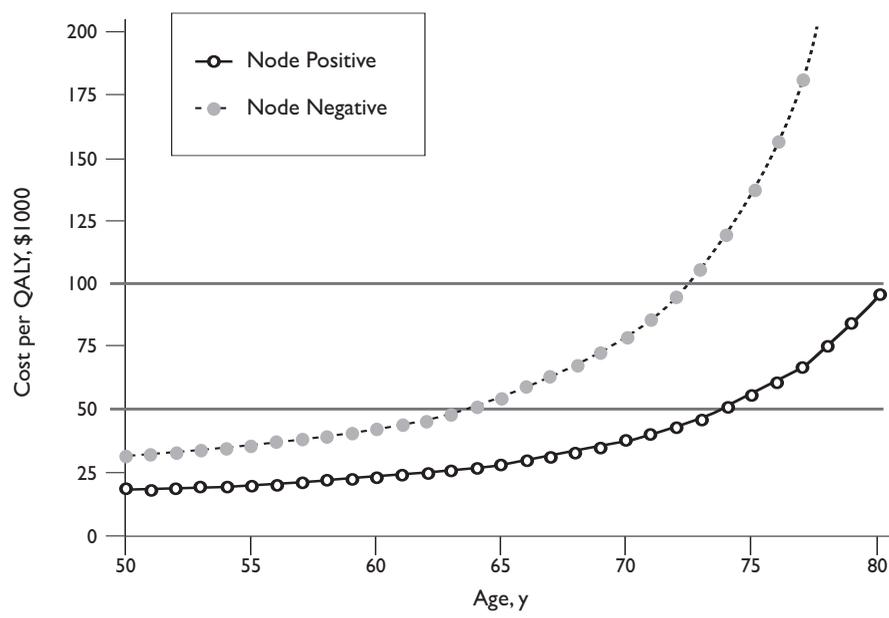
recurrence or contralateral tumor with no extended adjuvant therapy (Table 4). Results were insensitive to changes in other parameters, with cost-effectiveness less than \$35 000 per QALY in all other 1-way sensitivity analyses. Cost-effectiveness was virtually identical to our base-case result when we assumed that the distribution of recurrences by type would be the same for letrozole vs no extended adjuvant therapy, \$26 309 per QALY when we assumed that there are no carryover effects of endocrine therapy on risk of hip fracture, and \$34 085 per QALY when we assumed that all patients receiving letrozole would receive prophylactic bisphosphonates and that such prophylaxis would eliminate the excess risk of fractures with letrozole therapy

observed in the MA.17 trial. Costs per QALY gained are \$304 842, \$70 768, \$32 895, and \$28 679 with model time frames of 5, 10, 20, and 40 years, respectively. Cost-effectiveness was similar to our base-case estimate (\$29 664 per QALY) when we assumed only 3 years of treatment with letrozole but was substantially more favorable when we assumed a 5-year carryover effect for benefits of letrozole therapy (\$13 614 per QALY).

Results by Age and Nodal Status

Cost-effectiveness of letrozole therapy is more favorable in younger postmenopausal women and in node-positive patients (Figure 2). These results reflect the higher absolute risk of breast cancer events in node-

Figure 2. Sensitivity Analysis on Cost-effectiveness of Extended Adjuvant Letrozole by Age at Initiation of Letrozole Therapy and Nodal Status



QALY indicates quality-adjusted life-year.

positive patients (which results in greater absolute benefits for letrozole therapy assuming a similar relative risk reduction) and an increasing risk of non-breast cancer death with age (which results in fewer potential QALYs gained by preventing breast cancer events as age increases). Cost-effectiveness is less than \$100 000 per QALY for node-positive patients younger than 81 years and for node-negative patients younger than 73 years. It is less than \$50 000 per QALY for node-positive patients younger than 75 years and for node-negative patients younger than 65 years.

Probabilistic Sensitivity Analyses

Results of probabilistic sensitivity analyses are shown in Figure 3 and in Figure 4. The 2.5 and 97.5 percentiles of cost-effectiveness are \$18 169 and \$62 289 per QALY gained, respectively. Cost-effectiveness was less than \$50 000 per QALY gained in more than 94% of simulations and was less than \$100 000 per QALY gained in more than 99% of simulations.

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DISCUSSION

In the United States, there is no single generally accepted threshold for determining whether a particular intervention provides clinical benefits at a reasonable cost. Although \$50 000 per QALY has long been

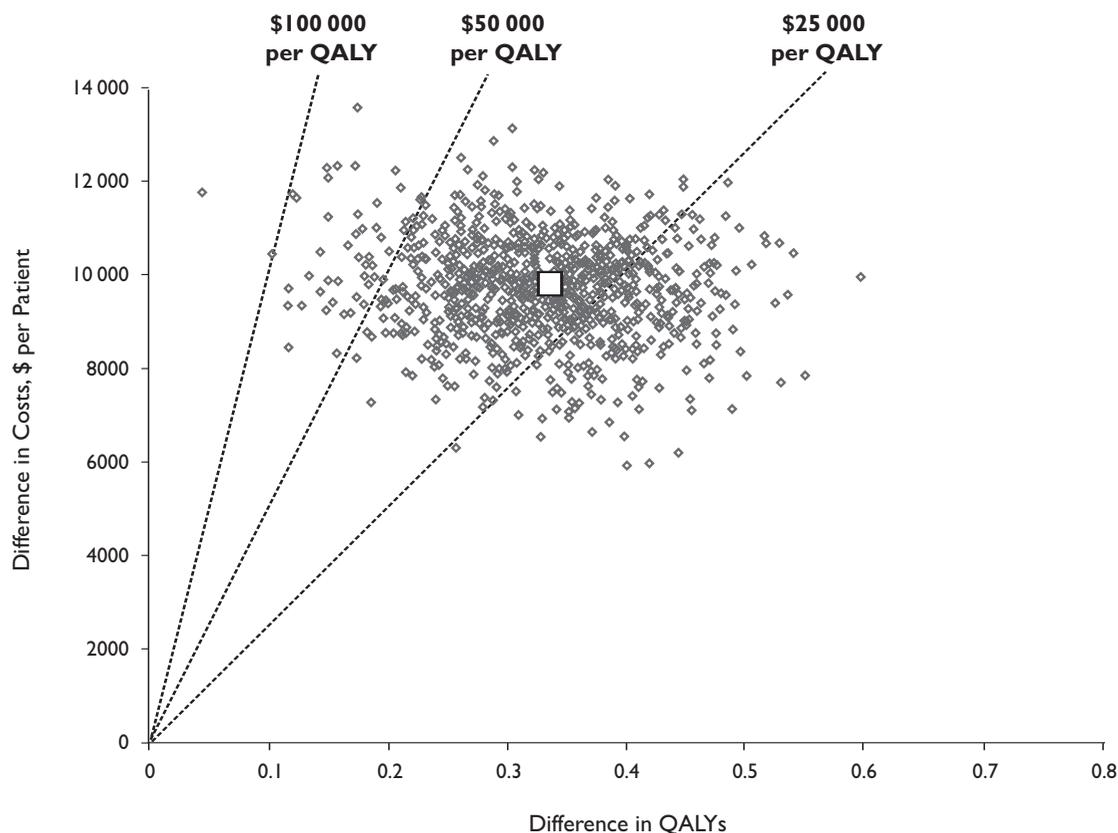
cited as a threshold for identifying therapies that are cost-effective,³⁹ the validity of this threshold has been questioned, and recent evidence suggests that societal willingness to pay for a QALY may be at least \$100 000 and possibly as high as \$200 000.^{40,41} Our estimate of the cost-effectiveness of letrozole therapy—\$28 728 per QALY gained—is substantially less than any of these thresholds. It also is less than that reported for early adjuvant therapy with anastrozole vs tamoxifen¹³ and is less than or similar to that reported for a variety of other widely accepted therapies for patients with cancer.⁴¹⁻⁴⁷ Although the cost-effectiveness of letrozole therapy was more favorable in younger and node-positive patients, the cost per QALY gained was estimated to be less

than \$100 000 for node-positive patients younger than 81 years and for node-negative patients younger than 73 years.

Our estimate of the cost-effectiveness of extended adjuvant letrozole from the US healthcare system perspective is somewhat less favorable than that reported in an analysis by Karnon et al⁴⁸ from the United Kingdom National Health System perspective (£10 338 per QALY [approximately \$20 000 per QALY] at 2004 exchange rates). Although the 2 studies differed in several respects, including the utilities used for various health states and the types of events considered (our study examined only hip fracture, whereas Karnon et al included other fractures), the 2 models used were similar, and the difference in results principally reflects the differences in the cost of letrozole therapy and breast cancer care between the 2 countries.

Our estimate of the cost-effectiveness of extended adjuvant letrozole is more favorable than that reported by Hillner¹³ for initial adjuvant anastrozole vs tamoxifen (\$40 600-\$75 900 per QALY). Punglia et al⁴⁹ conducted a decision analysis of different sequencing strategies for the use of tamoxifen or aromatase inhibitors in women with early breast cancer and concluded that sequential adjuvant therapy with tamoxifen followed by an aromatase inhibitor after 2.5 years yields improved outcomes compared with tamoxifen or

Figure 3. Probabilistic Sensitivity Analysis on the Difference in Costs and Quality-adjusted Life-years (QALYs) With Extended Adjuvant Letrozole vs No Extended Adjuvant Therapy



Each data point on the figure corresponds to an estimate of difference (letrozole vs no extended adjuvant therapy) in total costs and QALYs for a simulation. Base-case result is represented by square.

aromatase inhibitors alone or with crossover treatment to an aromatase inhibitor after 5 years of tamoxifen therapy. Results of these studies are not directly comparable to ours, however, as they examined newly diagnosed patients, whereas our study focused on patients who had already received 5 years of tamoxifen therapy.

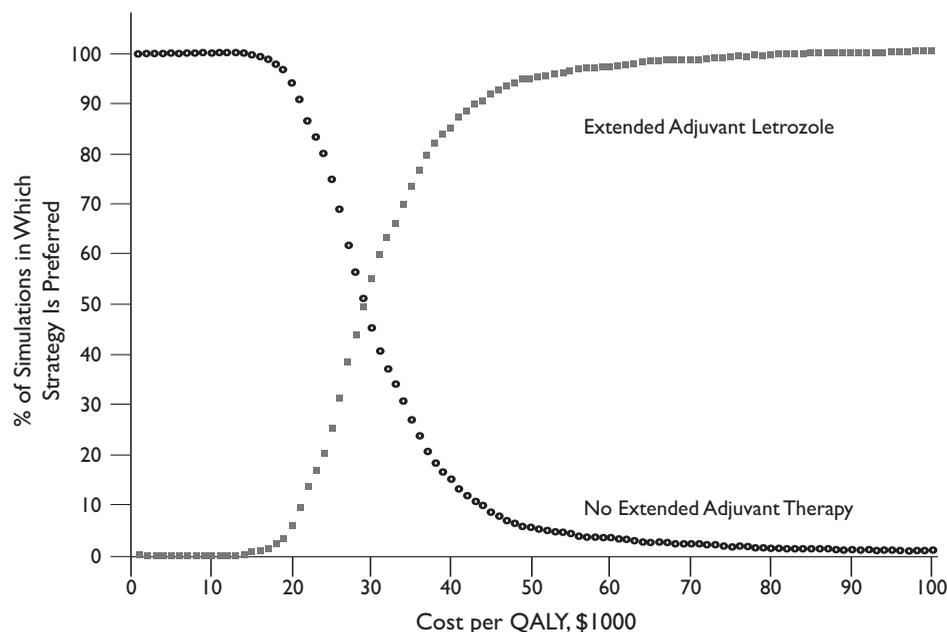
We found that cost-effectiveness was sensitive to the assumed model time frame. This reflects the fact that the cost of extended adjuvant letrozole is largely incurred during the first 5 years, whereas the benefits of such therapy in terms of breast cancer deaths avoided and QALYs gained are accrued slowly over time. Our use of a 30-year time frame, approximating a lifetime projection, is consistent with good modeling practices, as it captures the full costs and consequences of the treatment strategies considered.^{7,9}

Like most cost-effectiveness evaluations, our study is based on several necessary simplifying assumptions, and certain limitations must be recognized. First, although there was no significant increase in overall

survival among patients receiving letrozole in the MA.17 trial (there was a significant improvement in overall survival with letrozole therapy among node-positive patients), we assumed that the improvements in DFS with letrozole therapy observed in the MA.17 trial would result in improved survival for patients receiving letrozole in the long term. This assumption is based on previous research showing that the benefits of adjuvant therapy on DFS are predictive of benefits on survival.¹

Second, we assumed that patients receiving letrozole would be at increased risk of osteoporosis and that those developing osteoporosis would receive lifelong treatment with a bisphosphonate. Our estimates of the risk of osteoporosis in patients who do and do not receive letrozole were based on patient self-reports and may not reflect the actual incidence of diagnosed osteoporosis among postmenopausal women with early breast cancer seen in typical clinical practice. To the best of our knowledge, data on the latter are unavailable. Our estimate of the additional cost of osteoporosis treatment

Figure 4. Cost-effectiveness Acceptability Curve for Extended Adjuvant Letrozole vs No Extended Adjuvant Therapy



Values represent proportion of simulations ($n = 1000$) for which each strategy was preferred for a given threshold value for cost-effectiveness. QALY indicates quality-adjusted life-year.

in patients receiving letrozole may be high, as it assumes perfect compliance with bisphosphonate therapy, a goal rarely achieved in typical clinical practice. On the other hand, because we lacked data with which to reliably estimate the effects of osteoporosis on quality of life in women with breast cancer, we assumed in our base-case analyses that development of osteoporosis would have no effect on utilities. Although this may have biased our results in favor of letrozole therapy, results of sensitivity analyses suggest that the inclusion of quality-of-life effects for osteoporosis would not have materially affected our results or altered our conclusions.

Third, patients in our model receiving letrozole were assumed to have a lifelong increase in the risk of hip fracture. This assumption may be conservative, as we did not consider the potential beneficial effects of bisphosphonate therapy in women who develop osteoporosis.^{12,14} Also, data from the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial suggest that fracture risk is similar after discontinuation of anastrozole vs tamoxifen.³⁹

Fourth, for simplicity we modeled the long-term effects of hip fractures on utilities (as well as costs and survival) only for patients remaining disease free.

Because patients who experience breast cancer events may subsequently experience hip fracture or vice versa, we may have underestimated the negative effects of hip fracture on outcomes, thus biasing our results in favor of letrozole therapy. We know of no data, however, on the effects of hip fracture on outcomes in women with distant metastases (which comprise most breast cancer events). As the proportion of patients who would be expected to experience both a breast cancer event and a hip fracture is small, and the life expectancy of patients with metastatic disease is short, we believe that this simplification does not materially affect our findings.

Fifth, consistent with the methods used in an earlier study¹² of the cost-effectiveness of adjuvant anastrozole, we did not consider the potential effects of aromatase inhibitor therapy on the risks of nonhip fractures. Although all fractures are a concern, the morbidity, mortality, and costs of hip fractures are substantially greater than those of other fractures. Our model was insensitive to the assumed effects of hip fracture; therefore, we believe that any bias imparted by failure to include other fractures is likely small. We did not consider the effects on costs or quality of life of other adverse effects (eg, hot flashes, arthralgia or arthritis, and myalgia) that were more likely among patients receiving letrozole vs placebo in the MA.17 trial or vaginal bleeding, which was more likely in patients receiving placebo vs letrozol.^{5,6} Approximately 90% of these events were of mild-to-moderate severity, however, and few resulted in discontinuation of study therapy.^{5,6} Furthermore, in a substudy⁵⁰ of the MA.17 trial, letrozole therapy did not have a substantial adverse effect on overall quality of life.

Sixth, we assumed that age-specific rates of non-breast cancer mortality in women with breast cancer would be similar to those in the US general popula-

tion. Many women with early breast cancer receive adjuvant chemotherapy or radiotherapy, which may increase the risk of secondary neoplasms and cardiac mortality. However, as noted in the Early Breast Cancer Trialists' Collaborative Group meta-analysis,³⁷ the effects of adjuvant chemotherapy on non-breast cancer mortality are small (0.2% excess mortality from heart disease, leukemia, or lymphoma during 6 years of follow-up with chemotherapy based on cyclophosphamide, methotrexate, and fluorouracil). Also, while there is evidence that the radiotherapy regimens used before the 1980s were associated with increased long-term mortality from heart disease,^{51,52} the improvements in radiotherapy since that time have substantially reduced these risks.^{53,54} Any potential bias associated with this assumption is therefore probably small.

Because the MA.17 trial was terminated at the first interim analysis, the median follow-up was only 2.5 years, and few patients in the trial received 5 years of treatment. We examined the cost-effectiveness of 5 years of extended adjuvant letrozole, as this was consistent with the planned duration of treatment in the MA.17 trial. Also, the relative risk of breast cancer events among patients receiving letrozole vs placebo was based on all efficacy events before unblinding. Although the small numbers of patients with 3 to 5 years of follow-up reduced the precision of our estimates of the benefits and risks of letrozole therapy, we do not believe that they otherwise biased our results in favor of letrozole. To the contrary, our estimates of the cost-effectiveness of letrozole therapy may be conservative because the risk reduction estimate that we used was weighted more heavily by events occurring during the first few years of follow-up and because there was evidence in the MA.17 trial of increasing benefit of letrozole with longer duration of treatment.^{55,56} Also, our results were similar when we assumed that patients receiving letrozole would receive only 3 years of treatment.

In summary, the results of our study suggest that, for postmenopausal women with receptor-positive early-stage breast cancer, the cost-effectiveness of extended adjuvant letrozole is within the range of other generally accepted medical interventions in the United States. These findings support the recommendations of the American Society of Clinical Oncology¹² for the use of aromatase inhibitors as initial therapy or in sequence with tamoxifen as an appropriate treatment for postmenopausal women with receptor-positive early-stage breast cancer.

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REFERENCES

1. **Early Breast Cancer Trialists' Collaborative Group.** Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet*. 1998;351:1451-1467.
2. **Fisher B, Dignam J, Bryant J, Wolmark N.** Five versus more than five years of tamoxifen for lymph node-negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. *J Natl Cancer Inst*. 2001;93:684-690.
3. **Sapner T, Tormey DC, Gray R.** Annual hazard rates of recurrence for breast cancer after primary therapy. *J Clin Oncol*. 1996;14:2738-2746.
4. **Mouridsen H, Gershanovich M, Sun Y, et al.** Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group [published correction appears in *J Clin Oncol*. 2001;19:3302]. *J Clin Oncol*. 2001;19:2596-2606.
5. **Goss PE, Ingle JN, Martino S, et al.** A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med*. 2003;349:1793-1802.
6. **Goss PE, Ingle JN, Martino S, et al.** Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst*. 2005;97:1262-1271.
7. **Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB.** Recommendations of the Panel on Cost-effectiveness in Health and Medicine. *JAMA*. 1996;276:1253-1258.
8. **Sonnenberg FA, Beck JR.** Markov models in medical decision making: a practical guide. *Med Decis Making*. 1993;13:322-338.
9. **Weinstein MC, O'Brien B, Hornberger J, et al; ISPOR Task Force on Good Research Practices-Modeling Studies.** Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices-Modeling Studies. *Value Health*. 2003;6:9-17.
10. **Bureau of Labor Statistics.** *Consumer Price Index*. Washington, DC: US Dept of Labor; 2005. Available at: <http://www.bls.gov/cpi/home.htm>. Accessed April 1, 2005.
11. **Briggs AH.** A Bayesian approach to stochastic cost-effectiveness analysis. *Health Econ*. 1999;8:257-261.
12. **Winer EP, Hudis C, Burstein HJ, et al.** American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. *J Clin Oncol*. 2005;23:619-629.
13. **Hillner BE.** Benefit and projected cost-effectiveness of anastrozole versus tamoxifen as initial adjuvant therapy for patients with early-stage estrogen receptor-positive breast cancer. *Cancer*. 2004;101:1311-1322.
14. **Hillner BE, Ingle JN, Chlebowski RT, et al; American Society of Clinical Oncology.** American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer [published correction appears in *J Clin Oncol*. 2004;22:1351]. *J Clin Oncol*. 2003;21:4042-4057.
15. **Moran MS, Haffty BG.** Local-regional breast cancer recurrence: prognostic groups based on patterns of failure. *Breast J*. 2002;8:81-87.
16. **Doyle T, Schultz DJ, Peters C, Harris E, Solin LJ.** Long-term results of local recurrence after breast conservation treatment for invasive breast cancer. *Int J Radiat Oncol Biol Phys*. 2001;51:74-80.
17. **Haylock BJ, Coppin CML, Jackson J, Basco VE, Wilson KS.** Locoregional first recurrence after mastectomy: prospective cohort studies with and without immediate chemotherapy. *Int J Radiat Oncol Biol Phys*. 2000;46:355-362.
18. **Schmoor C, Sauerbrei W, Bastert G, Schumacher M.** Role of isolated locoregional recurrence of breast cancer: results of four prospective studies. *J Clin Oncol*. 2000;18:1696-1708.
19. **Kamy C, Sengelov L.** Pattern of dissemination and survival following isolated locoregional recurrence of breast cancer. *Breast Cancer Res Treat*. 1997;45:181-192.
20. **Borner M, Bacchi M, Goldhirsch A, et al; Swiss Group for Clinical Cancer Research.** First isolated locoregional recurrence following mastectomy for breast cancer: results of a phase III multicenter study comparing systemic treatment with observation after excision and radiation. *J Clin Oncol*. 1994;12:2071-2077.
21. **Toonkel LM, Fix I, Jacobsen LH, Wallach CB.** The significance of local recurrence of carcinoma of the breast. *Int J Radiat Oncol Biol Phys*. 1983;9:33-39.
22. **Koning C, Hart G.** Long-term follow-up of a randomized trial on adjuvant chemotherapy and hormonal therapy in locally advanced breast cancer. *Int J Radiat Oncol Biol Phys*. 1998;41:397-400.
23. **Melton LJ III, Crowson CS, O'Fallon WM.** Fracture incidence in Olmsted County, Minnesota: comparison of urban with rural rates and changes in urban rates over time. *Osteoporos Int*. 1999;9:29-37.
24. **Fisher B, Costantino JP, Wickerham DL, et al.** Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst*. 1998;90:1371-1388.
25. **Empaña JP, Dargent-Molina P, Bréart G; EPIDOS Group.** Effect of hip fracture on mortality in elderly women: the EPIDOS Prospective Study. *J Am Geriatr Soc*. 2004;52:685-690.
26. **Anderson RN.** United States Life Tables, 1998. National Vital Statistics Reports. 2001;48(18). Available at: <http://www.cdc.gov>. Accessed June 21, 2006.
27. **Centers for Disease Control and Prevention.** Deaths from each cause, by 5-year age groups, Hispanic origin, race for non-Hispanic population, and sex: United

- States, 1999, 2002-03. Available at: <http://www.cdc.gov/nchs/datawh/statab/unpubd/mortabs/gmwkhi.htm>. Accessed December 1, 2004.
28. **Lamerato L, Havstad S, Gandhi SK, Jones DA.** The economic burden of breast cancer recurrence: findings from a retrospective analysis of health system data. Poster presented at: 27th Annual San Antonio Breast Cancer Symposium; December 9, 2004; San Antonio, Tex. Abstract 2084. Available at: <http://www.sabcs.org>. Accessed January 1, 2005.
29. **Centers for Medicare & Medicaid Services.** 2004 payment impact file. Available at: <http://www.cms.hhs.gov>. Accessed April 1, 2005.
30. **Berkowitz N, Gupta S, Silberman G.** Estimates of the lifetime direct costs of treatment for metastatic breast cancer. *Value Health.* 2000;3:23-30.
31. **Warren JL, Brown ML, Fay MP, Schussler N, Potosky AL, Riley GF.** Costs of treatment for elderly women with early-stage breast cancer in fee-for-service settings. *J Clin Oncol.* 2002;20:307-316.
32. **Zhou Z, Redaelli A, Johnell O, Willke RJ, Massimini G.** A retrospective analysis of health care costs for bone fractures in women with early-stage breast carcinoma. *Cancer.* 2004;100:507-517.
33. **Red Book Update January 2005.** Montvale, NJ: Thomson Healthcare Inc; 2005.
34. **Centers for Medicare & Medicaid Services.** 2004 national Medicare fee schedule file. Available at: <http://www.cms.hhs.gov>. Accessed April 1, 2005.
35. **Sorensen S, Brown R, Benedict A, Flood E, Revicki D.** Patient-rated utilities in postmenopausal early breast cancer (EBC): a cross-country comparison: Contributed Podium Presentations. *Value Health.* 2004;7:637-657.
36. **Leibson CL, Tosteson AN, Gabriel SE, Ransom JE, Melton LJ.** Mortality, disability, and nursing home use for persons with and without hip fracture: a population-based study. *J Am Geriatr Soc.* 2002;50:1644-1650.
37. **Early Breast Cancer Trialists' Collaborative Group (EBCTCG).** Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet.* 2005;365:1687-1717.
38. **Howell A; ATAC Trialists' Group.** The ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial in postmenopausal women with early breast cancer: updated efficacy results based on a median follow-up of 5 years. Oral presentation presented at: 27th Annual San Antonio Breast Cancer Symposium; December 8, 2004. Abstract 1. Available at: <http://www.sabcs.org>. Accessed January 1, 2005.
39. **Earle CC, Chapman RH, Baker CS, et al.** Systematic overview of cost-utility assessments in oncology. *J Clin Oncol.* 2000;18:3302-3317.
40. **Hirth RA, Chernew ME, Miller E, Fendrick AM, Weissert WG.** Willingness to pay for a quality-adjusted life year: in search of a standard. *Med Decis Making.* 2000;20:332-342.
41. **Ubel PA, Hirth RA, Chernew ME, Fendrick AM.** What is the price of life and why doesn't it increase at the rate of inflation? *Arch Intern Med.* 2003;163:1637-1641.
42. **Elkin EB, Weinstein MC, Winer EP, Kuntz KM, Schnitt SJ, Weeks JC.** HER-2 testing and trastuzumab therapy for metastatic breast cancer: a cost-effectiveness analysis. *J Clin Oncol.* 2004;22:854-863.
43. **Orr RK, Col NF, Kuntz KM.** A cost-effectiveness analysis of axillary node dissection in postmenopausal women with estrogen receptor-positive breast cancer and clinically negative axillary nodes. *Surgery.* 1999;126:568-576.
44. **Lee JH, Glick HA, Hayman JA, Solin LJ.** Decision-analytic model and cost-effectiveness evaluation of postmastectomy radiation therapy in high-risk premenopausal breast cancer patients. *J Clin Oncol.* 2002;20:2713-2725.
45. **Hillner BE, Weeks JC, Desch CE, Smith TJ.** Pamidronate in prevention of bone complications in metastatic breast cancer: a cost-effectiveness analysis. *J Clin Oncol.* 2000;18:72-79.
46. **Cremieux PY, Finkelstein SN, Berndt ER, Crawford J, Slavin MB.** Cost effectiveness, quality-adjusted life-years and supportive care: recombinant human erythropoietin as a treatment of cancer-associated anaemia. *Pharmacoeconomics.* 1999;16(pt 1):459-472.
47. **Zbrozek AS, Cantor SB, Cardenas MP, Hill DP Jr.** Pharmacoeconomic analysis of ondansetron versus metoclopramide for cisplatin-induced nausea and vomiting. *Am J Hosp Pharm.* 1994;51:1555-1563.
48. **Karnon J, Delea T, Johnston SR, et al.** Cost effectiveness of extended adjuvant letrozole in postmenopausal women after adjuvant tamoxifen therapy: the UK perspective. *Pharmacoeconomics.* 2006;24:237-250.
49. **Punglia RS, Kuntz KM, Winer EP, Weeks JC, Burstein HJ.** Optimizing adjuvant endocrine therapy in postmenopausal women with early-stage breast cancer: a decision analysis. *J Clin Oncol.* 2005;23:5178-5187.
50. **Whelan TJ, Goss PE, Ingle JN, et al.** Assessment of quality of life in MA.17, a randomized placebo-controlled trial of letrozole in postmenopausal women following five years of tamoxifen [abstract]. *Proc Am Soc Clin Oncol.* 2004;23:6. Abstract 517.
51. **Early Breast Cancer Trialists' Collaborative Group (EBCTCG).** Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet.* 2000;355:1757-1770.
52. **Cuzick J, Stewart H, Rutqvist L, et al.** Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. *J Clin Oncol.* 1994;12:447-453.
53. **Patt DA, Goodwin JS, Kuo YF, et al.** Cardiac morbidity of adjuvant radiotherapy for breast cancer. *J Clin Oncol.* 2005;23:7475-7482.
54. **Giordano SH, Kuo YF, Freeman JL, Buchholz TA, Hortobagyi GN, Goodwin JS.** Risk of cardiac death after adjuvant radiotherapy for breast cancer. *J Natl Cancer Inst.* 2005;97:419-424.
55. **Goss PE, Ingle JN, Martino S, et al.** Updated analysis of the NCIC CTG MA 17 randomized placebo (P) controlled trial of letrozole (L) after five years of tamoxifen in postmenopausal women with early stage breast cancer [abstract]. *Proc Am Soc Clin Oncol.* 2004;23:87. Abstract 847.
56. **Ingle JN, Goss PE, Tu D.** Analysis of duration of letrozole extended adjuvant therapy as measured by hazard ratios of disease recurrence over time for patients on NCIC CTG MA 17 [abstract]. *Breast Cancer Res Treat.* 2005;94(suppl 1):S11. Abstract 17.