Benefit and Projected Cost-Effectiveness of Anastrozole versus Tamoxifen as Initial Adjuvant Therapy for Patients with Early-Stage Estrogen Receptor–Positive Breast Cancer

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BACKGROUND. Women who have estrogen receptor (ER)-positive disease with postmenopausal onset and who receive tamoxifen as standard adjuvant treatment constitute the largest subgroup of patients with breast cancer. Recent data from the ATAC ('Arimidex, Tamoxifen Alone or in Combination') randomized trial indicate that anastrozole significantly reduces breast cancer recurrence rates but does not provide any advantage in terms of survival at 4 years posttreatment. Furthermore, anastrozole and tamoxifen were found to have different toxicity profiles. The goals of the current study were to estimate the disease-free survival (DFS) rates and potential survival benefits associated with anastrozole use and to determine whether the incremental cost-effectiveness (ICE) was low enough to warrant an immediate switch to the use of this agent, as the long-term conclusions of the ATAC trial will not be available for several years.

METHODS. A computer simulation model assessed the outcomes of 64-year-old women with ER-positive breast cancer who subsequently received either anastrozole or tamoxifen for 5 years. Daily recurrence risks, as well as the relative risks associated with various treatment-related events, were calculated using data from the ATAC trial. Study endpoints included breast cancer recurrence–free survival, anticipated survival resulting from an anastrozole-induced decrease in systemic disease recurrence rates, and survival adjusted for quality of life and for hip fracture risk over periods of 4, 12, and 20 years.

RESULTS. After 4 years, the projected DFS benefit associated with anastrozole was 14 days, with an ICE of $167,500 per year. Projected 12 and 20 years into the future, DFS benefits increased to 2.9 months and 5.3 months, respectively. The corresponding benefits in terms of overall survival were 0.9 months and 2.0 months, respectively, with the ICE becoming $< $100,000 per life year once the projection horizon exceeded 12 years. The inclusion of quality-of-life weightings for nonfatal outcomes modestly favored anastrozole in the short term; however, if anastrozole use is associated with an increased risk of hip fracture, then the long-term benefit associated with this agent is reduced by approximately 25%.

CONCLUSIONS. Adjuvant anastrozole is projected to result in a substantial improvement in DFS for patients with breast cancer. If this DFS benefit were to ultimately lead to a survival benefit, then the ICE of anastrozole use would be acceptable for patients expected to live longer than 12 years. Decision models are useful for generating realistic projections for stakeholders who are considering competing options that impact survival and quality of life and have associated societal costs. *Cancer* **2004;101:1311–22.** © *2004 American Cancer Society.*

KEYWORDS: anastrozole, tamoxifen, adjuvant therapy, breast neoplasm, cost, cost analysis, cost-benefit analysis, decision modeling, survival analysis.

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In patients with early-stage breast cancer, the identification of a tumor as having positive estrogen receptor (ER) status provides critical prognostic and treatment-related information. In women with ER-positive disease, the benefit associated with tamoxifen (the prototypic and first known antiestrogen agent)—specifically, a reduction in the risk of metastatic disease—is measurable within the first few years of treatment and persists beyond the 5 years over which treatment typically is administered; this reduction in risk is similar for women with lymph node–negative disease and women with lymph node–positive disease.[1]{FNO}

Newer agents (e.g., anastrozole, letrozole, exemestane) that specifically target peripheral aromatase-mediated production of estrogen have been found to be as effective as or superior to tamoxifen in women with metastatic ER-positive breast cancer.[2,3] On the basis of these findings, large randomized controlled trials assessing the use of such agents in the adjuvant setting have been initiated. Results from one such study, the ATAC ('Arimidex, Tamoxifen Alone or in Combination') trial, have recently been reported.[4,5] That study, which involved 9366 postmenopausal women and stands as the largest adjuvant therapy trial ever initiated, posed 3 questions: 1) Is anastrozole at least as effective as tamoxifen? 2) Is the safety profile of anastrozole superior to that of tamoxifen? and 3) Could a combination involving anastrozole and tamoxifen offer additional efficacy or safety-related benefits compared with tamoxifen alone? The ATAC trial found that anastrozole use resulted in a statistically significant increase in disease-free survival (DFS) compared with tamoxifen alone, whereas the results documented in the combined treatment arm were similar to those observed in the tamoxifen arm.

Should clinical practice be modified on the basis of these initial findings? In 2002 and 2003, the American Society of Clinical Oncology Technology Task Force suggested that given the absence of an observed survival benefit and more mature safety data, replacement of tamoxifen as the standard treatment option was not yet warranted.[6,7] Nonetheless, in 2002, the Food and Drug Administration (FDA) approved a supplemental application for the use of anastrozole in adjuvant treatment.

Because anastrozole is an FDA-approved indication, postmenopausal women with ER-positive disease (who represent the largest subgroup of patients with breast cancer) and policymakers must consider a complex combination of factors in making decisions regarding adjuvant hormonal therapy. Previous experiments involving hormonal therapy have found that DFS benefit is predictive of an eventual benefit in terms of overall survival[1,8,9]; however, identification of a survival benefit in the ATAC trial may require years of additional follow-up, as only approximately 4% of all women in that trial had died after 4 years. Another consideration is that the two agents being compared have different toxicity profiles: the risk of developing thromboembolism and uterine complications is elevated during treatment with tamoxifen, whereas bone loss, which may increase a patient's future risk of fracture, is the dominant adverse effect associated with anastrozole.

In the current study, decision analysis was performed to compare the long-term consequences of these two treatment options, and a variety of endpoints were considered. Among these endpoints were future DFS, anticipated survival benefit resulting from the observed difference in systemic recurrence rates, and survival adjusted for quality of life and for hip fracture risk. Using various time frames, the question of how far into the future one must look before anastrozole use becomes cost effective was addressed. The current analysis was performed independently of support from the manufacturer or from any government regulatory agency and should assist stakeholders in the decision-making process.

MATERIALS AND METHODS

Study Design

Decision and cost-effectiveness (CE) analyses that simulated the most common clinical courses and health states experienced by women with early-stage ER-positive breast cancer were performed. Figure 1 summarizes the Markov model[10] that was created using the DATA decision analysis software package (Version 4.0; Treeage, Williamstown, MA).

ATAC Trial

A hypothetic group of women who met the entry criteria for the ATAC trial were considered. Details regarding study design and patient characteristics are discussed in the original report.[5] In brief, postmenopausal women with operable breast cancer who had undergone primary surgery and/or completed chemotherapy were double-blindly randomized to receive anastrozole (1 mg) plus placebo, active tamoxifen (20 mg) plus placebo, or anastrozole plus tamoxifen. Regimens were administered until the onset of disease recurrence, the observation of unacceptable side effects, or the completion of 5 years of treatment. The primary endpoint was DFS. The target cohort size of 9000 women gave the trial 90% power to confirm the noninferiority of anastrozole and 80% power to detect a 20% reduction in the number of events occurring in

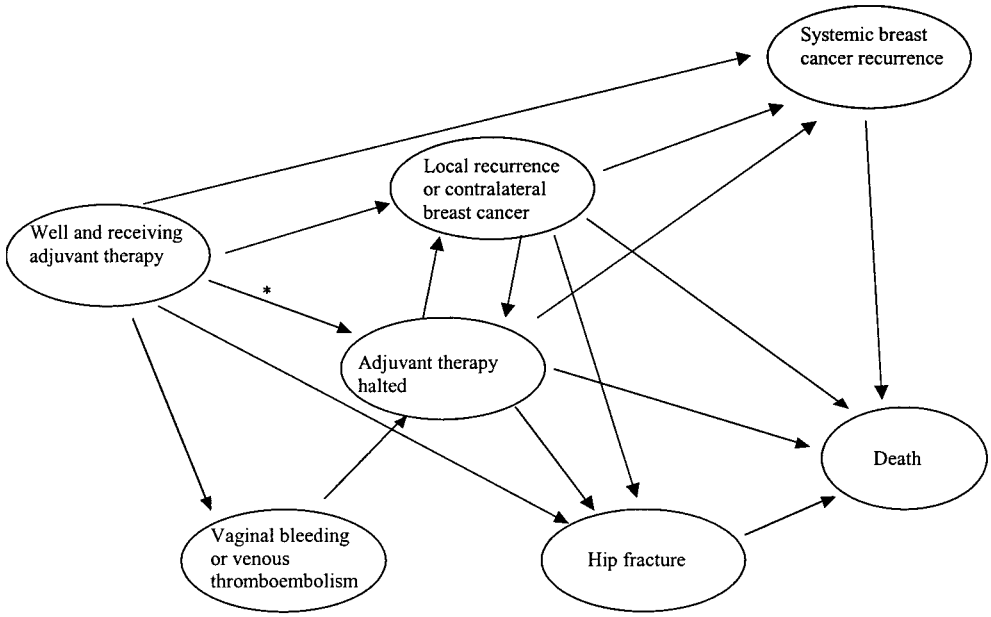

FIGURE 1. Markov model. All patients begin in the oval labeled 'Well and receiving adjuvant therapy'. Each day until death, patients have the potential to migrate to alternative health states. Patients with locally recurrent disease, contralateral breast cancer, vaginal bleeding, or venous thromboembolism incur short-term costs and quality-of-life losses. Adjuvant therapy is halted after 5 years (*) or if an adverse event occurs $<$ 5 years after the start of treatment. Event probabilities and relative risk ratios are listed in Table 2.

the anastrozole arm or in the number of events occurring in the combination therapy arm.

Endpoints and CE

The model considered three sequential endpoints. Initially, the projected breast cancer–free survival rate at various follow-up durations was taken to be the lone endpoint, and an incremental CE ratio that included the costs of all events and assigned a utility score of zero to survival after recurrence was calculated; this ratio corresponded to the cost (in dollars) per specified duration of breast cancer–free survival. Next, the anticipated (but not yet realized) survival benefit associated with the observed anastrozole-induced decrease in systemic breast cancer recurrence rates was considered; in this step, the incremental CE ratio measured the dollar cost per life year gained at various points in the future. Finally, quality-of-life weighting (i.e., a utility value) was assigned to each health state, and the differential risk of hip fracture was added to the model. In this step, the incremental CE ratio represented the dollar cost per quality-adjusted life year (QALY). The assigned utility weightings were consistent with those used in the literature, because a prospective quality-of-life assessment was not included in the ATAC trial.[11]

The time frames examined ranged from 4 years (corresponding to the current length of follow-up in the ATAC trial) to 20 years (corresponding to the current average life expectancy of a 64-year-old woman in the United States).[12] Costs and benefits were discounted at a rate of 3% per year.[13] The model reflected a third-party, or centralized-payer, perspective, as indirect medical care costs were not considered.

The Model and Its Assumptions

In the current model, a Markov process was used to track natural histories in two cohorts of women—one receiving treatment with anastrozole and the other receiving treatment with tamoxifen, just as if they had entered the ATAC trial. The model considered possible adverse events on a daily basis until patients were 90 years old (i.e., for 9500 cycles). Markov processes are widely used to model the natural history of breast cancer and other life-threatening conditions.[14–16] The probabilities of specific events were calculated using data from the ATAC trial. Potential adverse events included recurrent breast cancer, hip fracture, vaginal bleeding, venous thromboembolism, and death due to other causes. Table 1 summarizes the data and structural assumptions that were used to generate the current model.

Model Data Elements

The baseline probabilities, relative risks, costs, and utility values associated with various clinical events

TABLE 1
Features of and Assumptions Made by the Current Model

1. At the start of the trial, each participant was age 64 years, the age of the average ATAC trial participant.
2. All participants had confirmed ER-positive breast cancer.
3. The duration of adjuvant therapy was 5 years.
4. The difference in daily cost between anastrozole and tamoxifen was $5.50.
5. Breast cancer–related event probabilities were calculated using data obtained from the ATAC trial at 47 months from baseline.
6. The risk of each breast cancer–related adverse event was constant over a given participant's lifetime.
7. Contralateral breast cancer risk, local recurrence risk, and systemic recurrence risk were reduced to different extents by anastrozole.
8. If an adverse event did not occur, the relative benefits of anastrozole would persist indefinitely.
9. Treatment was halted for all patients who experienced adverse breast events, treatment-related toxicity, or death. There were no crossovers between treatment arms.
10. In the event that adjuvant therapy was halted before 5 years had elapsed, the subsequent breast cancer risk would increase and the risk of hip fracture (if considered) would return to the level associated with nonuse of adjuvant therapy.
11. After any type of breast recurrence, all benefit associated with reductions in the incidence of other forms of breast recurrence was lost.
12. After disease recurrence, the type of treatment received, the cost of treatment, and survival were the same in both arms.
13. The risk of non–breast cancer–related death varied from year to year and was calculated using population-based age-specific death rates.
14. When considered, the risk of death due to metastatic disease did not vary with age and was based on a median survival duration of 21 months.[a]
15. A cost of $50 per day was assigned to the treatment of metastatic disease. Because the intensity and cost of metastatic breast cancer treatment vary widely from country to country, a broad range of treatment cost estimates were tested.
16. When considered, vaginal bleeding and venous thromboembolism each could occur only once and could not occur beyond 5.5 years from the start of therapy.
17. When considered, the projected difference in hip fracture risk was due in equal part to a reduction in risk in the tamoxifen arm and an increase in risk in the anastrozole arm.
18. Estimates of age-related hip fracture risk were based on data from a Scandinavian cohort.
19. Women who experienced hip fracture had increased short-term (30-day) and long-term mortality rates.
20. Costs and benefits were discounted at a rate of 3% per year.

ATAC: Arimidex, Tamoxifen Alone or in Combination; ER: estrogen receptor.

[a] See: Chang J, Clark G, Allred D, Mohsin S, Chamness G, Elledge R. Survival of patients with metastatic breast carcinoma: importance of prognostic markers of the primary tumor. *Cancer*. 2003;97:545–553.[24]

are listed in Table 2. Probability estimates for breast cancer–specific events (namely, local recurrence, development of contralateral disease, and systemic recurrence) were derived from ATAC trial data recorded at 47 months.[4] Probabilities were calculated from observed rates using a standard conversion procedure and were assumed to be constant for the life of the patient.[17] Annual probabilities for breast cancer–related events were as follows: ~0.8% for local recurrence, ~0.3% for the development of contralateral disease, and ~1.9% for systemic recurrence.

Relative Risks

The benefits and risks of anastrozole use compared with tamoxifen use are reflected in the calculated relative risk ratios for adverse events. The ATAC investigators reported relative risk ratios for the overall study population and for the subpopulation of women with ER-positive disease (84% of all participants). Relative risk ratios with 95% confidence intervals (CIs) are available for initial breast events (diagnosis of breast cancer, breast cancer–related death, breast cancer recurrence in aggregate, and diagnosis of a second primary breast cancer), newly diagnosed contralateral disease, and breast cancer recurrence (local and systemic combined). Because relative risk ratios for local and systemic recurrence had not been reported, summary odds ratios for these endpoints were calculated using the available data.

Costs

Representative U.S. acquisition costs for 30-day supplies of anastrozole and generic tamoxifen were used in the current model.[18] The typical price difference between these two drugs was ~$5.50 per day. In Canada and the United Kingdom, this price differential was ~$3.50–4.50 per day.[19,20] The costs associated with local recurrence and contralateral breast cancer were calculated based on typical Medicare payments. These cost estimates were similar to those used in other cost-effectiveness models of breast cancer management.[21,22] Patients who experienced local recurrence were assumed to have undergone total mastectomy. Because the cost of treatment varies according to the type of local treatment and according to whether chemotherapy is administered, one-third of all women with newly diagnosed contralateral breast cancer were assumed to have received breast-conserving surgery and radiotherapy, two-thirds were assumed to have undergone mastectomy, and one-quarter were assumed to have received adjuvant chemotherapy.

Patterns of care for women with systemic recurrence vary according to the site of recurrence, patient age, and the patient's country of residence. Conse-

TABLE 2
Probability, Relative Risk, Cost, and Utility Estimates Used in the Current Model

	Point estimate (range)	Cost per event ($)	Source
Breast cancer–related events			
Incidence			
Local recurrence (% per yr)	0.8	6000	Baum et al., 2003[4]; Hayman et al., 1998[21]; Hayman et al., 2000[22]
New contralateral breast cancer per year (% per yr)	0.3	12,000	Baum et al., 2003[4]; Hayman et al., 1998[21]; Hayman et al., 2000[22]; Warren et al., 2002[50]
Systemic recurrence (% per yr)	1.8		Baum et al., 2003[4]; Wai et al., 2001[23]; Will et al., 2000[51]
Median time from systemic recurrence to death (mos)	21 (12–36)	50 per day	Chang et al., 2003[24]
RRs associated with anastrozole use			
New contralateral breast cancer	0.56 (0.32–0.98)		ATAC trial
Local recurrence	0.78 (0.54–1.14)		ATAC trial[a]
Systemic recurrence	0.835 (0.66–1.05)		ATAC trial[a]
Systemic recurrence resulting in death	1.0		
Death due to other causes	Varied according to age (1–2)		Anderson and DeTurk, 2002[52]
Daily cost ($)			
Tamoxifen	— (0.50–3.0)	1.25	Drugstore.com, Inc., 2004[18]
Anastrozole	— (5–10)	6.75	Drugstore.com, Inc., 2004[18]
Difference between anastrozole and tamoxifen	— (1–10)	5.5	
Treatment-associated relative risk ratios			
Hip fracture (overall)	1.6 (1.3–2.0)		ATAC trial
Hip fracture (tamoxifen)	0.77 (0.67–0.87)	—	
Hip fracture (anastrozole)	1.23 (1.13–1.34)	—	
Vaginal bleeding (anastrozole)	0.54 (0.4–0.8)	—	ATAC trial
Venous thromboembolism (anastrozole)	0.59 (0.5–1.0)	—	ATAC trial
Death (all causes) following hip fracture	1.5 (1.0–3.0)	—	
Yearly treatment-associated event probabilities (%)			
Hip fracture			
Ages 64–67 yrs	0.13 (—)	25,000	ATAC trial
Ages 67–70 yrs	0.27 (RR,0.5–1.0)	25,000	Ray et al., 1997[25]
Ages 71–75 yrs	0.54 (RR,0.5–1.0)	25,000	Ray et al., 1997[25]
Ages 76–80 yrs	1.0 (RR,0.5–1.0)	25,000	Ray et al., 1997[25]
Ages 81–85 yrs	1.8 (RR,0.5–1.0)	25,000	Ray et al., 1997[25]
Ages 86–90 yrs	3.1 (RR,0.5–1.0)	25,000	Ray et al., 1997[25]
30-day mortality following hip fracture	15 (0–50)	25,000	Hannan et al., 2001[53]
Vaginal bleeding[b] (tamoxifen cohort)	2.9	2000	Medverd and Dubinsky, 2002[54]
Hysterectomy required	25 (0–50)	10,000	Medverd and Dubinsky, 2002[54]
30-day mortality following vaginal bleeding	0 (0–1)		Medverd and Dubinsky, 2002[54]
Venous thromboembolism[b] (tamoxifen cohort)	1.3 (1–2)	10,000	Gould et al., 1999[29]
30-day mortality following venous thromboembolism	2 (0–5)	15,000	Gould et al., 1999[29]
Utility penalties			
Local breast recurrence	15 days (0–60 days)	—	Expert; HSPH, 2004[11]
Contralateral breast cancer	45 days (0–90 days)	—	Expert; HSPH, 2004[11]
Systemic recurrence	0.7 (0.5–1)	—	Expert; HSPH, 2004[11]
Hip fracture	0.7 (0.5–1)	—	Expert; HSPH, 2004[11]
Vaginal bleeding	15 days (0–45 days)	—	Expert; HSPH, 2004[11]
Venous thromboembolism	30 days (0–90 days)	—	Expert; HSPH, 2004[11]

ATAC: Arimidex, Tamoxifen Alone or in Combination; RR: risk ratio; HSPH: Harvard School of Public Health.

[a] Calculated odds ratios were available.

[b] Risk was present for a maximum of 5.5 years.

quently, the associated treatment costs will vary widely. As a baseline estimate, we used a daily treatment cost of $50, corresponding to a total treatment cost of $32,000 for a woman[23] with a survival duration equal to the median (21 months).[24]

The expenditures associated with evaluation and treatment of vaginal bleeding and venous thromboembolism were one-time costs, whereas the costs associated with hip fracture included short-term and long-term expenses.[25–29]

TABLE 3
Comparison of Observed Data[a] and Model Projections at 47 Months

	Anastrozole		Tamoxifen	
	Observed (%)	Projected (%)	Observed (%)	Projected (%)
Total incidence of first events[b]	11.1	11.0	13.3	13.1
Contralateral breast cancer	0.7	0.7	1.4	1.3
Local recurrence	1.9	1.8	2.4	2.2
Distant recurrence	5.1	5.1	6.1	6.1
Non–breast cancer–related death	3.4	3.5	3.5	3.5
Receiving treatment at 47 mos	Not reported	81.2	Not reported	74.3
Treatment halted due to non–breast cancer–related adverse event	Not reported	7.1	Not reported	12.4

[a] Data from patients with estrogen receptor–positive disease in: Buzdar A. 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 47 months. *Breast Cancer Res Treat.* 2003;77:295.[39]
[b] Total incidence rate does not necessarily equal the sum of the incidence rates for individual events, as individual rates were rounded to nearest one-tenth of a percent.

Treatment-Related Toxicities

In the ATAC trial, after a median treatment duration of 37 months, 5.6% of all patients in the anastrozole arm and 8.1% of all patients in the tamoxifen arm experienced treatment-related withdrawal.[30] The probability of vaginal bleeding and the probability of venous thromboembolism were calculated using data from the ATAC trial, and these risks were assumed to persist for 5.5 years (i.e., 6 months beyond the end of treatment). No deaths attributable to vaginal bleeding were included in the model.

An increased risk of fracture (and in particular, a potentially increased risk of hip fracture) is the dominant side effect associated with anastrozole use. In the ATAC trial, musculoskeletal symptoms and fractures of any type (relative risk, 1.6; 95% CI, 1.3–2.0) were more common among patients receiving anastrozole than among other patients.[31] To date, too few hip fractures have been observed to reveal any difference in risk among treatment arms. The observed difference in overall fracture risk may be attributable to the near-complete suppression of estrogen levels by anastrozole, to the partial estrogen-agonistic effect of tamoxifen on bone, or to a combination of the two. In the ATAC trial, such effects were noted in the 300 patients for whom biochemical markers of bone turnover and bone mineral density (BMD) were evaluated at baseline and at 1 year; patients in the anastrozole arm experienced increases in bone resorption marker levels and decreases in BMD, whereas patients in the tamoxifen arm experienced decreases in the former and increases in the latter.[32]

Genetic differences and differences in bone mineralization during the first 20 years of life, as well as rates of bone loss and risk of falling later in life, are among the factors that influence hip fracture risk. Hip fracture incidence varies widely from country to country, with the highest rates observed in Scandinavia and the United States and the lowest rates observed in the Middle East and South Asia.[33] Scandinavian estimates of age-specific hip fracture risk were used in the current model; the effect of using lower age-specific probability estimates was assessed in sensitivity analyses.[34,35]

RESULTS

A comparison of the current model's simulated results with the actual results of the ATAC trial is presented in Table 3. Relative to the ATAC trial, the model underestimated the incidence of events by 0.1% in the anastrozole cohort and by 0.2% in the tamoxifen cohort.

Table 4 summarizes the results of the current cost-effectiveness analysis. Incremental benefits in terms of DFS, event-free survival, and overall survival, as well as the overall incremental cost-effectiveness (ICE), were found to vary with time. Approximately 30% of all patients were projected to be free of disease at 20 years, whereas 58% were projected to have died.

DFS

The top section of Table 4 summarizes the results of the model when DFS is treated as the study endpoint. The difference in DFS between the anastrozole arm and the tamoxifen arm peaked at 4.1%, with this peak occurring at 12 years from baseline (i.e., age 76 years). DFS benefit was found to increase with each passing year, and this increase was accompanied by a decrease in ICE over time. At 4 years from baseline, the calculated DFS benefit was 14 days, with a relatively high ICE of $167,500 per disease-free year; at 20 years,

TABLE 4
Baseline Results in Anastrozole Arm and Baseline Differences between Anastrozole Arm and Tamoxifen Arm[a]

	Projection horizon (yrs)			
	4	8	12	20
Endpoint 1: DFS[b]				
DFS (%)	88.1	73.7	59.0	29.5
Increase in DFS (%)	1.8	3.4	4.1	3.4
Median increase in DFS duration (days)	14	47	88	161
Cost per yr of DFS gained ($)	167,500	60,700	32,800	16,700
Endpoint 2: Projected survival[c]				
Death rate (%)	5.8	16.3	28.9	58.2
Increase in overall survival (%)	0.4	1.1	1.6	1.8
Median increase in survival (days)	2	11	26	60
Increase in cost ($)	6353	7264	6907	6699
Cost per life yr gained ($)	1,112,000	235,400	96,000	40,600
Endpoint 3: Projected survival with quality-of-life adjustments for nonfatal outcomes and for projected differences in hip fracture risk				
Median increase in quality-adjusted survival (days)	4	14	26	45
Cost per QALY gained ($)	533,000	201,800	111,300	75,900

DFS: disease-free survival; QALY: quality-adjusted life years.

[a] Benefit estimates are rounded to the nearest whole day, and cost estimates are rounded to the nearest 100 dollars. Benefits and costs were discounted at a rate of 3% per year. Patients were age 64 years at baseline.

[b] Freedom from contralateral breast cancer, local recurrence, systemic recurrence, or death due to any cause.

[c] For the anastrozole arm, the overall survival projection included a survival benefit associated with an observed reduction in the risk of systemic recurrence.

the DFS benefit was 5.3 months, with an ICE of $16,700 per disease-free year.

Overall Survival

The middle section of Table 4 details the survival benefit expected to result from the observed reduction in the rate of systemic breast cancer recurrence. The projected survival benefit after 4 years was only 4 days, but this benefit increased to 2.0 months at 20 years. Nonetheless, the difference in overall survival rate between the two treatment arms increased slowly; even after 20 years, the projected benefit was only 1.8%. The incremental costs accompanying the projected benefits of anastrozole steadily decreased with time. By ~12 years, the calculated ICE had decreased to less than $100,000 per life year; by 20 years, it had decreased to $40,600 per life year.

Quality-Adjusted Survival and Hip Fracture Risk

Inclusion of the assigned quality-of-life adjustments for nonfatal outcomes and the projected anastrozole-induced increase in hip fracture risk has a complex effect on the results of the current model. Over shorter time periods (< 10 years), the benefits of anastrozole with respect to breast cancer recurrence, vaginal bleeding, and thromboembolism led to a modest increase in quality-adjusted survival benefit relative to overall survival benefit; however, at time points beyond 12 years from baseline, the overall benefit in terms of quality-adjusted survival leveled off at 45 days, due to the increased risk of age-related hip fracture. The ICE per QALY reached a nadir of $72,000 at 16 years and gradually increased thereafter, growing to $89,000 when the projection horizon was extended to 35 years (i.e., age 99 years) (data not shown).

Sensitivity Analysis

Sensitivity analyses of key variables were performed using a 20-year projection horizon (Table 5). This time frame was selected because it corresponds to the average life expectancy of a 64-year-old woman without breast cancer.

Anastrozole-induced reduction in relative risk of systemic recurrence

Ranges of benefits and ranges of cost-effectiveness ratios associated with various estimates of anastrozole's ability to reduce the incidence of systemic recurrence are reported in Table 2 and Figure 2, respectively. Each curve in Figure 2 represents a different study endpoint. The baseline reduction in risk (16.5%) is marked on the *x*-axis. With regard to DFS, benefits in terms of local recurrence and second breast cancer incidence alone lead to the projection of a long-term benefit. If the systemic risk were equal to zero, then the projected benefit would be 91 breast cancer–free days, with an ICE of $28,300 per disease-free year. At an ICE threshold of $100,000 per year, the corresponding reduction in relative risk of systemic recurrence was 6% when overall survival was used as the study

TABLE 5
Sensitivity Analyses of Survival Results at 20 Years

Variable	Survival benefit (days/$ per yr)[a]		
	Breast cancer–free survival	Projected overall survival[b]	Projected overall survival with quality-of-life adjustments for nonfatal outcomes and for projected differences in hip fracture risk
Anastrozole-induced reduction in relative risk of systemic recurrence (%)			
0	91/28,300	Dominated	Dominated
5	112/23,300	24/109,000	5/672,000
10	133/19,800	40/64,700	22/126,000
17	161/16,700	61/39,500	47/72,800
25	198/13,800	86/26,000	74/43,300
Additional cost of anastrozole ($)			
2	161/6,500	60/8,400	45/33,400
5.5	161/16,700	60/40,600	45/75,800
6.5	161/21,700	60/49,800	45/88,000
10	161/33,600	60/81,800	45/130,400
Relative risk of non–breast cancer–related death			
1.0	161/16,700	60/40,600	45/75,800
1.5	144/18,300	51/46,800	39/83,100
2.0	130/20,100	44/53,700	34/91,200
Relative risk of systemic recurrence			
0.75	147/18,300	47/54,200	
1.0	161/16,700	60/40,600	45/75,800
1.5	185/14,400	82/27,100	73/43,000
2.0	205/13,000	101/20,300	96/30,000
Survival with metastases (mos)			
0	—	89/33,200	66/60,000
21[b]	—	60/40,600	45/75,800
36	—	45/47,700	35/90,300
Overall relative risk of hip fracture[c]			
1.0	—	—	69/25,300
1.3 (RR: anastrozole, 1.13; tamoxifen, 0.87)	—	—	55/53,600
1.6[b] (RR: anastrozole, 1.23; tamoxifen, 0.77)	—	—	45/75,800
2.0 (RR: anastrozole, 1.34; tamoxifen, 0.67)	—	—	34/114,000
Risk of hip fracture relative to Scandinavian cohort			
0.5	—	—	58/50,000
0.9	—	—	47/69,000
1.0[b]	—	—	45/75,800

RR: risk ratio.

[a] Benefit estimates were rounded to the nearest whole day, and cost-effectiveness estimates were rounded to the nearest 100 dollars.

[b] Baseline estimate.

[c] Relative risk was assumed to be equally attributable to anastrozole-induced bone loss and the protective effects of tamoxifen against bone loss. Therefore, for each point estimate of overall risk, individual risk ratios for the tamoxifen arm and the anastrozole arm were needed.

endpoint and 14% when QALY (including hip fracture risk) was used as the study endpoint.

Cost of anastrozole

The current model exhibited significant sensitivity to the cost of anastrozole. Each 1-dollar increase in the price of anastrozole increased the calculated ICE by approximately $5000 per year of DFS, approximately $9200 per life year, and approximately $12,000 per QALY.

Risk of non–breast cancer–related death

Because clinical trial participants often are healthier than the overall population of individuals with a given condition, the sensitivity of the current model to changes in the risk of non–breast cancer–related death was explored. Doubling of age-specific risk ratios led to a modest decrease in benefit with respect to each of the endpoints that were examined; the calculated DFS benefit decreased by approximately 30 days, the overall survival benefit decreased by approxi-

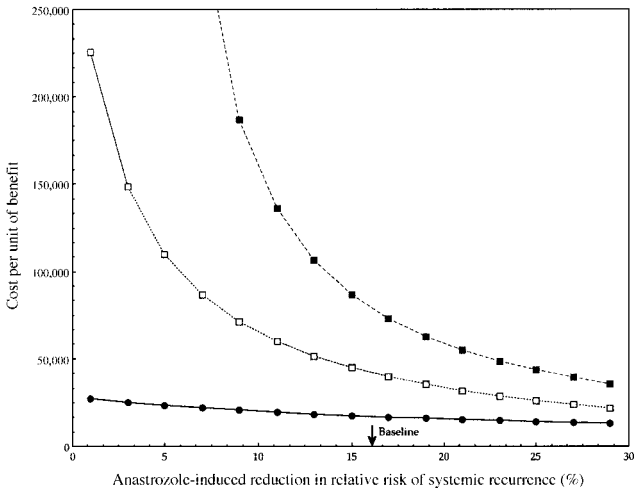

FIGURE 2. Sensitivity analysis: incremental cost-effectiveness of anastrozole as a function of the anastrozole-induced reduction in systemic recurrence risk. Incremental cost-effectiveness curves with respect to three endpoints—disease-free survival (filled circles), overall survival (open squares), and quality-adjusted survival (filled squares)—are shown. Arrow indicates baseline estimate of the percent reduction in systemic breast cancer recurrence risk (16.5%).

mately 15 days, and the quality-adjusted survival benefit decreased by approximately 11 days.

Relative risk of systemic breast cancer recurrence

Changes in the risk of systemic recurrence had a dramatic effect on the results generated by the current model. Doubling this risk from its initial value of 1.8% to a value of 3.6% approximates a situation in which all patients have 1–3 positive lymph nodes and a tumor size of 1.1–2.0 cm (Adjuvant Version 5.0; Adjuvant Inc., San Antonio, TX). In this scenario, the overall survival benefit increased from 60 days to 101 days, and the benefit with respect to quality-adjusted survival increased from 45 days to 96 days; furthermore, the calculated ICE values decreased by 50% and 60%, respectively, in this setting.

Survival with metastatic breast cancer

The estimated benefits for patients with metastatic disease were altered modestly at the survival extremes that were considered. In the absence of any survival, the cost per systemic recurrence–free year was $33,200. A median survival of 3 years corresponded to a cost of $90,300 per QALY.

Quality of life and hip fracture risk

As expected, the quality-adjusted life expectancy model was especially sensitive to assumptions regarding hip fracture risk. In the absence of an increased risk of hip fracture in association with anastrozole use, the quality-adjusted benefit resulting from confirmed reductions in breast cancer incidence, vaginal bleeding, and venous thromboembolism was estimated to be 69 days, with an ICE of $25,300 per QALY. Using the 95% CI for the overall relative risk of bone fracture as observed in the ATAC trial to generate a range of long-term hip fracture risk ratios for inclusion in the current model, it was calculated that the benefit associated with anastrozole use ranged from a maximum of 64 quality days to a minimum of 30 quality days, with associated costs per QALY ranging from $45,600 to $137,000. When patients with an ethnicity-specific risk of hip fracture that was one-half the original hip fracture risk were considered, the calculated ICE decreased to $50,000 per QALY.

DISCUSSION

There is a worldwide consensus that adjuvant hormonal therapy should be recommended to postmenopausal women with ER-positive breast cancer regardless of patient age, axillary lymph node status, and tumor size (except in cases in which the tumor is extremely small).[36,37] Tamoxifen has been the endocrine therapy agent of choice since being approved in the U.S. in 1986. There is a vast body of experience and a deep pool of evidence pertaining to the use of tamoxifen in the adjuvant setting. As Ingle[38] noted in his review of endocrine therapy, tamoxifen has established a lofty benchmark against which novel agents for the treatment of postmenopausal women must be measured.

The current study was initiated after the FDA approved the use of anastrozole for women meeting the entry criteria and after a follow-up report on the ATAC trial was released in December 2002.[39] The current decision analysis model was constructed to assist patients, physicians, and policymakers in the decision-making process. This model incorporates the components of the clinical matrix, assesses economic consequences, and considers various time frames.[40] The data elements considered by the current model represent a combination of observable effects and speculative concerns. Furthermore, the model transcends the scope of current data to project long-term breast cancer DFS rates and, subsequently, the overall survival consequences associated with observed benefits in terms of disease recurrence, financial considerations, and treatment-related side effects (e.g., vaginal bleeding, thromboembolism, and bone fracture).

When the time frame analyzed is limited to 4 years (corresponding to the follow-up period associated with current clinical data), the benefit associated with anastrozole use is modest, and the cost of realizing

this benefit is high; however, when longer time periods are considered, the projected benefit in terms of DFS becomes substantial. Consideration of such extended time frames is appropriate, as national recommendations state that cost-effectiveness models should cover periods that are sufficiently long so that all notable benefits, harms, and expenses can be captured.[13] Using a 20-year projection horizon (which corresponds to the average life expectancy of a 64-year-old woman without breast cancer), the current model predicts an average DFS benefit of $>$ 5 months.

Previous investigations of hormonal therapy for ER-positive breast cancer have revealed that DFS benefits are predictive of eventual benefits in terms of overall survival. Thus, the current model quantifies the magnitude of the overall survival benefit that is expected to result from a clinically observed 17% reduction in systemic recurrence rates. Given the overall low rate of recurrence and the extended survival of women with ER-positive metastatic breast cancer relative to women with ER-negative metastatic breast cancer, the current model found that even after 20 years, the overall survival rate in the anastrozole arm would be less than 2% greater than the corresponding rate in the tamoxifen arm. On average, this benefit would result in approximately 2 additional months of survival, with an incremental cost per life year of $40,600.

Tamoxifen and anastrozole also differ in terms of their toxicity profiles. The inclusion of confirmed differences in treatment-induced vaginal bleeding and venous thromboembolism risks as well as a potential difference in treatment-induced hip fracture risk yielded quality-adjusted projections of the benefits associated with anastrozole use. This quality-adjusted model, like most models of its type, assigned utility scores to specific adverse events. Within this limitation, the model determined that anastrozole use increased overall QALY in the short term by leading to fewer toxic events; however, the net benefit in terms of QALY leveled off after 12 years due to an increase in anastrozole-induced hip fracture incidence.

Given the eventual arrival of more mature follow-up data from the ATAC trial, why is the current model necessary? First, the data included in the next report from the ATAC trial may still be insufficiently mature to allow detection of a difference in survival, because only 6–8% of all women in the trial will have died by the time of that report. Second, the current model indicates that any anticipated benefit will require at least 10 years to become evident. Third, within the realm of public policy, there is agreement that a long-term or lifetime projection horizon is preferable to shorter time frames.[13] (The current average life expectancies of U.S. women ages 55, 65, and 75 years are approximately 27, 19, and 12 years, respectively, and the current model projected a median life expectancy of 18 years for women age 64 years; nonetheless, for most individuals [with or without breast malignancies], it is difficult to contemplate life more than 5 or 10 years into the future.) Finally, since the start of the current project, two other randomized studies of aromatase inhibitors in the adjuvant setting for patients with early-stage breast cancer have reported treatment-related DFS benefits.[41,42]

Is the switch from tamoxifen use to anastrozole use reasonable from a societal or payer-centered perspective? One approach to deciding when a new therapeutic option should be adopted involves the consideration of minimum thresholds in terms of benefit or cost per life year.[43] If one uses the common (but arbitrarily selected) thresholds of $50,000 or $100,000 per life year, then threshold values for specific variables or combinations of variables can be calculated. Most sensitivity analyses indicated that the ICE of anastrozole use was less than $50,000 or between $50,000 and $100,000 if the projection horizon exceeded 12 years. Using a threshold of $100,000 per life year, the current model found that anastrozole use was 'cost effective' if the time frame considered (or the patient's life expectancy) was longer than 12 years. While not directly comparable, this time frame is similar to the 10-year life expectancy threshold that has been recommended for prostate cancer screening.[44] Nonetheless, a switch to anastrozole use will require increased spending when all considerations are accounted for. The current model demonstrated the impact of the price difference between anastrozole and generic tamoxifen on the ICE of this switch.

The quality-adjusted survival model was intentionally biased against anastrozole use via the assumption that the observed 4-year difference in overall fracture incidence would eventually lead to a difference in hip fracture incidence. Due in equal part to a tamoxifen-induced reduction in risk and an anastrozole-induced increase in risk, it was assumed that patients receiving anastrozole had an elevated relative risk of hip fracture. Some clinicians suggest the use of bisphosphonates, such as weekly oral alendronate or yearly intravenous zoledronic acid, in conjunction with anastrozole.[45] The use of such agents clearly increases treatment costs. Thus, the current analysis was repeated under the assumption that oral alendronate was administered in combination with anastrozole and that this bisphosphonate prevented bone loss such that there was no difference in hip fracture risk between the anastrozole arm and the tamoxifen arm. Given this scenario, the net survival benefit associated

with the use of anastrozole in conjunction with alendronate was projected to be 67 days, with an ICE of $66,800 per QALY.

From a patient-centered perspective, anastrozole use was preferred in all situations that were modeled (including situations in which anastrozole use did not affect the risk of systemic recurrence) provided that DFS was the primary endpoint of interest. The importance of potential increases in hip fracture risk is dependent on the patient's ethnicity. The benefits of anastrozole use are likely to be even greater for women whose risk of hip fracture is lower than that of Northern European and Caucasian American women. The current model supports recent recommendations suggesting that BMD be measured before the initiation of hormonal therapy.[46]

Aside from decision analysis, several other quantitative techniques, including parametric survival analysis and 'quality-adjusted time without symptoms or toxicity' analysis, have been developed, applied, and refined with the specific goal of assisting patients, clinicians, and policymakers in weighing and balancing risks, benefits, and the effects of possible future events.[47–49] The current model indicates that although anastrozole provides only a small annual benefit relative to tamoxifen, the risk of breast cancer recurrence and the concurrent risk of non–breast cancer–related death are so low that the average woman will experience an overall lifetime benefit as a result of anastrozole use. From a societal perspective, the incremental cost of this benefit lies near the upper limit of the range of incremental costs associated with commonly accepted new therapies and is quite sensitive to increases in the price of anastrozole.

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