Journal of Health Economic and Policy Research
JHEPR Vol. 4 No. 1 Year 2026
ISSN 3025-5198

Cost-Effectiveness Analysis of Letrozole Versus Tamoxifen in Early-Stage Breast Cancer for Postmenopausal Women: Systematic Review

Lucia Shinta Ratnaningtyas[1], **Tri Murti Andayani**[2]*, Dwi Endarti [3]

[1]Master Program of Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia;
[2]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia;
[3]Department of Pharmaceutics, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia.

Article Information:

Submitted : *October 7th, 2025*
Revised : *January 11th, 2026*
Accepted : *March 16th, 2026*

***Corresponding author:**
trimurtia@ugm.ac.id

DOI: https://doi.org/10.30595/jhepr.v4i1.301

Abstract

Background: Breast cancer presents a significant global burden, including rising treatment costs. Cost-Effectiveness Analysis (CEA) is important for optimising resource use. Letrozole and tamoxifen are commonly used in postmenopausal women with hormone receptor-positive early breast cancer, with letrozole showing higher efficacy but greater cost.

Objectives: This review aims to systematically examine and integrate current findings on the Cost-Effectiveness of letrozole versus tamoxifen in treating early-stage breast cancer in postmenopausal patients.

Methods: A structured literature review was conducted in April 2025 using PubMed, ScienceDirect, and SpringerLink. Study quality was assessed with the CHEERS checklist. Five studies met PICOT criteria, focusing on postmenopausal women with early-stage HR+ breast cancer, comparing letrozole with tamoxifen, and evaluating economic outcomes (ICERs, NMBs, and QALYs).

Results: All included studies reported that letrozole provided greater clinical benefit compared to tamoxifen in terms of reducing recurrence and extending disease-free survival in the target population. However, these clinical gains were linked to increased treatment costs and a unique spectrum of side effects. While letrozole was associated with a higher risk of bone and cardiovascular events, however have a lower risk of endometrial cancer and thromboembolism than tamoxifen. Economic evaluations from various countries, such as China, Canada, the USA, the UK, and Germany, consistently found that letrozole led to greater QALYs. Moreover, its Incremental ICERs generally remained within acceptable national thresholds.

Conclusion: Letrozole is a cost-effective alternative to tamoxifen for postmenopausal women with early-stage hormone receptor-positive breast cancer, with improved efficacy justifying its higher costs.

Keywords: *Cost-effectiveness, Early-Stage Breast Cancer, Letrozole, Postmenopausal, Tamoxifen.*

Introduction

Breast cancer remains a major global health concern due to its high incidence and potential for recurrence, underscoring the need for effective long-term management strategies. In the context of HR+ early breast cancer, endocrine therapies such as tamoxifen and letrozole are extensively utilized and researched, particularly among postmenopausal patients. Both agents are effective in decreasing recurrence rates and improving survival outcomes[1–3]. The National Comprehensive Cancer Network (NCCN) guidelines advocate for individualized endocrine therapy strategies based on menopausal status and clinical risk. For postmenopausal women, either tamoxifen or an AI can be initiated, with the possibility of extending therapy up to ten years depending on response and tolerance. For those intolerant to AIs, extended tamoxifen remains a viable alternative. The guidelines also emphasize the importance of considering factors such as bone health, CYP2D6 enzyme activity, and potential drug interactions in determining the most suitable treatment plan[4].

Breast cancer continues to pose a major global health burden, not only due to its clinical severity but also because of the increasing financial demands associated with its management, such as systemic therapies and hospital-related care[5,6]. In light of these challenges, CEA has become a crucial framework for assessing the economic value of treatment strategies. CEA serves to reconcile limited healthcare budgets with the goal of maximizing therapeutic outcomes, often using QALYs as a standardized measure of benefit[7,8]. Incorporating real-world evidence into CEA further strengthens its applicability by ensuring that conclusions reflect a broader patient population and support more contextually relevant clinical and policy decisions[9]. Through the use of ICERs, CEA enables prioritization of interventions that deliver the most substantial health gains relative to their costs[7,10].

Evidence from randomized trials has consistently indicated that letrozole, AI, surpasses tamoxifen in enhancing disease-free survival and lowering the risk of distant metastases, particularly in patients with nodal involvement [11]. Nevertheless, each therapy is associated with a distinct profile of adverse effects that must be taken intoaccount.

ISSN 3025-5198

Letrozole may negatively affect bone density and increase cardiovascular risks, while tamoxifen is linked with elevated risks of thromboembolism and endometrial carcinoma [12,13]. In real-world clinical settings, the decision between tamoxifen and AIs like letrozole is often influenced by individual patient profiles, including menopausal status, comorbidities, and risk of side effects. AIs are generally preferred in postmenopausal patients due to their superior efficacy in reducing recurrence risk [14,15]. However, tamoxifen may be more beneficial for patients with osteoporosis or elevated fracture risk due to its bone-protective properties [16,17]. Conversely, patients with underlying cardiovascular conditions may require caution with AIs, given their potential to induce hypertension and lipid abnormalities [18]. Additionally, the overall impact on quality of life including musculoskeletal symptoms and cognitive changes with letrozole, or vasomotor and gynaecologic effects with tamoxifen can influence treatment adherence [19,20].

Considering the therapeutic and economic trade-offs between tamoxifen and letrozole, comprehensive Cost-Effectiveness evaluations are essential. Letrozole, although associated with higher direct treatment costs, has consistently demonstrated superior clinical efficacy [21,22]. Reported ICERs for letrozole in comparison to tamoxifen range widely-from approximately ¥38,092 per QALY in China to $23,743 per QALY in Western countries-underscoring its value despite the increased expenditure [22,23]. In settings with limited healthcare resources, it is particularly important to assess whether the long-term clinical advantages of letrozole can justify the financial burden[21]. The potential to reduce recurrence and mortality in the long term may enhance the overall value proposition of letrozole in diverse clinical environments[22,23]. This review systematically examines the Cost-Effectiveness of letrozole versus tamoxifen for the treatment of early-stage HR+ breast cancer in postmenopausal women. By synthesizing both clinical outcomes and economic evidence, the study aims to support rational resource allocation and contribute to informed healthcare decision-making that prioritizes both patient benefit and fiscal sustainability.

Methods

Data Sources and Searches

This systematic review was conducted using the PICOT framework to ensure methodological transparency and reproducibility. The research question was defined as follows: Population (P) postmenopausal women with early-stage hormone receptor–positive (HR+) breast cancer; Intervention (I) letrozole as adjuvant endocrine therapy; Comparator (C) tamoxifen; Outcome (O) economic outcomes, including incremental Cost-Effectiveness ratios (ICERs) or net monetary benefits (NMBs) expressed in quality-adjusted life years (QALYs); and Time horizon (T) as specified in each included study.

A systematic literature search was conducted in PubMed/MEDLINE, Embase, Scopus, and Web of Science. Additional records were identified through manual searches of publisher websites and reference lists of relevant articles. Search terms included combinations of “letrozole,” “tamoxifen,” “cost-effectiveness,” “economic evaluation,” “QALY,” and “early breast cancer.” Only peer-reviewed articles published in English were included.

Rationale for Country Selection

Five countries, China, Canada, Germany, the United Kingdom, and the United States, were included in this review. These countries were selected to capture variation in healthcare systems and economic contexts, while ensuring the availability of high-quality and comparable economic evaluations. All five countries have established health technology assessment (HTA) processes and consistently report Cost-Effectiveness outcomes for adjuvant endocrine therapy in early-stage breast cancer. Moreover, evidence from these settings provides useful external reference values for countries with limited local economic data, including Indonesia.

Study Selection

Studies were eligible for inclusion if they met the following criteria: (1) postmenopausal women with early-stage, hormone receptor-positive breast cancer as the target population; (2) direct comparison of letrozole versus tamoxifen as adjuvant endocrine therapy; (3) full economic evaluations reporting ICERs or NMB; and (4) use of a cost-utility analysis framework with QALY as the outcome measure. Studies that lacked comparative analysis, did not report QALY outcomes, or failed to meet transparency standards were excluded.

Screening and Data Extraction

Title and abstract screening followed by full-text assessment was conducted manually based on predefined eligibility criteria. Rayyan software was not used, as the number of retrieved studies was manageable and manual screening was sufficient to ensure accurate selection. Data were extracted systematically using a standardized template aligned

with the CHEERS (Consolidated Health Economic Evaluation Reporting Standards) checklist.

Risk of Bias Assessment

The CHEERS checklist as utilized to evaluate the potential risk of bias in the selected studies. The assessment covered several key domains, including: the stated analytical perspective, clarity in the description of the comparator, specification of the time horizon, application and explanation of discounting for both costs and health outcomes, transparency in the model structure (including visual representations where available), detailed reporting of the target population, presentation of ICER values with appropriate units, inclusion of sensitivity analyses, and declaration of funding sources and any conflicts of interest.therapy in early-stage breast cancer. Moreover, evidence from these settings provides useful external reference values for countries with limited local economic data, including Indonesia.

Study Selection

Studies were eligible for inclusion if they met the following criteria: (1) postmenopausal women with early-stage, hormone receptor-positive breast cancer as the target population; (2) direct comparison of letrozole versus tamoxifen as adjuvant endocrine therapy; (3) full economic evaluations reporting ICERs or NMB; and (4) use of a cost-utility analysis framework with QALY as the outcome measure. Studies that lacked comparative analysis, did not report QALY outcomes, or failed to meet transparency standards were excluded.

Screening and Data Extraction

Title and abstract screening followed by full-text assessment was conducted manually based on predefined eligibility criteria. Rayyan software was not used, as the number of retrieved studies was manageable and manual screening was sufficient to ensure accurate selection. Data were extracted systematically using a standardized template aligned with the CHEERS (Consolidated Health Economic Evaluation Reporting Standards) checklist.

Risk of Bias Assessment

The CHEERS checklist as utilized to evaluate the potential risk of bias in the selected studies. The assessment covered several key domains, including: the stated analytical perspective, clarity in the description of the comparator, specification of the time horizon, application and explanation of discounting for both costs and health outcomes, transparency in the model structure (including visual representations where available), detailed reporting of the target population, presentation of ICER values with appropriate units, inclusion of sensitivity analyses, and declaration of funding sources and any conflicts of interest.

Result

Study Selection

A total of 222 articles were retrieved from Scopus, alongside 18 from ScienceDirect and 14 from PubMed. After removing 24 duplicate entries, 230 unique records remained for initial screening based on titles and abstracts (Figure 1). Following this stage, 232 records were excluded. The remaining 8 articles proceeded to full-text evaluation. After thorough assessment, 3 of these were excluded, resulting in 5 studies that met the criteria for inclusion in the final systematic review.

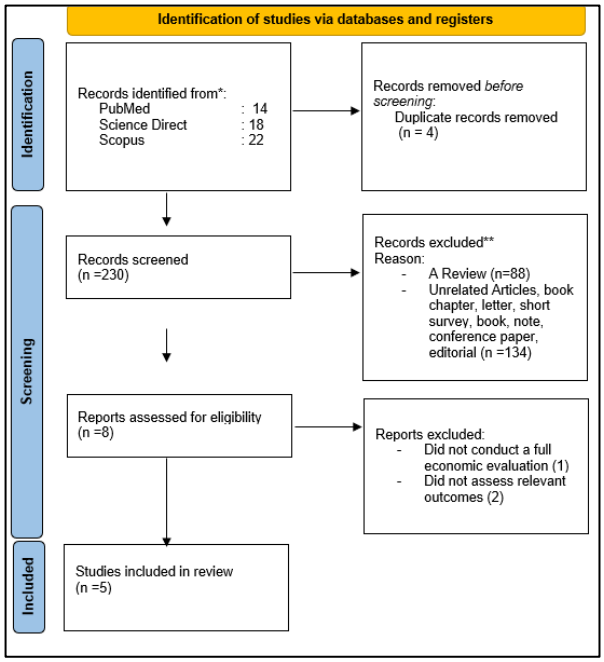

Figure 1. PRISMA Flow Diagram of Study Selection

Risk of Bias Assessment

All included studies applied standard economic evaluation practices and were assessed across key quality domains, including perspective, choice of comparator, target population, model structure, time horizon, discount rate, data sources, and reporting of ICER. The studies from Canada, UK, and USA used validated Markov models with long-term (lifetime) horizons and discounted both costs and outcomes appropriately, indicating low risk of bias. The Chinese study followed a similar model structure with one-month cycles and used local clinical and cost data, enhancing contextual relevance

despite limited national screening programs. The German study adopted a hybrid model integrating real-world price scenarios and used Inverse Probability of Censoring Weighting (IPCW) analysis to enhance robustness. Overall, all five studies were considered to have low to moderate risk of bias, with strong adherence to health economic modelling standards and transparent reporting.

Characteristics of Studies

The five selected countries provide representative evidence from different healthcare financing systems and income levels, allowing for a broader interpretation of Cost-Effectiveness findings and their potential applicability to settings such as Indonesia. The five studies included in this synthesis were conducted in China, Canada, the United Kingdom, the United States, and Germany. Each study employed a decision-analytic modelling approach, predominantly using Markov models, with a lifetime time horizon ranging from 30 to 50 years to capture long-term outcomes such as recurrence, survival, and treatment-related adverse events. The basic characteristics are described in Table 1.

Discount rates for both costs and outcomes were consistently applied, typically at 3% annually in high-income country studies (Canada, UK, USA, Germany) and 5% in the Chinese study, in accordance with local guidelines. All studies measured outcomes in terms of QALYs, adhering to cost-utility analysis methodology. The primary clinical input across all studies was derived from the BIG 1-98 trial, with additional data from meta-analyses and local registries used to populate model parameters such as recurrence rates, adverse events, and mortality.

Drug acquisition costs, utility values, and health system resource utilization varied across countries, reflecting differences in pricing, reimbursement mechanisms, and clinical practice. Notably, the German study incorporated future generic pricing scenarios, showing the impact of price reductions on cost-effectiveness. The Chinese study highlighted affordability concerns in a resource-limited setting, while the studies from Canada, the UK, and the USA focused on healthcare system perspectives and used established WTP thresholds for interpreting ICERs. Despite methodological consistency, differences in local economic contexts, healthcare infrastructure, and pricing strategies led to variations in absolute cost and ICER outcomes across the studies (Table 2).

Table 1. General Characteristics of Included Studies

Prespective Country	Mortality Stratum[1]	Target Population	Modelling Approach	Time Horizon (Years)	Discount Rate (Cost/Benefit, %)	Sensitivity Analysis	Most Sensitive Parameter	Authors (Year)2
US healthcare system	High	Postmenopausal women with early-stage HR+ breast cancer	Markov model	40	3% / 3%	Deterministic & Probabilistic	RR of breast cancer events	Delea et al. (2007)[22]
Canadian public payer	High	Postmenopausal women with early-stage HR+ breast cancer	Markov model	20–40	5% / 5%	Deterministic & Probabilistic	RR of breast cancer recurrence	Delea et al. (2008)[24]
UK NHS	High	Postmenopausal women, ER+ early breast cancer post-surgery	Markov model	50 (lifetime)	3.5% / 3.5%	One-way, two-way, and Probabilistic	RR for distant metastasis & adverse events	Karnon et al. (2006)[25]
German health insurance	High	Postmenopausal women with early breast cancer	Markov model	Lifetime	3% / 3%	One-way & Probabilistic	Age at initiation of therapy	Lux et al. (2010)[26]
Chinese healthcare system	Medium	Postmenopausal women with HR+ early-stage breast cancer	Markov model	Lifetime	3% / 3%	One-way & Probabilistic	Patient age and RR for recurrence	Ye et al. (2018)[21]
Prespective Country	Mortality Stratum[1]	Target Population	Modelling Approach	Time Horizon (Years)	Discount Rate (Cost/Benefit, %)	Sensitivity Analysis	Most Sensitive Parameter	

[1]Mortality stratum indicates the relative level of cancer-related mortality assumed in the model (high: substantial recurrence- or metastasis-related mortality; medium: moderate excess mortality compared with the general population).
[2]References were managed using Mendeley reference manager.

Table 2. Characteristics of Intervention and Economic Evaluation

Authors (Year, Country)	Intervention	Comparator	Price per Dose ($)	ICER (Base Case)	Unit of ICER	% GDP per Capita	Conclusion of EE Study
Delea et al. (2007)[22]	Letrozole 2.5 mg/day	Tamoxifen 20 mg/day	TAM: $0.28/day LET: $2.78/day	$23,743	per QALY	~47% (GDP: ~$50,000)	Letrozole is cost-effective
Delea et al. (2008)[24]	Letrozole 2.5 mg/day	Tamoxifen 20 mg/day	TAM: C$0.26/day LET: C$2.83/day	C$23,662	per QALY	~54% (GDP: C$43,500)	Letrozole is cost-effective
Karnon et al. (2006)[25]	Letrozole 2.5 mg/day	Tamoxifen 20 mg/day	TAM: £0.20/day LET: £2.45/day	£10,379	per QALY	~39% (GDP: £26,500)	Letrozole is cost-effective
Lux et al. (2010)[26]	Letrozole 2.5 mg/day	Tamoxifen 20 mg/day	TAM: €0.78/day LET: €6.71/day	€29,375.15	per QALY	~77% (GDP: €38,000)	Letrozole is cost-effective
Ye et al. (2018)[21]	Letrozole 2.5 mg/day	Tamoxifen 20 mg/day	TAM: ¥1.44/day LET: ¥12.6/day	¥38,092	per QALY	~74% (GDP: ¥51,000)	Letrozole is cost-effective

Table 3. Risk of Bias of Letrozole and Tamoxifen Economic Evaluation

Authors (Year, Country)	Delea et al. (2006, USA)	Delea et al. (2008, Canada)	Karnon et al. (2008, UK)	Lux et al. (2011, Germany)	Ye et al. (2018, China)
Perspective	⊕	⊕	⊕	⊕	⊕
Comparator	⊕	⊕	⊕	⊕	⊕
Target Population	⊕	⊕	⊕	⊕	⊕
Model Type	⊕	⊕	⊕	⊕	⊕
Model Figure	⊕	⊕	⊕	⊕	⊕
Time Horizon	⊕	⊕	⊕	⊕	⊕
Cost Discounting	⊕	⊕	⊕	⊕	⊕
Outcome discounting	⊕	⊕	⊕	⊕	⊕
Drug Price	⊕	⊕	⊕	⊕	⊕
Conversion Rate	⊕	⊕	⊕	⊕	⊕
Model Parameter Reported	⊕	⊕	⊕	⊕	⊕
ICER Reported	⊕	⊕	⊕	⊕	⊕
Conflict of interest declared	⊕	⊕	⊕	⊕	⊕
Source of Funding Declared	⊕	⊕	⊕	⊕	⊕

⊕ = *Low risk of bias*

ISSN 3025-5198

Sensitivity Analysis

All five country-specific studies performed sensitivity analyses to test the robustness of their economic evaluations. One-way (univariate) sensitivity analysis was applied in all studies to examine how variations in individual parameters influenced outcomes. Additionally, probabilistic sensitivity analysis (PSA) was conducted in the studies from China, Canada, the UK, and the USA, while the German study complemented its model with scenario analyses involving various future price assumptions for generic drugs. Across these evaluations, the most influential parameters varied: the cost of letrozole was identified as the most sensitive variable in the studies from China, Canada, and Germany. In contrast, the UK and USA analyses emphasized the importance of letrozole's treatment effect-specifically its benefit in reducing recurrence-and the assumed duration of its carry-over effect after discontinuation.

Perspectives

The most commonly used perspective across the five studies was the healthcare system perspective, which was adopted in the evaluations from China, Canada, the UK, and the USA. These studies focused primarily on direct medical costs associated with treatment, adverse events, and disease management. In contrast, the German study used a broader societal perspective that incorporated not only direct healthcare costs but also broader implications related to pricing policy and long-term budget impact in the context of generic drug introduction. The choice of perspective directly influenced the Cost-Effectiveness outcomes and was aligned with each country's policy-making and reimbursement environment.

Cost-Effectiveness Results

All five country-specific studies reported that letrozole was a cost-effective or highly cost-effective option compared to tamoxifen as adjuvant hormonal therapy in postmenopausal women with hormone receptor-positive early breast cancer. In China, letrozole yielded better health outcomes with an ICER well below the willingness-to-pay threshold, making it a cost-effective strategy in a resource-limited setting. Similarly, from the perspectives of the Canadian, UK, and US healthcare systems, letrozole demonstrated substantial clinical benefits with acceptable ICER values ranging from approximately $23,000 to $24,000 per QALY gained. The UK study found letrozole to be more cost-effective than anastrozole and tamoxifen, especially under the assumption of a treatment carry-over effect. The German study showed that the Cost-Effectiveness of letrozole improved significantly as drug prices declined with patent expiration, achieving an ICER as low as €4,215/QALY at 25% of the original price, confirming letrozole's value even in a high-cost healthcare system.

Discussion

To our knowledge, this is the first review that systematically consolidates the Cost-Effectiveness comparison between letrozole and tamoxifen across five countries, utilizing consistent reporting of ICERs and standardized modelling assumptions. The included studies-conducted in China, Canada, the United Kingdom, the United States, and Germany-uniformly support the conclusion that letrozole is either cost-effective or highly cost-effective when compared with tamoxifen, although the scale of benefit and associated costs varied depending on national healthcare settings.

For instance, in China, letrozole's ICER was found to be below the country's WTP threshold, indicating Cost-Effectiveness in a constrained resource environment. In high-income nations like the USA and Canada, letrozole was associated with added QALYs at ICERs of approximately $23,000–$24,000 per QALY, which fall well within accepted Cost-Effectiveness thresholds. Similarly, in the UK, an ICER of £10,379 per QALY was reported, which improved further under models that incorporated long-term carry-over effects. In Germany, Cost-Effectiveness was significantly enhanced under future scenarios involving lower generic drug prices, with ICERs falling to €4,215 per QALY in the most favourable pricing assumptions.

All studies utilized Markov modelling techniques, applied appropriate discount rates, and adopted long-term (typically lifetime) horizons, although some variation in methodology was observed. These differences included the analytic perspective (e.g., healthcare system vs societal), discount rates ranging between 3% and 5%, and the scope of sensitivity analyses conducted. Despite these methodological variations, each study adhered to recognized standards for economic evaluations and reported credible and well-validated findings. Some models, notably in Germany and China, tested multiple pricing scenarios due to the high sensitivity of outcomes to drug affordability. The German study uniquely incorporated IPCW methods to improve the robustness of survival extrapolation-an advanced approach rarely seen in other models.

Despite the overall consistency in outcomes, caution is advised in generalizing results across different countries. Variability in drug pricing structures, healthcare delivery models, population demographics, and clinical practices can significantly

influence Cost-Effectiveness results. Moreover, differences in model assumptions such as utility weights, recurrence probabilities, and duration of treatment effects can lead to notable shifts in ICER values. For example, while Canadian and American models assumed a five-year carry-over effect from letrozole, the UK model evaluated both the presence and absence of this effect, revealing a marked impact on the ICER.

In the absence of local Cost-Effectiveness studies, these international findings may offer helpful benchmarks for decision-makers. Clinical outcomes comparing letrozole and tamoxifen have been shown to be largely consistent across different racial and ethnic populations. Major randomized trials, particularly the BIG 1-98 study, included patients from multiple regions and demonstrated that the relative benefits of letrozole in reducing recurrence and improving disease-free survival were maintained across geographic subgroups. Although ethnic differences may influence baseline risk profiles, comorbidities, and access to healthcare, there is no robust evidence suggesting a clinically meaningful interaction between race or ethnicity and the comparative efficacy of letrozole versus tamoxifen. Consequently, differences in Cost-Effectiveness outcomes across countries are more plausibly driven by variations in drug pricing, healthcare systems, and willingness-to-pay thresholds rather than by differential clinical effectiveness. Policymakers are encouraged to adapt global evidence to their specific settings, and tools like ICERs and QALYs, combined with newer approaches such as Incremental Net Benefit pooling or scenario-based modelling, can help inform such adaptations and cross-country comparisons.

In conclusion, the five studies reviewed consistently support the economic and clinical value of letrozole over tamoxifen in postmenopausal women with hormone receptor-positive early breast cancer. While letrozole incurs higher upfront costs, its ability to reduce recurrence and improve survival outcomes makes it a worthwhile investment in most settings. The degree of cost-effectiveness, however, depends significantly on drug pricing and the economic landscape of each country. These findings enrich the global Cost-Effectiveness literature and offer a useful reference for local health policy planning, particularly in countries where such analyses remain scarce.

Conclusions

Although Letrozole incurs higher treatment costs compared to Tamoxifen, its enhanced effectiveness in lowering recurrence rates and improving survival outcomes supports its classification as a cost-effective therapy for postmenopausal women with early-stage, hormone receptor-positive breast cancer.

Acknowledgment

The author expresses gratitude to the Indonesian Ministry of Finance's Indonesia Endowment Fund for Education (LPDP) for providing financial support for the publication of this article and the Master Program in Clinical, Faculty of Pharmacy at Universitas Gadjah Mada for the author's pursuit of postgraduate education.

Author Contribution

Study Design	:	LSR, TMA
Data Acquisition	:	LSR, TMA
Data Analysis	:	LSR, TMA, DE
Manuscript Writing	:	LSR, TMA, DE

Competing Interests

The author has disclosed that there are no competing interests or personal relationships that could have influenced the results reported in this study.

Abbreviation

AI	:	Aromatase Inhibitor
CEA	:	Cost-Effectiveness Analysis
CHEERS	:	Consolidated Health Economic Evaluation Reporting Standards
HR+	:	Hormone Receptor-Positive
ICERs	:	Incremental Cost-Effectiveness Ratios
INB	:	Incremental Net Benefit
IPCW	:	Inverse Probability of Censoring Weighted
LET	:	Letrozole
NHS	:	National Health Service
NMBs	:	Net Monetary Benefits
PSA	:	Probabilistic Sensitivity Analysis
TAM	:	Tamoxifen
QALYs	:	Quality- Adjusted Life Years
WTP	:	Willingness to Pay

References

1. Paepke, S. *et al.* Treatment strategies that effectively reduce early recurrence risk in postmenopausal women with endocrine-sensitive breast cancer: AIs upfront vs. switching. *Journal of Cancer Research and Clinical Oncology* vol. 133 905–916 Preprint at https://doi.org/10.1007/s00432-007-0297-7 (2007).

2. Jänicke, F. Continuing with letrozole offers greater benefits. *Journal of Cancer Research and Clinical Oncology* vol. 133 445–453 Preprint at https://doi.org/10.1007/s00432-006-0185-6 (2007).

3. Kennecke. New guidelines for treatment of early hormone-positive breast cancer with tamoxifen and aromatase inhibitors. (2006).

4. NCCN. NCCN Updates its Treatment Guidelines for Breast Cancer | CancerNetwork. https://www.cancernetwork.com/view/nccn-updates-its-treatment-guidelines-breast-cancer (2021).

5. Dahlberg, L., Lundkvist, J. & Lindman, H. Health care costs for treatment of disseminated breast cancer. *Eur. J. Cancer* **45**, 1987–1991 (2009).

6. Hassett, M. J. & Elkin, E. B. What does breast cancer treatment cost and what is it worth? *Hematology/Oncology Clinics of North America* vol. 27 829–841 Preprint at https://doi.org/10.1016/j.hoc.2013.05.011 (2013).

7. Alshreef, A. *et al.* Cost-Effectiveness of Docetaxel and Paclitaxel for Adjuvant Treatment of Early Breast Cancer: Adaptation of a Model-Based Economic Evaluation From the United Kingdom to South Africa. *Value Health Reg. Issues* **19**, 65–74 (2019).

8. Grusenmeyer, P. A. & Wong, Y. N. Interpreting the economic literature in oncology. *Journal of Clinical Oncology* vol. 25 196–202 Preprint at https://doi.org/10.1200/JCO.2006.09.0738 (2007).

9. Morton, R., Sayma, M. & Sura, M. S. Economic analysis of the breast cancer screening program used by the UK NHS: Should the program be maintained? *Breast Cancer: Targets and Therapy* vol. 9 217–225 Preprint at https://doi.org/10.2147/BCTT.S123558 (2017).

10. Tollens, F., Baltzer, P. A. T., Froelich, M. F. & Kaiser, C. G. Economic evaluation of breast MRI in screening - a systematic review and basic approach to Cost-Effectiveness analyses. *Frontiers in Oncology* vol. 13 Preprint at https://doi.org/10.3389/fonc.2023.1292268 (2023).

11. Keshaviah, A. *et al. A Comparison of Letrozole and Tamoxifen in Postmenopausal Women with Early Breast Cancer The Writing Committee (Beat Thürli-Mann. n engl j med* vol. 353 www.nejm.org (2005).

12. Tenti, S., Correale, P., Cheleschi, S., Fioravanti, A. & Pirtoli, L. Aromatase inhibitors-induced musculoskeletal disorders: Current knowledge on clinical and molecular aspects. *International Journal of Molecular Sciences* vol. 21 1–38 Preprint at https://doi.org/10.3390/ijms21165625 (2020).

13. Boszkiewicz, K., Piwowar, A. & Petryszyn, P. Aromatase Inhibitors and Risk of Metabolic and Cardiovascular Adverse Effects in Breast Cancer Patients-A Systematic Review and Meta-Analysis. *Journal of Clinical Medicine* vol. 11 Preprint at https://doi.org/10.3390/jcm11113133 (2022).

14. Cucciniello, L. *et al.* Estrogen deprivation effects of endocrine therapy in breast cancer patients: Incidence, management and outcome. *Cancer Treatment Reviews* vol. 120 Preprint at https://doi.org/10.1016/j.ctrv.2023.102624 (2023).

15. Cardoso, F. *et al.* Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* **30**, 1194–1220 (2019).

16. Hsu, S. H., Chen, L. R. & Chen, K. H. Primary Osteoporosis Induced by Androgen and Estrogen Deficiency: The Molecular and Cellular Perspective on Pathophysiological Mechanisms and Treatments. *International Journal of Molecular Sciences* vol. 25 Preprint at https://doi.org/10.3390/ijms252212139 (2024).

17. Lippuner, K. The future of osteoporosis treatment - A research update. *Swiss Medical Weekly* vol. 142 Preprint at https://doi.org/10.4414/smw.2012.13624 (2012).

18. Laroche, F. *et al.* Quality of life and impact of pain in women treated with aromatase inhibitors for breast cancer. A multicenter cohort study. https://doi.org/10.1371/journal.pone.0187165 (2017) doi:10.1371/journal.pone.0187165.

19. Kadakia, K. C. *et al.* Patient-Reported Outcomes and Early Discontinuation in Aromatase Inhibitor-Treated Postmenopausal Women With Early Stage Breast Cancer. *Oncologist* **21**, 539–546 (2016).

20. Peddie, N. *et al.* The impact of medication side effects on adherence and persistence to hormone therapy in breast cancer survivors: A qualitative systematic review and thematic synthesis. *Breast* vol. 58 147–159 Preprint at https://doi.org/10.1016/j.breast.2021.05.005 (2021).

21. Ye, M., Lu, J., Yang, F. & Wu, B. Economic Evaluation of Letrozole for Early Breast Cancer in a Health Resource-Limited Setting. *Biomed Res. Int.* **2018**, (2018).

22. Delea, T. E. *et al.* Cost-Effectiveness of letrozole versus tamoxifen as initial adjuvant therapy in hormone receptor-positive postmenopausal women with early-stage breast cancer. *Clin. Breast Cancer* **7**, 608–618 (2007).

23. Karnon, J., Delea, T. & Barghout, V. Cost utility analysis of early adjuvant letrozole or anastrozole versus tamoxifen in postmenopausal women with early invasive breast cancer: The UK perspective. *European Journal of Health Economics* **9**, 171–183 (2008).

24. Delea, T. E., El-Ouagari, K., Karnon, J. & Sofrygin, O. Cost-Effectiveness of letrozole versus tamoxifen as initial adjuvant therapy in postmenopausal women with hormone-receptor positive early breast cancer from a Canadian perspective. *Breast Cancer Res. Treat.* **108**, 375–387 (2008).

25. Karnon, J. *et al. Cost-Effectiveness of Extended Adjuvant Letrozole in Postmenopausal Women after Adjuvant Tamoxifen Therapy The UK Perspective*. *Pharmacoeconomics* vol. 24 (2006).

26. Lux, M. P. *et al.* Cost-Effectiveness analysis of anastrozole versus tamoxifen in adjuvant therapy for early-stage breast cancer - A health-economic analysis based on the 100-month analysis of the atac trial and the German health system. *Onkologie* **33**, 155–166 (2010).