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A Systematic Literature Review of Economic Evidence in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Positive Advanced or Metastatic Breast Cancer

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Objective

To systematically review and summarize the economic evidence associated with hormone receptor-positive (HR+)/human epidermal growth factor 2-positive (HER2+) advanced or metastatic breast cancer (mBC; stage IIIB, IIIC, and IV), including economic burden, and economic evaluations of first-line (1L) pharmacological treatments.

Conclusions

- The evidence on economic burden among patients with HR+/HER2+ mBC, though limited, suggests that patients with HR+/HER2+ mBC are associated with higher economic burden than patients with HR-/HER2+ mBC.
- Despite heterogeneity in study design and cohort population characteristics of economic burden studies in HER2+ BC, most reported direct medical costs. The observed medical costs increased with disease progression and by treatment line and might be driven by treatment costs.
- There is a lack of studies assessing the direct non-medical costs, indirect costs and intangible costs, indicating the need of future research to uncover full patient and societal economic burden of patients with HR+/HER2+ mBC.
- Economic evaluations identified are heterogeneous in the study settings (e.g., study region, perspective, time horizon), and most of them focused on the evaluation of lapatinib+letrozole while other treatments were not widely assessed, resulting in limited evidence to inform treatment selection and decision making in drug reimbursement. In addition, as the treatment landscape for HR+/HER2+ mBC has evolved since the publication of the identified studies, more contemporary economic models are warranted to evaluate current treatments available for patients with HR+/HER2+ mBC.

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References: Please see e-Supplement 3.

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Background

- Breast cancer (BC) is the most common cancer diagnosed among women, with an estimated 2.3 million incident cases and 685,000 deaths observed globally in 2020. The total annual medical cost of breast cancer care in the US alone surmounts to $16.5 billion, the highest medical costs of any cancer type in 2010.[1-3]
- Metastatic breast cancer (mBC) is an incurable disease and comprises approximately 6% of new cases of breast cancer.[4] Yet, over the past decade, advancements in treatment strategies targeting hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) pathways have resulted in substantial improvements in clinical outcomes and new standards of care for patients with HR+ and/or HER2+ mBC.[5-7]
- To better inform patient and provider health care decision making in treatment selection and drug reimbursement recommendation, importance of comparative evidence on healthcare resource use, costs, and treatment outcomes associated with different treatments (i.e., economic evaluations) is increasingly recognized.[8]
- Although the heavy economic burden and the economic evaluations of various treatments in BC have been well summarized,[9-11] such data are limited for first-line therapies in the management of HR+/HER2+ mBC.

Methods

SEARCH STRATEGY

- A systematic search was performed according to PRISMA guidelines in MEDLINE, Embase, and the Cochrane library via Ovid to identify economic evidence associated with HR+/HER2+ mBC, including real-world economic burden studies and model-based economic evaluations of first-line pharmacologic treatments.[12]
- English-language studies published between January 1, 2000, and May 3, 2021 which met the prespecified population, intervention, comparator, outcomes, and study design (PICOS) criteria were included in this review (**Table 1**).
- A supplemental gray literature search was conducted via advanced search in Google Scholar; references of selected systematic literature reviews published recently were also reviewed to identify all relevant records.

STUDY SELECTION & DATA EXTRACTION

- Two-level screening and data extraction were conducted by two independent reviewers. Any disagreements were resolved by discussion or independent arbitration by a third reviewer.

Table 1. Prespecified PICOS criteria applied in selection of economic burden studies and economic evaluations

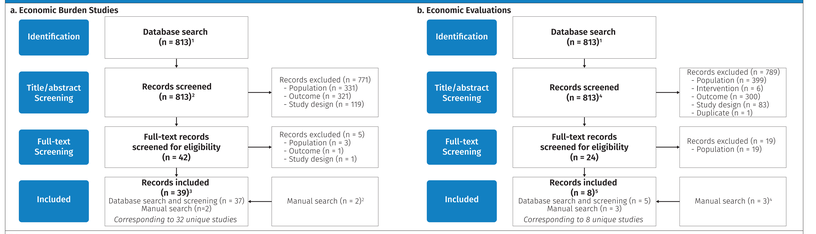
	Economic Burden Studies	Economic Evaluation Studies
Population	• Male and female adults (≥18 years) with HR+/HER2+ breast cancer*, and • Advanced or metastatic (stage IIIB, IIIC, and IV) breast cancer	• Male and female adults (≥18 years) with HR+/HER2+ breast cancer, and • Advanced or metastatic (stage IIIB, IIIC, and IV) breast cancer, and • Receiving induction or maintenance therapy in the first-line setting
Intervention and Comparator	Any, including no interventions	Induction or maintenance therapy in the first-line setting
Outcomes	• Healthcare resource use • Direct medical costs (e.g., treatment costs, monitoring costs, AE management costs) • Direct non-medical costs (e.g., transportation cost, personnel cost, patient out-of-pocket expense) • Indirect costs • Intangible costs	• ICER (e.g., incremental cost per QALY, incremental cost per LY) • Summary cost outcomes (e.g., cost of illness) • Budget impact
Study Design	Real-world studies (e.g., registry, chart review, electronic health records, administrative claims)	Model-based studies (e.g., CEA, CUA, CBA, CMA, COI, BIA)
Language	English	
Publication Types	All full-text articles and conference abstracts published between January 1, 2000 and May 3, 2021	

Abbreviations: BIA=budget impact analysis; CBA=cost-benefit analysis; CEA=cost-effectiveness analysis; CMA=cost-minimization analysis; COI=cost-of-illness; CUA=cost-utility analysis; HR+=hormone receptor positive; HER2+=human epidermal growth factor receptor 2 positive; LY=life year; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year.
*A feasibility assessment was conducted before the systematic search to evaluate the availability of evidence in target population (i.e., patients with HR+/HER2+ mBC). Based on the feasibility assessment, evidence on economic burden in target population was limited. Therefore, the inclusion criteria for economic burden were relaxed to include patients with HER2- mBC. Outcomes by HR biomarker status were extracted and summarized if reported.

Results

- Among 813 total records screened, 39 economic burden studies (based on 32 unique studies) and 8 economic evaluations (based on 8 unique studies) were eligible for data extraction (**Figure 1a** and **1b**).
- **Economic burden studies (n=32)**
  - Economic burden studies encompassed 30 retrospective observational studies, 1 prospective observational study, and 1 cross-sectional survey evaluated in different settings (i.e., study population, perspective, study region) within different types of studies (**e-Supplement 1a**).
  - Total direct medical costs reported in studies conducted in similar settings were summarized by HR biomarker status,[13,14] progression status,[15,16] and line of treatments,[17,18] and compared across studies (**Table 2a**), while other studies in heterogeneous settings were summarized in **e-Supplement 2**.
  - Treatment costs were found to be a driver of total direct medical costs in the US (**Table 2b**). The total treatment costs ranged from USD 111,616 to USD 183,797 in the first year after the diagnosis of mBC or USD 6,390 to USD 7,202 monthly from diagnosis in the US, which contributed to over 50% of the total direct medical costs.[19-21]
  - Direct non-medical costs (travel) were reported in 1 study (**Table 2b**).[22] Indirect costs due to productivity loss were assessed in 2 studies (**Table 2b**).[15,16,23] Intangible costs were not assessed in any studies.
- **Economic evaluations (n=8)**
  - Economic evaluations of various study types in different settings (e.g., study region, perspective, time horizon) were included (**e-Supplement 1b**).
  - Among them, 6 were cost-utility analyses (CUAs) in the United Kingdom (UK) and Canada. All of them were conducted from a healthcare system perspective with direct medical costs considered only, and one in Canada also included societal perspective in which indirect costs associated with productivity loss were assessed.
  - Lapatinib+letrozole, a guideline-recommended anti-HER2 therapy (AHT) + endocrine therapy (ET), was evaluated in all 6 CUAs in comparison with another guideline-recommended therapy (e.g., AHT+ET, AHT, or ET alone), and results showed a higher chance of lapatinib+letrozole being cost-effective when compared with trastuzumab+anastrozole than with ET alone (e.g., letrozole or anastrozole alone) (**Table 2c**). The cost-effectiveness conclusions were consistent from the healthcare system perspective vs. from the societal perspective in the study with two perspectives.[24]
  - One cost-effectiveness analysis (CEA) in Australia with the study perspective not specified, and 1 cost-of-illness (COI) study in Spain from a societal perspective were identified. The CEA compared costs and survival benefits of first-line chemotherapy with or without targeted therapy vs. no use of chemotherapy in the first-line setting, while the COI study assessed direct and indirect costs of active treatments in up to three lines. Compared to direct costs, the indirect costs, measured by lost productivity due to missed days of work for the working patients, were not significant (EUR 290,029 vs. EUR 317), probably because of the relatively small proportion of patients at the working age. The study results are presented in **Table 2c**.

Figure 1. PRISMA Diagrams for Economic Burden Studies and Economic Evaluations



Notes:
1. The database search on MEDLINE, EMBASE, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database, Cochrane Central Register of Controlled Trials and National Health Service (NHS) Economic Evaluation Database for studies published from 2000 onwards was conducted on May 3, 2021.
2. In the economic burden studies, two studies (Frederix 2015[17] and Woronoff 2013[15]) were manually added, based on the manual search on Google using keywords (e.g., "HER2+", "breast cancer", "burden") and the review of references in a recent systematic literature review. Studies identified from the manual search were screened against the inclusion/exclusion criteria along the search.
3. In the economic burden studies, in total, 39 records were identified, including 17 journal articles and 22 conference abstracts, corresponding to 32 studies.
4. In the economic evaluations, three studies (Beauchemin 2016[28], Hastings 2010[30], and pCODR10019 2013[31]) were manually added, based on the manual search on Google using keywords (e.g., "HER2+," "breast cancer," "economic evaluation", "cost-effectiveness") and the review of references in three recent systematic literature reviews. Studies identified from the manual search were screened against the inclusion/exclusion criteria along the search.
5. In the economic evaluations, in total, 8 records were identified, including six journal articles, one conference abstract, and two health technology assessment reports, corresponding to 8 studies.

Table 2a. Total Direct Medical Costs by HR Biomarker Status, Treatment Lines and Progression Status

First author (year)	Patient group	Cost year and currency	Measurement period	Mean total direct medical cost
HR+/HER2+ vs. HR-/ HER2+				
Schneider (2021)[13]	HR+/HER2+ mBC	2017 EUR	From the date of diagnosis (i.e., date of pathological conformation, or else date of imaging) of mBC until date of death or censoring	Monthly, unadjusted: 2,656
				Lifetime, unadjusted: 81,591
				Lifetime, adjusted for death/censoring: 92,272
	HR-/HER2+ mBC			Monthly, unadjusted: 3,076
				Lifetime, unadjusted: 60,729
				Lifetime, adjusted for death/censoring: 69,079
Song (2014)[14]	HER2+ mBC	USD, cost year NR	Diagnosis until end of enrollment or death	Monthly, all-cause, by ER status: ER+: 10,359 ER-: 12,924
				Monthly, BC-related, by ER status: ER+: 6,869 ER-: 6,757
By treatment line				
Albanell (2016)[16] / Colomer (2017)[16]	HER2+ mBC (locoregional recurrent and unresectable, or metastatic recurrent)	EUR, cost year NR	Overall (up to five lines of therapy) among all patients	Total: 208,682
			During first line of therapy among patients who received first-line	Total: 38,511
			During fifth line of therapy among patients who received fifth line	Total: 308,869
Post-progression vs. stable disease				
Frederix (2015)[17] / Frederix (2013)[18]	HER2+ mBC	2013 USD	Stable disease	Monthly: 4,158
			Progressive disease month 1	Monthly: 5,576
			Progressive disease month 2	Monthly: 5,610
			Progressive disease month 3	Monthly: 3,607
			Progressive disease month 4	Monthly: 3,553
			Progressive disease month 5	Monthly: 3,281
			Progressive disease month 6	Monthly: 2,791
			Progressive disease month 7	Monthly: 3,210
			Progressive disease month 8	Monthly: 3,319

Abbreviations: mBC=advanced or metastatic breast cancer; ER=estrogen receptor; EUR=Euro; HER2+=human epidermal growth factor 2; HR+=hormone receptor; NR=not reported; USD=United States dollar
Notes:
In total, 6 records were included in this table, corresponding to 4 studies.

Table 2b. Treatment Costs, Direct Non-Medical Costs, And Total Indirect Costs from Economic Burden Studies

First author (year)	Patient group	Cost year and currency	Measurement period	Mean treatment cost
Treatment costs				
Forero-Torres (2020)[19]	HER2+ mBC treated with trastuzumab	USD, cost year NR	1-year follow-up period from a pharmacy claim of anti-HER2 therapy	Total pharmacy: 115,453
	HER2+ mBC with CNS metastasis treated with trastuzumab			Total pharmacy: 118,388
	HER2+ mBC without CNS metastasis treated with trastuzumab			Total pharmacy: 111,616
	HER2+ mBC treated with trastuzumab + chemotherapy (including capecitabine or taxanes)			Total pharmacy: 149,609
	HER2+ mBC treated with lapatinib, with or without chemotherapy			Total pharmacy: 119,319
Mahtani (2021)[20]	HER2+ mBC	USD, cost year NR	First year following the index date (the initiation date of the HER2-targeted agent)	Annual HER2-targed therapies: 183,797
			Second year following the index date (the initiation date of the HER2-targeted agent)	Annual HER2-targed therapies: 104,384
Montero (2012)[21]	mBC patients treated with HER2-targeted therapy	USD, cost year NR	From patients' index diagnosis (initial diagnosis of secondary malignancy) to their last claim or disenrollment of their insurance plan, whichever occurred first	Monthly inpatient treatment, outpatient treatment and pharmacy, including anti-cancer and non-anti-cancer treatment: 7,202
	mBC treated with HER2-targeted therapy and endocrine therapy			Monthly inpatient treatment, outpatient treatment and pharmacy, including anti-cancer and non-anti-cancer treatment: 6,390
Direct Non-Medical Costs				
Nerich (2014)[22]	HER2+ mBC treated with trastuzumab plus docetaxel	2012 EUR	First to the last cycle of first-line therapy	Total healthcare travel: 2,826
	HER2+ mBC treated with trastuzumab plus paclitaxel			Total healthcare travel: 2,997
Indirect Costs				
Albanell (2016)[16] / Colomer (2017)[16]	HER2+ mBC (locoregional recurrent and unresectable, or metastatic recurrent)	EUR, cost year NR	Overall (up to five lines of therapy) among all patients	Total: 26,456
			During first line of therapy among patients who received first-line	Total: 12,397
			During fifth line of therapy among patients who received fifth-line	Total: 49,131
Lin (2020)[23]	HER2+ mBC	USD, cost year NR	From the first mBC diagnosis to the end of follow-up	Annual: 15,771

Abbreviations: EUR=Euro; HER2+=human epidermal growth factor 2; NR=not reported; mBC= advanced or metastatic breast cancer; USD=United States dollar

Table 2c. Outcomes for HR+/HER2+ mBC of Economic Evaluations

First author (year)	Interventions	Comparators	Perspective	Cost year and currency	ICER (cost/QALY), if not otherwise specified
Beauchemin (2016)[28]	Lapatinib+Letrozole	Letrozole alone	Canadian healthcare system	CAD, 2015	131,811
		Trastuzumab+ Anastrozole			56,211
		Anastrozole alone			102,477
Delea (2013) Canada[26]	Lapatinib+Letrozole	Letrozole alone	Canadian health care system (a) and societal (b)	CAD, cost year NR	(a) Health care system perspective: 152,344 (b) Societal perspective: 140,679
		Trastuzumab+ Anastrozole			(a) Health care system perspective: 24,561 (b) Societal perspective: 10,266
		Anastrozole alone			(a) Health care system perspective: 118,868 (b) Societal perspective: 107,207
Delea (2013) UK[25]	Lapatinib+Letrozole	Letrozole	UK NHS	GBP, cost year NR	74,448
		Anastrozole			59,895
		Anastrozole+ Trastuzumab			21,836
Fleeman (2011)[29]	Lapatinib+Letrozole	Letrozole alone	UK NHS/PSS	GBP, cost year NR	225,131
	Trastuzumab+Anastrozole	Anastrozole alone			69,514
	Trastuzumab+Anastrozole	Anastrozole alone		GBP, cost year NR	54,151
		Lapatinib+ Letrozole			17,914
		Letrozole alone			54,174
Hastings (2010)[30]	Lapatinib+Letrozole	Anastrozole+ Trastuzumab	UK NHS	GBP, cost year NR	Lapatinib+Letrozole was dominant
pCODR10019 (2013)[31]	Lapatinib+Letrozole	Letrozole alone	Canadian healthcare system	CAD, cost year NR	152,344
		Trastuzumab+ Anastrozole			24,561
Jacob (2020)[32]	First-line chemotherapy ± targeted therapy	No use of chemotherapy in the first-line setting	NR	AUD, cost year NR	ΔCost/ΔLY: 330,978
de las Heras (2020)[33]	Up to three lines of therapy	NA	Societal	2016 EUR	Direct costs (5 years): 290,029 Indirect costs (5 years): 317

Abbreviations: mBC=advanced or metastatic breast cancer; AUD=Australian dollar; CAD= Canadian dollar; GBP= British Pound; HER2+=human epidermal growth factor 2; ICER=incremental cost-effectiveness ratio; LY=life year; NA=not applicable; NR=not reported; QALY=quality-adjusted life year; UK NHS=United Kingdom National Health Service; PSS= Personal Social Services

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