Original article

Risk of recurrence among patients with HR-positive, HER2-negative, early breast cancer receiving adjuvant endocrine therapy: A systematic review and meta-analysis

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ABSTRACT

Background: A systematic review and meta-analysis was conducted to assess breast cancer (BC) outcomes among patients with early-stage hormone receptor positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) BC, receiving adjuvant endocrine therapy.
Methods: Randomized controlled trials (RCTs) and real-world evidence (RWE) studies were identified using Ovid MEDLINE®, Embase, and Evidence-Based Medicine Reviews. Clinical and methodological similarities including alignment of outcome definitions with standardized definitions for efficacy endpoints criteria were assessed to evaluate feasibility of conducting a meta-analysis. Where feasible, 5-year probabilities of BC recurrence or death were estimated using a Bayesian hierarchical arm-based model.
Results: Of 21 included studies, 8 RCTs and 4 RWE studies reported outcome data of interest. There was heterogeneity in outcome reporting, as well as variation in recurrence risk amongst studies with aligned reporting. Of the 12 studies, 10 were considered for inclusion in a meta-analysis of BC recurrence or death. Only a subgroup analysis of node-positive patients (3 studies; n = 7307) was deemed feasible. The 5-year probability of BC recurrence or death was 17.2% (95% credible interval: 14.6%–20.3%).
Conclusion: Although studies reporting recurrence outcomes were limited, there remains a high risk of BC recurrence, especially among node-positive patients. Approximately 1 in 6 women with node-positive HR+/HER2- early-stage BC receiving endocrine therapy experience recurrence or death within 5-years of initiating treatment, suggesting a need for novel treatments for this population.

1. Introduction

Within breast cancer (BC), the main molecular subtypes are characterized by key tumor markers that include the hormone receptors (HR) (estrogen [ER] and progesterone receptors [PR]) and human epidermal growth factor receptor-2 (HER2) [1]. Among the four distinct subtypes of BC (HR+/HER2-, HR+/HER2+, HR-/HER2+ and triple-negative [TNBC]), HR+/HER2- disease represents the most common invasive cancer subtype in women, accounting for 70% of all BC cases [1,2]. Further, more than 90% of primary diagnoses in HR+/HER2- BC occur in non-metastatic early stages (stages I-III) [3].

In recent years, several studies have concluded that disease prognosis, treatment options, and the response to BC therapies vary based on disease subtype [4]. For example, cytotoxic chemotherapy is widely used in the treatment of TNBC while the combination of a HER2-targeted monoclonal antibody with chemotherapy is used in the treatment of HER2+ BC [5]. In HR + patients, endogenous hormones interact with hormone receptors on the cancer cells to further augment proliferation. Considering the main goals of early BC therapy, current clinical practice guidelines recommend the use of endocrine therapy (ET), such as tamoxifen and aromatase inhibitors (AI), in the adjuvant setting to reduce the risk of disease recurrence and death [6,7]. Despite the effectiveness of standard ET, as many as 41% of women diagnosed with HR+ early-stage BC will

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experience distant (or metastatic) recurrence, with risk varying by tumor characteristics [8]. In particular, greater nodal involvement is a key determinant of AJCC cancer stage [9], and has been associated with an increased risk of disease recurrence in HR+ breast cancer [8,10]. Metastatic BC remains an incurable disease with poor prognosis and a substantial negative impact on quality of life, highlighting the limitations of current therapies and further reducing the risk of recurrence [3].

While clinical trials are often designed to investigate HR+ disease, patients with any HER2 status are often enrolled, as endocrine therapies used in patients with HER2-disease are also used in patients with HER2+ disease [11]. This prevents a full understanding of prognosis and treatment efficacy in HR+/HER2- disease. Although subgroup analyses examining subtype-specific recurrence rates may be reported, such subgroups are often small and result in imprecise estimates of risk. To our knowledge, there are no published systematic literature reviews (SLRs) that have examined adjuvant ETs in women with HR+/HER2- early BC. In this study, we sought to summarize the current literature surrounding the impact of adjuvant ETs on recurrence or death in women with HR+/HER2- early BC and, if feasible, conduct a meta-analysis (including subgroups based on nodal status), synthesizing data around expected recurrence rates in the contemporary era of AIs, where heterogeneous ET regimens are considered holistically.

2. Methods

2.1. Study selection and data synthesis

Two systematic searches of published literature were conducted on July 24, 2019 to identify eligible randomized controlled trials (RCTs) and observational or real-world evidence (RWE) studies reporting any recurrence outcomes (e.g., recurrence-free survival [RFS], disease-free survival [DFS], recurrence events) for adult patients with HR+/HER2- early BC receiving adjuvant ETs. Ovid MEDLINE®, MEDLINE® In-Process, Embase, and Evidence-Based Medicine Reviews (including the Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials [CENTRAL]) were searched, restricting to articles published in the prior 15 years to reflect contemporary clinical practice, including the widespread approval for the most common AIs (i.e., letrozole, anastrozole, exemestane). The literature searches were conducted by an information specialist and peer-reviewed using the Peer Review of Electronic Search Strategies Guideline [12]. Recent scientific congresses and relevant systematic reviews or meta-analysis articles were also reviewed. Citation titles and abstracts identified in the literature searches were screened for relevance then further evaluated in full-text form based on the same selection criteria. Literature searches, study selection, data extraction, and quality assessments were performed by duplicate independent reviewers (where a third reviewer resolved any discrepancies), according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. [13] The review protocol was registered with the International Prospective Register of Systematic Reviews (CRD161470). The full search strategy, eligibility criteria, and list of excluded articles are available in the Supplementary.

For studies meeting eligibility, data relating to trial design and methodology, details of interventions, patient eligibility criteria, reported baseline characteristics, and recurrence outcome measures were extracted. Quality of each RCT was assessed using the National Institute for Health and Care Excellence (NICE) Quality Appraisal checklist for quantitative intervention studies, whereas the quality of each RWE study was assessed using the Newcastle-Ottawa Scale [14,15].

2.2. Assessing the feasibility of a meta-analysis

The validity of any results generated through meta-analysis is dependent on the evidence meeting the exchangeability assumption [16]. Under this assumption, all interventions studied could have been included as comparators in a clinical trial; thus, all treatments under study are truly competing interventions. Failure to meet this assumption can result in biased estimates of effect. To ascertain whether this assumption was met, included studies reporting common outcomes (defined herein as either local recurrence events, distant recurrence events, any recurrence events, or RFS) were examined to assess their clinical and methodological similarities. Studies reporting the incidence of recurrence events were grouped based on the location of recurrence (i.e., local, distant, or any location). A distinct feasibility assessment was conducted for each incident event by location. Where outcomes were reported as a composite (e.g., DFS, RFS), consistency across studies was measured and compared to standardized definitions for efficacy endpoints (STEEP)-defined criteria for both the invasive disease-free survival (iDFS) outcome and the RFS outcome, which excludes secondary cancers (i.e., contralateral BC or non-BC) [17]. Only studies reporting composite outcomes aligning with STEEP-iDFS or STEEP-RFS definitions were considered when evaluating meta-analysis feasibility. Studies were excluded if outcome data of interest was only available in graphical form and required digitization.

In addition to an assessment of trial-specific outcome definitions, a rigorous qualitative assessment of between-trial heterogeneity for the following elements was conducted: study design (e.g., RCT, retrospective, prospective, enrolment periods, follow-up), study eligibility criteria (e.g., prior therapy restrictions), baseline patient characteristics (e.g., age, menopausal status, nodal status, tumor status, hormone receptor status), intervention, and comparators (e.g., treatments and their corresponding regimens) [18]. All details related to the assessment of clinical heterogeneity were built upon existing recommendations [19–21]. Subgroups defined by nodal status (node-positive and node-negative) were considered.

2.3. Statistical analysis

A Bayesian hierarchical arm-based meta-analysis was performed using the methods outlined by the NICE Decision Support Unit Technical Support Documents [22]. Bayesian methods were selected for the base case analysis owing to increased clinical interpretability, and consideration of uncertainty in the data [22,23]. The base case analysis was conducted using a random-effects model with uninformative (or vague) priors for the overall treatment effects and common heterogeneity standard deviation. Each model was run with 4 separate chains and 40,000 iterations with 40,000 burn-in iterations. Absolute probabilities and 95% credible intervals (CrIs) were calculated. All Bayesian analyses were performed using Just Another Gibbs Sampler (JAGS) version 4.3.0, and R Statistical Software version 3.6.1. Sensitivity analyses were conducted to assess the robustness of the base case analysis. To assess the influence of study design on results, sensitivity analyses were conducted where RWE studies were down weighed 50% compared with RCT studies [24,25]. Additional sensitivity analyses included using fixed-effect models and a direct (i.e., frequentist) meta-analysis for all outcomes, where statistical heterogeneity tests were performed using I^2. The Comprehensive Meta-Analysis software was used to perform all direct meta-analyses [26].

3. Results

3.1. Study selection and characteristics

A total of 5397 RCTs and 3409 RWE studies published between 2011 and 2019 were identified. Of these, 12 RCTs corresponding to 9 unique trials and 12 RWE studies were considered for full-text review. In total, 9 RCTs and 12 RWE studies were identified that fulfilled the inclusion criteria (Fig. 1). Finally, 8 RCTs and 4 RWE studies were included for meta-analysis feasibility assessment after screening for the reporting of relevant recurrence outcomes of interest (Fig. 1). Two studies provided poor reporting of recurrence data of interest and thus were subsequently excluded from the compilation of recurrence outcomes; however, study and patient baseline characteristics information from these studies were compiled [27,28].

Table 1 summarizes the key characteristics of the included studies. Overall, data were reported from 34,582 women with HR+/HER2- early-stage BC enrolled (or identified) from 1977 through 2015. All RCTs were phase III studies. Most RWE studies were retrospective with one prospective study [29] and one bidirectional (prospective-retrospective) study included [30]. Median follow-up varied between 4 and 10 years, considering recurrence outcomes [28,30–34]. While all RCTs were conducted across multiple continents [35–40], two were based in Europe, [32,41,42] and one in Japan [31,33]. Conversely, the majority of RWE studies were conducted in Asia [27,29,34,43–48]. Nine of the 12 included RWE studies were single-arm investigations of ET [29,30,34,44–49]. The remaining RCTs compared ET to a combination of ET and

chemotherapy [27,28,43]. Collectively, AIs such as letrozole were administered in 48% of all studies [30,35–37,39–42,44,46,47], and tamoxifen in 52% [30,32,36–38,43–45,47–49]. Ovarian function suppression [38,44], fulvestrant [41,42,50], luteinizing hormone-releasing hormone agonist (LHRHa) [31,33], and gonadotropin hormone-releasing hormone agonist (GnHRHa) were also investigated [43,48]. See Table 2 for the interventions evaluated in the included RCT and RWE studies.

Individual trials used different endpoints for recurrence. DFS was reported in all included RCTs, whereas only 5 RWE studies reported this outcome [27,28,43,44,47] (the remainder reported PFS [34], RFS [29,48], or DDFS [49]). Several studies also examined the incidence of recurrence events, often by location [30,32,37,41–43,47].

The included RCTs were all well-conducted, and the risk of bias was low to moderate based on internal and external validity scores (Supplementary Table 2). For the included RWE studies, Newcastle-Ottawa Scale quality scores ranged from 5 to 8 points out of a maximum of 9 points (Supplementary Table 3).

3.2. Recurrence outcomes

3.2.1. Composite outcomes (disease- and recurrence-free survival)

DFS reported in 3 RWE studies ranged from 76.2% [44] to 98.9% [43] with follow-up periods ranging from 5 to 6 years (Table 3) [43,44,47]. Where provided, DFS definitions differed in the inclusion of all-cause death [43,44]. In 8 RCTs, DFS was reported in HR+/HER2- patients for timepoints ranging from 1.8 years (reported as 96 weeks) [31,33] to 10 years [36] (Table 4), and provided DFS
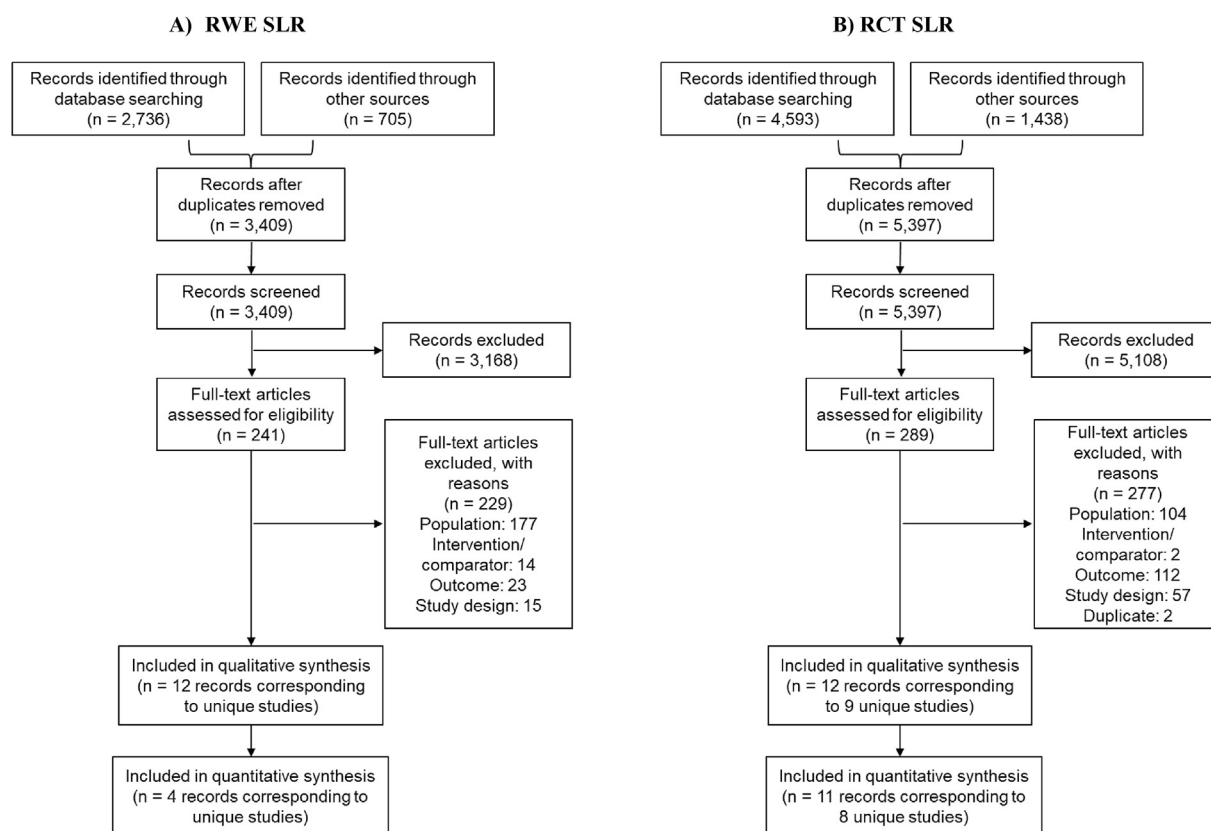

Fig. 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram summarizing the process for the identification of the eligible studies. Abbreviations: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomized controlled trials; RWE = real-world evidence; SLR = systematic literature review.

Table 1
Study design elements amongst studies included in the SLR.

Study	Study Design				Enrolment Dates	Country/Region	Patients (n)	Median Follow-up (years)	Recurrence Descriptors Reported for HR+/HER2- eBC Patients
	RCT			RWE					
	Phase	Blinding	Data Source	Design					
DBCG 77C	III	Open-label	Parallel	—	1977—1982	Denmark	1716	Recurrence: 10 Survival: 30	BCRR
BIG 1—98[a]	III	Double-blind	Parallel	—	1998—2003	International	2923	8.1	DFS
TEAM[a]	III	Open-label	Parallel	—	2001—2006	Europe	6120	9.8	DFS
SOFT[a]	III	Open-label	Parallel	—	2003—2011	United States, Canada, Switzerland	3066	5.6	DFS
FACE[a]	IIIb	Open-label	Parallel	—	2005—2008	International	4172	5.4	DFS
DATA[a]	III	Open-label	Parallel	—	2006—2009	Netherlands	1860	4.2	DFS
SOLE[a]	III	Open-label	Parallel	—	2007—2012	International	4884	5.0	DFS
GEICAM/2006—10[a]	III	Open-label	Parallel	—	2008—2010	Spain	870	6.4	DFS, LR, DR, any R, TTR
Kurebayashi (2017)[a] NCT01546649	III	Open-label	Parallel	—	2012—2014	Japan	167	1.8	DFS, DDFS
Moon (2011)		—		Retrospective	1994—2004	Korea	819	6.4	RFS
Ohnstad (2017)		—		Retrospective	1995—1998	Norway	653	DDFS: 7.1	DDFS
Wright (2012)		—		Retrospective	1999—2009	United States	582	3.7	PFS
Laenkholm (2018)[a]		—		Prospective-retrospective	2000—2003	Denmark	2558	9.2	DR, TTR
Ohara (2015)		—		Retrospective	2002—2012	Japan	184	3.8	RFI
Sohn (2016)		—		Retrospective	2003—2008	Korea	994	7.4	RFS
Kwak (2015)[a]		—		Retrospective	2003—2011	Korea	242	5.1	DFS
Babacan (2015)		—		Retrospective	2003—2014	Turkey	634	NR	PFS/DFS[b]
Park (2017)		—		Retrospective	2004—2013	Korea	851	4.3	DFS
Sun (2014)		—		Prospective	2008—2010	China	541	4.4	RFS
Alramadhan (2016)[a]		—		Retrospective	2008—2013	Korea	406	4.3	DFS, LR, DR, any R
Shimazu (2019)[a]		—		Retrospective	2008—2015	Japan	340	5	DFS, DR

Abbreviations: BCRR = breast cancer recurrence rate; DDFS = distant disease-free survival; DFS = disease-free survival; DR = distant recurrence; eBC = early breast cancer; HER2: human epidermal growth factor receptor 2; HR = hormone receptor; LR = local recurrence; PFS = progression-free survival; R = recurrence; RFS = recurrence-free survival; RCT = randomized controlled trial; RFI = recurrence-free interval; RFS = recurrence-free survival; RWE = real-world evidence; TTR = time to recurrence.
[a] Studies eligible for quantitative synthesis.
[b] Babacan et al. (2015) study used the terms PFS and DFS interchangeably and did not provide outcome definitions.

definitions were broadly aligned. Kurebayashi et al. reported the most short-term DFS, at 1.8 years, to be approximately 97% (95% CI: 93.6%—100%) for both LHRHa regimens [31,33]. Five-year DFS was reported in 5 studies [35,38—41,50] ranging from 79.7% (95% CI: 76.2%—83.3%) [40] to 91% (95% CI: 88.2%—93.9%) [41,50]. Ten-year DFS was reported for patients with HR+/HER2- disease in the TEAM trial at approximately 67% [36].

Four RWE studies reported RFS or RFI, ranging from 88.4% to 96.5% [29] for follow-up periods ranging from 4 to 11 years (Table 5) [29,45,46,48]. Outcome definitions were not aligned across these studies — RFS events were defined as either distant relapse [29], locoregional and distant recurrences [45], or recurrences and death [48]. Ohara et al. defined RFI as the time to cancer recurrence [46].

A single RWE study reported PFS, defined as the time to locoregional recurrence, distant metastasis, or death [34]. Outcome information for the overall patient cohort was unavailable. Instead, HR+/HER2- patient data were stratified based on patient traits such as race [34]. At approximately 12 years, black patients had worse outcomes compared to other races, and these differences were statistically significant in the analyses of post-menopausal patients (39.9% versus 73.5%) and PR+ patients (27.5% versus 63%) [34].

Outcomes termed time to recurrence (TTR) and breast cancer recurrence rate (BCRR) were also identified in RCTs, both of which considered only recurrence events [32,41]. At 5 years, TTR ranged from 92.7% to 94% between treatment arms in the GEICAM/2006-10

study (Table 6) [41]. 10-year BCRR reported by Knoop et al. in the DBCG 77C trial was much lower, ranging from 40.8% to 57.0% in patients receiving ET, where a significant benefit of tamoxifen in addition to radiotherapy was reported [32]. The 10-year BCRR rates in DCBG 77C were appreciably high, which is consistent with the high-risk profile of recruited participants [32].

3.2.2. Location-specific outcomes (locoregional, distant, and any site recurrence)

Six RWE studies reported location-specific recurrence outcomes (Table 7) [30,43,46—49]. Two of these studies reported DDFS [49] or distant relapse-free survival (DRFS) [47]. However, the provided definitions considered only distant recurrence. For follow-up periods of less than 6 years, more than 94% of patients were free from distant recurrence [43,46,48], and more than 96% of patients were free from local recurrence [46,48]. Shimazu et al. (2019) reported 6-year DRFS exceeding 90% in their assessment of node-negative patients [47]. Laenkholm et al. (2018) reported a sequential increase in the incidence of distant recurrence at 10 years based on the number of lymph nodes involved (86% for patients with 2 lymph nodes, 77.3% for patients with 3 affected lymph nodes) [30]. Ohnstad et al. (2017) reported DDFS stratified by Prosigna-determined risk of recurrence (ROR) groups, where DDFS at 8 years was 74.3% for high-risk patients as defined by ROR grouping [49].

Table 2
Endocrine therapies investigated amongst studies included in the SLR.

Study	Design	Intervention Model	Intervention		Comparator		Addtional Therapies
			Therapy	Dosage	Therapy	Dosage	
DBCG 77C	RCT, OL	Parallel	• Tamoxifen • RT	10 mg, three times daily 40.92 Gy (22 fractions; 5 per week) or 36.60 Gy (12 fractions; 2 per week)	RT	40.92 Gy in 22 fractions (5 per week) or 36.60 Gy in 12 fractions (2 per week)	NR
BIG 1-98*	RCT, DB	Parallel	Letrozole	2.5 mg daily, 5 years	Tamoxifen	20 mg daily, 5 years	NR
TEAM*	RCT, OL	Parallel	Tamoxifen **followed by** exemestane	20 mg daily, 2.5-3 years 25 mg daily, 2-2.5 years	Exemestane	25 mg daily, 2-2.5 years	RT per local practice
SOFT*	RCT, OL	Parallel	Tamoxifen	20 mg daily, 5 years	• Tamoxifen • Triptorelin **or** bilateral oophorectomy **or** bilateral ovarian irradiation	20 mg daily, 5 years 3.75 mg every 28 days	NR
FACE*	RCT, OL	Parallel	Letrozole	2.5 mg daily, 5 years	Anastrozole	1 mg daily, 5 years	NR
DATA*	RCT, OL	Parallel	Anastrozole (following tamoxifen)	1 mg daily, 3 years	Anastrozole (following tamoxifen)	1 mg daily, 6 years	NR
SOLE*	RCT, OL	Parallel	Letrozole (continuous)	2.5 mg daily, 5 years	Letrozole (intermittent)	**Years 1-4:** 2.5 mg daily during months 1-9, break during months 10-12 **Year 5:** 2.5 mg daily	NR
GEICAM/2006-10*	RCT, OL	Parallel	Anastrozole	1 mg daily, 5 years	• Anastrozole • Fulvestrant	1 mg daily, 5 years **Cycle 1:** 500 mg on day 1, 250 mg on days 14 and 28 **Subsequent cycles:** 250 mg on day 1, until 3 years	NR
Kurebayashi (2017) NCT01546649*	RCT, OL	Parallel	• TAP-144-SR (6M)	22.5 mg, every 6 months, 24 months	• TAP-144-SR (3M)	11.25 mg, every 3 months, 24 months	-

Study	Design	Intervention	Intervention		Comparator		Addtional Therapies
			• Tamoxifen	20 mg daily, 24 months	• Tamoxifen	20 mg daily, 24 months	
Moon (2011)	RWE, R	Single-arm	Tamoxifen **or** tamoxifen followed by switch to AI	20 mg daily, 5 years NR	-		• **Axillary nodal involvement or high-risk node-negative:** CMF, FAC, AC followed by taxanes, AC, others • **Some patients:** whole-breast radiotherapy
Ohnstad (2017)	RWE, R	Single-arm	Tamoxifen	5 years	-		NR
Wright (2012)	RWE, R	Single-arm	• Pre-menopause: tamoxifen • Post-menopause: AI	NR	-		• **Some patients:** chemotherapy (platinum/ anthracycline/taxane, anthracycline/taxane, trastazumab-containing, other or unknown • **Some pre-menopausal patients:** LHRHa
Laenkholm (2018)*	RWE, PR	Single-arm	Tamoxifen **or** AI	5 years 5 years	-		NR
Ohara (2015)	RWE, R	Single-arm	Anastrozole (52.2%) **or** letrozole (45.7%) **or** exemestane (28.8%)	NR	-		• **High-risk:** 4 cycles AC, every 3 weeks • **Node-positive:** 4 cycles docetaxel, every 3 weeks
Sohn (2016)	RWE, R	Parallel	• Goserelin **or** leuprolin • Tamoxifen	3.6 mg/kg 3.75 mg/kg; 2 years 20 mg daily, 5 years	• AC • Tamoxifen	4 cycles 20 mg daily, 5 years	NR
Kwak (2015)*	RWE, R	Parallel	• Pre-menopause: tamoxifen • Pre-menopause: oopherec-tomy **or** GnRHa • Post-menopause: AI	20 mg daily, 5 years 3.6 mg every 28 days, 2 years 5 years	Chemotherapy	NR	NR
Babacan (2015)	RWE, R	Parallel	Tamoxifen **and/or** AI	NR	• AC • Tamoxifen **and/or** AI	NR	NR
Park (2017)	RWE, R	Parallel	Tamoxifen **or**	NR	• AC followed by docetaxel	NR	**Some patients:** GnRHa (3.6 mg) every

Study	Design	Intervention	Intervention		Comparator		Addtional Therapies
			AI		**or** AC followed by weekly paclitaxel **or** CAF followed by taxanes • Endocrine therapy		28 days, 2 years
Sun (2014)	RWE, P	Single-arm	• Pre-menopause: tamoxifen • Post-menopause: AI	NR	-		• **Some patients:** 4 cycles EC • **HER2+ patients:** trastuzumab
Alramadhan (2016)*	RWE, R	Parallel	• Goserelin • Tamoxifen	3.78 mg, once per 28 days 20 mg daily, 5 years	• AC (89.4%) **or** FAC (11.6%) • Tamoxifen	4 cycles 4 cycles 20 mg daily, 5 years	NR
Shimazu (2019)*	RWE, R	Single-arm	Tamoxifen **or** AI **or** tamoxifen + LHRHa	NR	-		NR

*Studies eligible for quantitative synthesis
Note: Red shading denotes chemotherapy-containing regimens.

Abbreviations: AC = adriamycin + cyclophosphamide; AI = aromatase inhibitor; CAF = cyclophosphamide + doxorubicin + 5-fluorouracil; DB = double-blinded; EC = epirubicin + cyclophosphamide; FAC = fluorouracil + adriamycin + cytoxan; GnRHa = gonadotropin hormone-releasing hormone agonist; HER2 = human epidermal growth factor receptor 2; LHRHa = luteinizing hormone releasing hormone agonist; NR = not reported; OL = open-label; P = prospective; PR = prospective-retrospective; R = retrospective; RCT = randomized controlled trial; RT = radiotherapy; RWE = real-world evidence.

Table 3
Disease-free survival in RWE studies.

First Author (year)	Follow-up	Event-free (%)
Kwak (2015)	5 years	ET arm: 76.2
Alramadhan (2016)	5 years	ET arm: 98.9
Shimazu (2019)	6 years	osN0: 92.4
		pN0: 87.0

Abbreviations: ET = endocrine therapy; osN0 = negative sentinel lymph nodes assessed by one-step nucleic acid amplification; pN0 = negative sentinel lymph node assessed by pathology; RWE = real-world evidence.

A single RCT reported a location-specific recurrence outcome: Kurebayashi et al. defined DDFS events as distant recurrence, second primary cancer, and death. Over a short-term follow-up of 1.8 years, DDFS for participants treated with LHRHa regimens was approximately 99% (Table 8). [31,33].

3.3. Meta-analysis

Study characteristics and reported recurrence outcomes, respectively, of the subset of 12 studies included in the meta-analysis assessment [30,31,33,35–44,47,50] are summarized in Tables 1 and 9. For the included RCTs, 5 of the 8 trials fulfilled all STEEP-defined iDFS criteria [31,33,35,37,38,40], whereas the remaining 3 trials did not report whether their definitions considered a second primary or non-breast cancer [36,39,41,42]. The definitions of DFS as reported in 3 of the included RWE studies [43,44,48] did not meet all STEEP-defined iDFS criteria (Table 10). Specifically, Alramadhan et al. did not report whether non-BC deaths, death from unknown causes, or secondary cancers (contralateral BC and non-BC) were part of their DFS criteria [43]. Definitions of DFS reported by Shimazu et al. and Kwak et al. met many of the STEEP iDFS criteria; however, the inclusion of secondary cancers in their definitions was unclear [44,47]. All included RCTs and RWE studies reported efficacy endpoints that were consistent with criteria meeting the STEEP-defined RFS definition, except one [43]. As such, 10 studies (8 RCTs and 2 RWE studies) reported outcomes that were considered similar and consistent with STEEP-defined RFS to be included in a potential meta-analysis [31,33,35–42,44,47]. Incidence of recurrence events were consistently defined (i.e., local recurrences, distant recurrences, and/or any location recurrences) among the included studies. The feasibility assessment presented herein pertain to studies aligning with the STEEP-defined RFS outcome. A meta-analysis of recurrence events was not determined to be feasible.

A detailed assessment of the comparability of selected baseline demographic characteristics (e.g., age, menopausal status), disease-related characteristics (e.g., nodal status, tumor size), and study eligibility criteria across the studies reporting RFS, as defined by STEEP, are presented as Supplementary. Clinical heterogeneity amongst the studies was deemed substantial, and heterogeneity was noted for traits that were considered plausible effect modifiers. Given the marked between-trial differences in patient characteristics (e.g., nodal status), eligibility criteria, and study characteristics among the included studies, it was determined that a meta-

Table 4
Disease-free survival in RCTs.

First Author (year) or NCT record number [trial name]	Intergroup Difference			Intervention		Comparator	
	Effect Estimate	95% CI	p-value	Treatment	Proportion	Treatment	Proportion (95% CI)
96-week (2 year) DFS							
Kurebayashi 2017; NCT01546649	Difference: 1.2%	−5.2 - 7.8	NR	TAP-144-SR (6 month depot)	97.3% (95% CI: 93.6 −100.0)	TAP-144-SR (3 month depot)	97.5% (95% CI: 94.1 −100.0)
5-year DFS							
Ruiz-Borrego (2019); NCT00543127 [GEICAM/2006−10]	NR	NR	NR	Anastrozole + fulvestrant	91.0% (95% CI: 88.2 −93.9)	Anastrozole	90.8% (95% CI: 88.0 −93.6)
Smith (2017) [FACE]	HR: 0.96	0.82 −1.13	NR	Letrozole	84.7% (95% CI: 82.9 −86.3)	Anastrozole	83.4% (95% CI: 81.6 −85.1)
Tjan-Heijnen (2017)[a] [DATA]	HR: 0.79	0.61 −1.03	NR	Anastrozole (6 years)	83.2% (95% CI: 79.7 −86.7)	Anastrozole (3 years)	79.7% (95% CI: 76.2 −83.3)
Colleoni (2018) [SOLE]	HR: 1.12	0.94 −1.33	NR	Intermittent letrozole	85.0%	Continuous letrozole	86.6%
Francis (2015) [SOFT]	HR: 0.88	0.69 −1.13	NR	Tamoxifen + OFS	86.3%[b] (95% CI: NR)	Tamoxifen	85.3%[b] (95% CI: NR)
7-year DFS							
Ruiz-Borrego (2019); NCT00543127 [GEICAM/2006−10]	HR: 0.84	0.58 −1.22	0.352	Anastrozole + fulvestrant	86.9% (95% CI: 83.3 −90.6)	Anastrozole	83.3 (95% CI: 79.2 −87.5)
8-year DFS							
Filho (2015) [BIG 1−98]	HR for ILC: 0.48	0.31 −0.74	NR	Letrozole	82% (95% CI: NR)	Tamoxifen	66% (95% CI: NR)
	HR for IDC: 0.80	0.68 −0.94			82% (95% CI: NR)		75% (95% CI: NR)
10-year DFS							
Derks (2017) [TEAM]	NR	NR	NR	Tamoxifen → exemestane	67% (95% CI: 66−69)	Exemestane	68% (95% CI: 66−70)

Abbreviations: CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; NR = not reported; OFS = ovarian function suppression; RCT = randomized controlled trial.
[a] Study included patients who were disease-free after 3 years, as such the DFS outcome was termed 5-year "adapted" DFS.
[b] Reported in-text as proportion experiencing DFS events; subtracted from 100%.

Table 5
Recurrence-free survival and recurrence-free interval in RWE studies.

First Author (year)	Outcome	Follow-up	Event-free (%)
Moon (2011)	RFS	10 years	88.6
Sun (2014)	RFS	5 years	Luminal A: 96.5[a]
			Luminal B: 88.4[a]
Ohara (2015)	RFI	3.8 years	91.3
Sohn (2016)	RFS	10.9 years	ET arm: 90.5

Abbreviations: ET = endocrine therapy; RFI = recurrence-free interval; RFS = recurrence-free survival; RWE = real-world evidence.
[a] Values obtained by digitizing available Kaplan-Meier curves.

analysis combining all 8 RCTs and 2 RWE studies to determine the risk of recurrence or death (RFS as defined by STEEP) or for any location-specific event were not feasible.

The feasibility of subgroup analyses defined by nodal status was assessed for inclusion in a meta-analysis of recurrence or death (RFS as defined by STEEP). We determined that a subgroup defined as HR+/HER2- early-stage BC patients receiving adjuvant ET with ≥ 99% node-positive status was feasible to meta-analyze. A total of 3

studies (2 RCTs [35,39] and 1 RWE study [44]) reporting RFS were considered in this evidence network. Patient characteristics were similar across all 3 studies (Table 11). No subgroups evaluating the incidence of recurrence events were determined to be feasible (see Supplementary).

In the base case analysis using a Bayesian framework (Fig. 2), the pooled 5-year probability of recurrence or death in patients with node-positive HR+/HER2- early-stage BC receiving adjuvant ETs was 17.2% (95% CrI: 14.6%−20.3%). Results of sensitivity analyses (e.g., frequentist framework, fixed-effect model) confirmed the robustness of the base case analysis: pooled 5-year probabilities of recurrence or death ranged from 15.1% to 17.2% (Supplementary Figure 2). The impact of downweighing or excluding the single RWE study in sensitivity analyses had a minimal impact on the overall estimates. Additionally, an exploratory analysis was conducted for completeness, including more broadly defined patient populations (ie., not restricted to patients with node-positive status; see Supplementary). In addition to large dispersion in risk across the studies included therein, the between trial heterogeneity (indicated as standard deviation) was approximately five times

Table 6
Other recurrence outcomes in RCTs.

First Author (year) [trial name]	Intergroup Difference			Intervention		Comparator	
	Hazard Ratio	95% CI	p-value	Treatment	Proportion	Treatment	Proportion
TTR at 5 years							
Ruiz-Borrego (2019) [GEICAM/2006−10]	NR	NR	0.406	Anastrozole	92.7%	Anastrozole + fulvestrant	94.0%
BCRR at 10 years							
Knoop (2014) [DBCG 77C]	LA: 0.66	0.53−0.84	NR	Tamoxifen + radiotherapy	40.8%	Radiotherapy alone	55.1%
	LB: 0.54	0.39−0.74	NR		57.0%		69.1%

Abbreviations: BCRR = breast cancer recurrence rate; CI = confidence interval; LA = luminal A; LB = luminal B/HER2-; NR = not reported; RCT = randomized controlled trial.

Table 7
Distant and local recurrence outcomes in RWE studies.

First Author (year)	Outcome Term	Follow-up	Proportion of Patients
Distant recurrence			
Ohara (2015)	Distant recurrence (free of)	~4 years	94.0%
Alramadhan (2016)	Distant recurrence (free of)	~4 years	ET arm: 99.5%
Sohn (2016)	Distant metastasis (free of)	5 years	96.7%
Ohnstad (2017)	DDFS[a]	8 years	*ROR group*
			Low-risk: 87.8%
			Intermediate risk: 77.7%
			High-risk: 74.3%
Laenkholm (2018)	Distant recurrence (free of)	10 years	*Lymph nodes involved*
			0 lymph nodes: 89.5%
			1 lymph node: 87.9%
			2 lymph nodes: 86.0%
			3 lymph nodes: 77.3%
Shimazu (2019)	DRFS	6 years	osN0: 99.5%
			pN0: 90.1%
Local recurrence			
Ohara (2015)	Local recurrence (free of)	~4 years	97.3%
Sohn (2016)	Locoregional recurrence (free of)	5 years	96.5%

Abbreviations: DDFS = distant disease-free survival; DRFS = distant relapse-free survival; ET = endocrine therapy; osN0 = negative sentinel lymph nodes assessed by one-step nucleic acid amplification; pN0 = negative sentinel lymph node assessed by pathology; ROR = risk of recurrence.
[a] Values were collected by digitizing available Kaplan-Meier curves.

Table 8
Distant disease-free survival at 1.8 years (Kurebayashi et al., 2017).

First Author (year) or NCT record number [trial name]	Intergroup Difference			Intervention		Comparator	
	Difference	95% CI	p-value	Treatment	Proportion	Treatment	Proportion
Kurebayashi 2017; NCT01546649	−0.3%	−4.0 − 3.4	NR	TAP-144-SR (6 month depot)	98.5% (95% CI: 95.7 −100.0)	TAP-144-SR (3 month depot)	98.8% (95% CI: 96.4 −100.0)

Note: timepoint was more specifically reported by authors as 96 weeks and has been converted to years.
Abbreviations: CI = confidence interval; NR = not reported.

Table 9
Recurrence outcomes reported in studies eligible for quantitative synthesis.

Study	Study Design	Recurrence Descriptors Reported for HR+/HER2- eBC Patients					
		DFS	DDFS	LR	DR	Any R	Other
BIG 1-98	RCT	X					
TEAM	RCT	X					
SOFT	RCT	X					
FACE	RCT	X					
DATA	RCT	X					
SOLE	RCT	X					
GEICAM/2006-10	RCT	X		X	X	X	TTR
Kurebayashi (2017) NCT01546649	RCT	X	X				
Laenkholm (2018)	RWE				X		TTR
Kwak (2015)	RWE	X					
Alramadhan (2016)	RWE	X		X	X	X	
Shimazu (2019)	RWE	X			X		

Abbreviations: R = recurrence; DDFS = distant disease-free survival; DFS = disease-free survival; DR = distant recurrence; eBC = early breast cancer; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; RCT = randomized controlled trial; RWE = real-world evidence; TTR = time to recurrence.

greater as compared with the node-positive subgroup.

4. Discussion

We conducted a comprehensive literature review to understand recurrence outcomes in patients with HR+/HER2- disease receiving adjuvant ET. Where outcome data were deemed comparable, considerable variation was noted in the rate of disease recurrence among patients with HR+/HER2- BC, likely reflecting clinical heterogeneity, which was explored in our meta-analysis feasibility assessment. Indeed, only one subgroup meta-analysis was deemed appropriate to conduct. We found that approximately 1 in 6

patients with node-positive disease, will experience recurrence within 5 years of initiating endocrine therapy. To our knowledge, this is the first review to summarize the literature for patients with HR+/HER2- BC. Existing literature reviews and meta-analyses often narrow the study population to HR+ BC, including patients with HER2+ disease, which likely confounds disease recurrence estimates. These findings contrast broad perceptions that the vast majority of recurrences in HR+/HER2- disease occur later (i.e., more than 5 years after diagnosis) [51–53]. Furthermore, these results suggest a substantial impact of high-risk features on patient prognosis, particularly node-positive disease.

This study also evaluated author-reported recurrence outcome

Table 10
Assessment of recurrence outcome definition comparability using the STEEP system.

Study Design	STEEP Outcome/ Study[a]	Invasive Ipsilateral Breast Tumor Recurrence	Local/Regional Invasive Recurrence	Distant Recurrence	Death from Breast Cancer	Death from Non-Breast Cancer Cause	Death from Unknown Cause	Invasive Contra-lateral Breast Cancer	Second Primary Invasive Cancer (non-breast)
_	**STEEP: iDFS**	X	X	X	X	X	X	X	X
_	**STEEP: RFS**	X	X	X	X	X	X		
RCT	BIG 1-98	X	X	X	X	X	X	X	X
RCT	TEAM	X	X	X	X	X	X	X	
RCT	SOFT	X	X	X	X	X	X	X	X
RCT	FACE	X	X	X	X	X	X	X	
RCT	DATA	X	X	X	X	X	X	X	X
RCT	SOLE	X	X	X	X	X	X	X	X
RCT	GEICAM/ 2006-10	X	X	X	X	X	X	X	
RCT	Kurebayashi (2017) NCT01546649	X	X	X	X	X	X	X	X
RWE	Kwak (2015)	X	X	X	X	X	X	X	
RWE	Alramadhan (2016)	X	X	X	X				
RWE	Shimazu (2019)	X	X	X	X	X	X		

Abbreviations: iDFS = invasive disease-free survival; RCT = randomized controlled trial; RFS = recurrence-free survival; RWE = real-world evidence; STEEP = standardized definitions for efficacy end points.
[a] Obtained from study by Hudis et al. [17].

Table 11
Comparability of patient baseline characteristics amongst studies reporting RFS for node-positive patients (subgroup).

Parameter	SOLE	FACE	Kwak (2015)
Study design	RCT	RCT	RWE
Age (median)	LC: 60[c] LI: 60[c]	L: 62[c] A: 62[c]	48.5[a]
Post-menopausal (%)	LC: 77[c] LI: 76[c]	L: 100 A: 100	51.5
T1 (%)	LC: 47[c] LI: 58[c]	L: 47[c, b] A: 45.5[c, b]	51.5
Stage 1 (%)	NR	0	25.2
ER+ (%)	LC: 98[c] LI: 97.9[c]	L: 98.4[c] A: 98.9[c]	93.2
PR+ (%)	LC: 80[c] LI: 78[c]	L: 79.8[c] A: 79.4[c]	81.6

Abbreviations: A = anastrozole; ER = estrogen receptor; L = letrozole; LC = continuous letrozole; LI = intermittent letrozole; NR = not reported; PR = progesterone receptor; RCT = randomized controlled trial; RFS = recurrence-free survival; RWE = real-world evidence.
[a] Mean age.
[b] Includes T1 and T0 patients.
[c] Full cohort (not exclusively HR+/HER2-).

definitions to ensure the appropriateness of combining and analyzing different studies. It was concluded that a combination of results across several studies reporting similar outcomes (either RFS or recurrence events) was not feasible. However, cross-trial heterogeneity was largely resolved upon isolation of a more narrowly defined subgroup of node-positive patients. In the meta-analysis of node-positive HR+/HER2- patients with low clinical heterogeneity, the probability of recurrence or death was 17.2% over 5 years. These findings indicate that the risk of recurrence or death in HR+/HER2- patients is greater than expected when patients have high-risk features such as node-positive status.

Although patients with key risk features such as node-positive status are seldom investigated exclusively in clinical trials, the results of published studies investigating risk factors for recurrence in HR+ disease are aligned with our findings [8,10]. In a longer-term assessment, Pan et al. assessed 88 trials of early-stage ER+ BC patients who received ET and found that the risk of distant recurrence in the first 5 years was closely related to number of positive nodes (6% in women without positive nodes and 22% in women with 4–9 positive nodes) [8]. Colleoni et al. noted that difference in recurrence risk according to nodal status was the highest in the first 5 years [10]. This work should be considered complimentary to the meta-analyses conducted by Pan et al., which were more broad and focused on numerous disease-related traits [8]. In contrast, our analyses considered the impact of heterogeneity by focusing on more narrowly defined subgroups in order to yield more precision in the effect estimates (ie., we considered nodal status within the HR+/HER2- population, and treatments that focused on endocrine therapy alone).

The existence of high-risk groups within the HR+/HER2- subtype indicates an unmet need in the treatment landscape for the prevention of recurrence. Several phase III studies evaluating the efficacy of cyclin-dependent kinase 4/6 inhibitors in the adjuvant setting for non-metastatic BC are ongoing [54–57]. In the context of the present study, the results of high-quality trial data considering high-risk patients as a compliment to data considering broader cohorts will allow clinicians to tailor treatments to the unique risk profiles of individual patients.

A strength of this review was its comprehensive search strategy, rigorously developed in collaboration with an experienced information specialist. Furthermore, we adhered to the PRISMA method to ensure complete and transparent reporting of studies. Combining clinically heterogeneous studies introduces the potential to bias pooled effect estimates, leading to inaccurate estimates of BC recurrence risk. Similarly, a comprehensive evaluation of cross-trial heterogeneity was critical to mitigating potential sources of bias.

This study should also be considered in the context of several limitations. Despite our efforts to minimize cross-trial imbalances by examining subgroups, baseline patient characteristics were often not reported for the target population. Therefore, it is possible that imbalances between subpopulations persisted, which may have led to underestimation of cross-trial heterogeneity. However, this was difficult to confirm without additional information that was not reported. Furthermore, our focus on patients with HR+/HER2- early BC limited the number of studies identified for this review. However, excluding other BC subtypes ensured identification of the existing evidence in addition to gaps in the literature
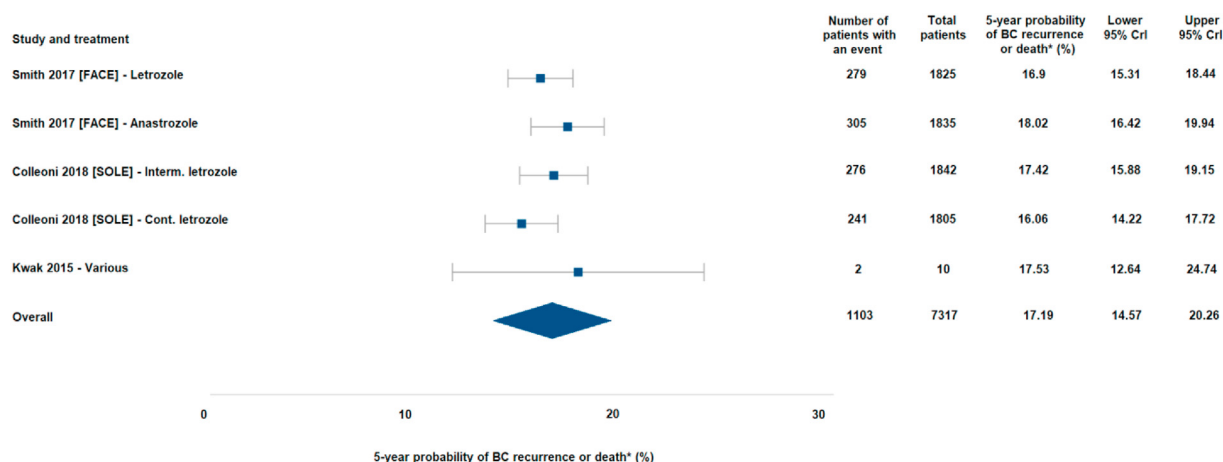
Fig. 2. Forest plot of the base-case meta-analysis of RFS events in HR+/HER2- node-positive patients from RCT and RWE.
Abbreviations: BC = breast cancer; CrI = credible interval. *Mean probability of patients experiencing a recurrence event was based on recurrence-free survival (RFS) events as defined by STEEP (any breast cancer recurrence or all-cause death).

related to real-world effectiveness and RCT data in these patients. The lack of studies evaluating recurrence in this subtype highlights a need for the investigation of risk factors involved in recurrence as well as potential targets for interventions to further reduce recurrence and potential metastases after diagnosis of HR+/HER2- early BC.

5. Conclusion

Although this study identified a dearth of evidence regarding HR+/HER2- BC recurrence in both RCT and real-world settings, a synthesis of published studies was feasible in order to ascertain the probability of recurrence or death in this population. Together with prior literature, our results indicate an unmet need to further reduce recurrence risk early in the treatment of patients with high-risk non-metastatic disease. Additional randomized and real-world studies investigating the risk of recurrence in HR+/HER2- early BC patients are needed to improve our understanding of this clinically heterogeneous disease.

Declarations of competing interest

EMS, AOR, AS, CC, and IAS have disclosed that they are employees of EVERSANA, who were paid consultants to Pfizer Inc in connection with the development of this manuscript. CC has disclosed that he is also a shareholder of EVERSANA. JC and EHL are employed by Pfizer Inc. EHL has disclosed that he is also a shareholder of Pfizer Inc.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.02.009.

Role of Funder

The funders had a role in study design and editorial assistance. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Author contributions

All authors made substantive intellectual contributions to this study to qualify as authors. All authors participated in study design through drafting or approval of the protocol. EMS, AOR, and IAS contributed to the literature search. EMS and AOR worked on data collection. EMS, AOR, AS, CC, and IAS analyzed and interpreted the data. EMS and IAS wrote the manuscript draft. EL and JC assisted with manuscript revisions. All authors reviewed and approved the final version of the manuscript.

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