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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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

https://doi.org/10.1016/j.breast.2021.02.009
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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+/HER2- 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 all 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 the 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 weighted 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 included 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
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% [39] for follow-up periods ranging from 4 to 11 years (Table 5) [39,45,46,48]. 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 DFS, 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].

Outcome terms 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 DCB 77C were appreciably high, which is consistent with the high-risk profile of recruited participants [32].

### 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 |
|-------|--------------|-----------------|----------------|-------------|--------------------------|----------------------------------------------------------|
| **BCRR** | **RWE** | **RCT** | **Phase** | **Blinding** | **Data Source** | **Parallel** | **1977–1982** | **Denmark** | **1716** | **Recurrence: 10 Survival: 30** | **BCRR** |
| **DBCG 77C** | | | III | Open-label | Parallel | | | | |
| **BIG 1–98** | | | III | Double-blind | Parallel | | | | |
| **TEAM** | | | | | | | | | |
| **SOFT** | | | III | Open-label | Parallel | | | | |
| **FACE** | | | IIIb | Open-label | Parallel | | | | |
| **DATA** | | | III | Open-label | Parallel | | | | |
| **SOLE** | | | III | Open-label | Parallel | | | | |
| **GEICAM/2006–10** | | | III | Open-label | Parallel | | | | |
| **Kurebayashi (2017)** | | | III | Open-label | Parallel | | | | |

| Study | Study Design | Enrolment Dates | Country/Region | Patients (n) | Median Follow-up (years) | Recurrence Descriptors Reported for HR+/HER2- eBC Patients |
|-------|--------------|-----------------|----------------|-------------|--------------------------|----------------------------------------------------------|
| **Moon (2011)** | | | | | | |
| **Ohnstad (2017)** | | | | | | |
| **Wright (2012)** | | | | | | |
| **Laenkholm (2018)** | | | | | | |
| **Ohara (2015)** | | | | | | |
| **Sohn (2016)** | | | | | | |
| **Kwik (2015)** | | | | | | |
| **Babacan (2015)** | | | | | | |
| **Park (2017)** | | | | | | |
| **Sun (2014)** | | | | | | |
| **Alramadhan (2016)** | | | | | | |
| **Shimazu (2019)** | | | | | | |

| Study | Study Design | Enrolment Dates | Country/Region | Patients (n) | Median Follow-up (years) | Recurrence Descriptors Reported for HR+/HER2- eBC Patients |
|-------|--------------|-----------------|----------------|-------------|--------------------------|----------------------------------------------------------|
| **Country/Region** | **Patients (n)** | **Median Follow-up (years)** | **Recurrence Descriptors Reported for HR+/HER2- eBC Patients** |
| **Korea** | **819** | **6.4** | **DFS** |
| **Norway** | **653** | **7.1** | **DDFS** |
| **United States** | **582** | **3.7** | **DFS** |
| **Japan** | **2558** | **9.2** | **DFR, TTR** |
| **Japan** | **184** | **3.8** | **RFS** |
| **Turkey** | **634** | **NR** | **DFS/PFS** |
| **Korea** | **851** | **4.3** | **DDFS** |
| **China** | **541** | **4.4** | **RFS** |
| **Korea** | **406** | **4.3** | **DFS, DR, any R** |
| **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; RWE — real-world evidence; TTR — time to recurrence.

### 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 DDFFS at 8 years was 74.3% for high-risk patients as defined by ROR grouping [49].
| Study             | Design | Intervention Model | Intervention Model | Comparator | Additional Therapies |
|------------------|--------|--------------------|--------------------|------------|---------------------|
| DBCG 77C         | RCT, OL| Parallel           | Tamoxifen 10 mg, three times daily | 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 20 mg daily, 2.5-3 years followed by exemestane 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 20 mg daily, 5 years or Triptorelin or bilateral oophorectomy or bilateral ovarian irradiation | 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) Year 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 1 mg daily, 5 years or Fulvestrant 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 | Comparator                  | Additional Therapies                                                                 |
|------------------|--------|--------------|-----------------------------|--------------------------------------------------------------------------------------|
| Moon (2011)      | RWE, R | Single-arm   | Tamoxifen 20 mg daily, 24 months or Tamoxifen followed by switch to AI NR | • Axillary nodal involvement or high-risk node-negative: CMF, PAC, AC followed by taxanes, AC, others • Some patients: whole-breast radiotherapy |
| Ohnstad (2017)   | RWE, R | Single-arm   | Tamoxifen 5 years           | -                                                                                    | • Some patients: chemotherapy (platinum/anthracycline/taxane, anthracycline/taxane, trastuzumab-containing, other or unknown • Some pre-menopausal patients: LHRHa |
| Wright (2012)    | RWE, R | Single-arm   | • Premenopause: tamoxifen • Postmenopause: AI NR | -                                                                                   | • Some patients: chemotherapy (platinum/anthracycline/taxane, anthracycline/taxane, trastuzumab-containing, other or unknown • Some pre-menopausal patients: LHRHa |
| Laenholm (2018)* | RWE, R | Single-arm   | Tamoxifen or AI 5 years     | -                                                                                    |                                                                                       |
| 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 3.6 mg/kg; 3.75 mg/kg; 2 years or Tamoxifen 20 mg daily, 5 years | -                                                                                    |                                                                                       |
| Kwak (2015)*     | RWE, R | Parallel     | • Premenopause: tamoxifen • Premenopause: oophorectomy or GnRHa • Postmenopause: AI 5 years | Chemotherapy NR                                                                      |                                                                                       |
| Babacan (2015)   | RWE, R | Parallel     | Tamoxifen and/or AI NR      | • AC • Tamoxifen and/or AI NR                                                        |                                                                                       |
| Park (2017)      | RWE, R | Parallel     | Tamoxifen or NR             | • AC followed by docetaxel NR                                                        | Some patients: GnRHa (3.6 mg) every |
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 [31,33,35,37,40], whereas the remaining 3 trials did not report whether their definitions considered a secondary 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).

| 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.

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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-
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.

Table 4

| First Author (year) or NCT record number | Intergroup Difference | Treatment (RFS) | Comparator (RFS) |
|----------------------------------------|-----------------------|-----------------|-----------------|
|                                       | Effect Estimate       | 95% CI | p-value | Treatment | Proportion | Treatment | Proportion (95% CI) |
| 96-week (2 year) DFS                  |                       |       |         |           |            |           |                  |
| Kurebayashi et al. (2017), NCT01546049 | 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) |
| Ruiz-Borrego et al. (2019), NCT00543127 [GECAM/2006–10] | HR: 0.96 (95% CI: 0.82 - 1.13) | -1.13 | NR | Letrozole | 84.7% (95% CI: 82.9 - 86.3) | Anastrozole | 90.8% (95% CI: 88.0 - 93.6) |
| Smith (2017) [FACE]                   | HR: 0.79 (95% CI: 0.61 - 0.97) | -0.103 | 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 (95% CI: 0.94 - 1.33) | -1.33 | NR | Intermittent letrozole | 85.0% | Continuous letrozole | 86.6% |
| Francis (2015) [SOFT]                 | HR: 0.88 (95% CI: 0.69 - 1.13) | -1.13 | NR | Tamoxifen + DFS | 86.3% (95% CI: NR) | Tamoxifen | 85.3% (95% CI: NR) |
| 7-year DFS                            |                       |       |         |           |            |           |                  |
| Ruiz-Borrego et al. (2019), NCT00543127 [GECAM/2006–10] | HR: 0.84 (95% CI: 0.58 - 0.52) | 0.352 Anastrozole + fulvestrant | 86.9% (95% CI: 83.3 - 90.6) | Anastrozole | 83.3% (95% CI: 79.2 - 87.5) |
| Filho (2015) [BIG 1–98]               | HR for ILC: 0.31 (95% CI: 0.17 - 0.58) | -0.43 | NR | Letrozole | 82% (95% CI: NR) | Tamoxifen | 66% (95% CI: NR) |
|                                       | HR for IDC: 0.65 (95% CI: 0.43 - 0.97) | -0.94 | NR | Anastrozole (3 years) | 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.

Table 5

| First Author (year) | Outcome | Follow-up | Event-free (%) |
|---------------------|---------|-----------|----------------|
| Moon (2011)         | RFS     | 10 years  | 88.6           |
| Sun (2014)          | RFS     | 5 years   | Luminial A: 96.5 |
|                     |         |           | Luminial B: 88.4 |
| Ohara (2015)        | RFI     | 3.8 years | 91.3           |
| Söhü (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.

* Values obtained by digitizing available Kaplan-Meier curves.

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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
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.

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

| Study Design | STEEP: iDFS | Local/Regional Breast浸润 | Distant Recurrence | Death from Breast Cancer | Death from Non-Breast Cancer | Death from Unknown Cause | Invasive Contralateral Breast Cancer | Second Primary Invasive Cancer (non-breast) |
|-------------|-------------|---------------------------|-------------------|-------------------------|---------------------------|------------------------|-----------------------------------|-----------------------------------|
| RCT BIG 198 | X           | X                         | X                 | X                       | X                        | X                      | X                                  | X                                  |
| RCT TEAM    | X           | 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                                  | 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 | X |
| RCT Kurebayashi (2017) | X | X | X | X | X | X | X | X |
| RCT Kwak (2015) | X | X | X | X | X | X | X | X |
| RCT Alramadhan (2016) | X | X | X | X | X | X | X | X |
| RCT Shimazu (2019) | X | X | X | X | X | X | X | X |

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

| Parameter | SOLE | FACE | Kwak (2015) |
|-----------|------|------|-------------|
| Age (median) | LC: 60 | L: 62 | 48.5 a |
| | LI: 60 | A:62 | |
| Post-menopausal (%) | LC: 77 | L: 100 | 51.5 |
| | LI: 76 | A: 100 | |
| T1 (%) | LC: 47 | L: 47 a | 51.5 |
| | LI: 58 | A: 45.5 b | |
| Stage 1 (%) | NR | 0 | 25.2 |
| ER+ (%) | LC: 98 c | L: 98.4 | 93.2 |
| | LI: 97.9 | A: 98.5 | |
| PR+ (%) | LC: 80 | L: 79.8 | 81.6 |
| | LI: 78 | A: 79.4 | |

### 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; STEEP = standardized definitions for efficacy end points.

a Obtained from study by Hudis et al. [17].
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.

Funding

Sponsorship for this study was provided by Pfizer Inc.

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.

Acknowledgements

The authors thank Rana Qadeer for his analytical insights and Ashfaqul Azraf for his editorial assistance. The authors also thank Catarina Aniceto da Silva, Sheryl Fogarty, and Becky Skidmore for assistance with the literature review.

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.

References

[1] Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst 2014;106(5):dju055.
[2] DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, et al. Breast cancer statistics, 2019. CA. Canc J Clinic 2019;69(6):438-51.
[3] Waks AG, Winer EP. Breast cancer treatment: a review. Jama 2019;321(3):288-300.
[4] Yang SX, Polley EC. Systemic treatment and radiotherapy, breast cancer subtypes, and survival after long-term clinical follow-up. Breast Canc Res Treat 2019;175(2):287-95.
[5] Hoelerlin LA, E Challant C, Park MA. Challenges in the treatment of triple negative and HER2-overexpressing breast cancer. J Surgery Sci 2013;1(1):3-7.
[6] Baioc M, Thomsen C, Wurztlein R, Canant M, Harbeck N, St. Gallen/vienna 2019: a brief summary of the consensus discussion on the optimal primary breast cancer treatment. Breast Care 2019;14(2):103-10.
[7] Rao RD, Cobleigh MA. Adjuvant endocrine therapy for breast cancer. Oncology (Williston Park) 2012;26(6):541-7; 550, 552 passim.
[8] Pan H, Gray R, Braybrooke J, Davies C, Taylor C, et al. 20-Year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. N Engl J Med 2017;377(19):1836-46.
patients enrolled in the BDCG 77C trial. Eur J Canc 2014;50(8):1412.

Kurebayashi J, Toyama T, Sumino S, Miyajima E, Fujimoto T, Efficacy and safety of letrozole 2.5 mg: a 2-year phase 3 randomised, double-blind, placebo-controlled trial in postmenopausal women with hormone receptor-positive breast cancer: the J-ALEX trial. Lancet Oncol 2017;18(1):161–70.

Wangchinda P, Ithimakin S. Factors that predict recurrence later than 5 years after initial treatment in operable breast cancer. World J Surg Oncol 2015;13:60.

E.M. Salvo, A.O. Ramirez, J. Cueto et al. The Breast 57 (2021) 5
plus fulvestrant on overall survival in hormone receptor–positive, ERBB2-
negative breast cancer that progressed on endocrine therapy—MONARCH 2:  
a randomized clinical trial. JAMA Oncol 2020;6(1):116–24.

[55] Im S-A, Lu Y-S, Bardia A, Harbeck N, Colleoni M, et al. Overall survival with  
ribociclib plus endocrine therapy in breast cancer. N Engl J Med 2019;381(4):  
307–16.

[56] National Library of Medicine (U.S.). A Study of palbociclib in addition to  
standard endocrine treatment in hormone receptor positive Her2 normal  
patients with residual disease after neoadjuvant chemotherapy and surgery  
(PENELOPE-B). Identifier NCT01864746. Available online at: https://  
clinicaltrials.gov/ct2/show/record/NCT01864746; 2021. 2013, May 14,  
February 2.

[57] Mayer E, DeMichele A, Gnant M, Barry W, Pfeiler G, et al. Abstract OT3-05-08:  
PALLAS: PALbociclib CoLlaborative Adjuvant Study: a randomized phase 3  
trial of palbociclib with standard adjuvant endocrine therapy versus standard  
adjuvant endocrine therapy alone for HR+/HER2– early breast cancer. Canc  
Res 2018;78(4 Supplement). OT3-05-08.