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Review

Safety of menopausal hormone therapy in breast cancer survivors older than fifty at diagnosis: A systematic review and meta-analysis

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ABSTRACT

Due to the higher incidence of hormone responsive tumours in women >50, the safety of hormone replacement therapy (HRT) in older breast cancer survivors may differ from younger age groups. The primary outcome in this review was the risk of tumour recurrence and secondary outcome the relationship with breast cancer-related mortality. Medline, CINAHL, Cochrane, Google Scholar and EMBASE databases were searched through August 2018 for studies reporting exposure to HRT in survivors ≥50 at primary diagnosis. Random effects models were used to estimate the combined relative risk (RR) of tumour recurrence and breast cancer-related mortality using the Mantel-Haenszel method and the quality of evidence determined for the primary outcome. Overall, nine studies (four cohort, one case-control, four RCTs; n = 16,002) were included. Very low quality evidence from observational studies demonstrated no adverse effect on tumour recurrence with HRT use (RR 0.80, 95% CI 0.53 to 1.19; $I^2 = 66\%$; n = 11,984), while moderate quality evidence from RCTS demonstrated an adverse effect (RR 1.46, 95% CI 1.20 to 1.77; $I^2 = 17\%$; n = 4108). Similarly, observational studies demonstrated no adverse effect on breast cancer-related mortality (RR 0.32, 95% CI 0.21 to 1.49; $I^2 = 0\%$, n = 2182), while RCTs demonstrated a non-significant higher risk (RR 1.07, 95% CI 0.77 to 1.49; $I^2 = 0\%$; n = 3918). Ultimately, despite conflicting findings, evidence of sufficient quality suggests that HRT may increase the risk of tumour recurrence in older survivors. However, adverse effect on mortality is unlikely. Caution with HRT use in survivors is further advised.

Contents

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1. Introduction

The GLOBOCAN (Global Cancer Observatory) 2018 estimates reflect that slightly over two million new cases of breast cancer were diagnosed in women worldwide as at September 2018 and approximately 600,000 related deaths had been reported [1], an incidence that is markedly higher than previous years [2]. Based on these same estimates, by the year 2035 approximately 2.6 million women will be diagnosed with the disease annually worldwide, with approximately 850,000 related deaths [3], highlighting a need for effective preventive strategies.

The peak incidence of breast cancer in women is between the ages 50–69, coinciding with the period during which women often experience menopausal symptoms [4]. The decline in sex hormone levels during menopause can have both short-term and long-term effects on a woman's health. Short-term effects of deficiency may present as either psychological, urogenital or vasomotor symptoms, the most common of which are hot flashes, night sweats and palpitations, while long-term effects include osteoporosis and cognitive impairment [5]. In women undergoing bothersome menopausal symptoms, the use of hormone replacement therapy (HRT) plays a central role in preventing or managing these effects, which if uncontrolled may impair their quality of life [6]. However, research has demonstrated that use of HRT is associated with a higher incidence of primary breast cancer in this group of women, with an attributable risk of approximately 8 more cases per 1000 users of combined oestrogen-progestin therapy [4].

The symptoms of menopause in women previously treated for breast cancer often do not occur through the usual process of reproductive ageing but as a more intense and accelerated consequence of the chemotherapy and endocrine treatments instituted for cancer management [7]. The use of chemotherapy has a cytotoxic effect on the ovaries that results in premature ovarian failure in 20%–80% of those affected, essentially resulting in sex hormone deficiency as the ovary is the primary site for oestrogen production [8]. Among women diagnosed with breast cancer at an older postmenopausal age (≥50), this scenario is often further complicated by the need to discontinue any form of ongoing sex hormone replacement therapy, more so if the diagnosis is of a hormone responsive tumour, following the documented association of oestrogen based therapies with a higher risk of the disease [9].

Older breast cancer survivors are therefore often forced to suffer through the short-term and long-term effects of sex hormone deficiency, this being a result of their unwillingness to use therapy and a reluctance among clinicians to restart HRT after the primary cancer treatment for fear of recurrence [7].

The available scientific evidence on the safety of HRT in breast cancer survivors is limited and evidence is lacking on the appropriateness of therapy use in women diagnosed at an older postmenopausal age (≥50), a sub-group of interest given the increase in frequency of hormone responsive tumours with increasing age [2,10]. In women >50, it has been hypothesised that the potential risk of disease recurrence may differ from younger women, who often have non-hormone responsive disease [11,12]. Previous systematic reviews on this topic, in women across all ages or of younger age at primary diagnosis (<50), have found conflicting evidence [8,13–15].

Meurer and Lena [14], from observational studies, demonstrated a non-significant lower risk of tumour recurrence in survivors across all ages, relative risk (RR) 0.72 (95% confidence interval [CI], 0.47–1.10), and a lower risk of all-cause mortality, RR 0.18 (95% CI, 0.10–0.31), with HRT use. Batur and colleagues [15] demonstrated similar findings with a lower risk of breast cancer-related deaths among HRT users, odds ratio (OR) 0.3 (95% CI, 0.0–0.6), and a 50% lower risk of tumour recurrence, OR 0.5 (95% CI, 0.2–0.7). However, Col and colleagues [13] demonstrated a higher risk of tumour recurrence with HRT use from randomised controlled trials (RCTs), RR 3.41 (95% CI 1.59–7.33), while observational studies suggested a lower risk, RR 0.64 (95% CI 0.50–0.82), in survivors across all ages. In a recent systematic review by Wang and colleagues which focussed on younger premenopausal survivors (<50) [8], observational studies demonstrated a nonsignificant higher risk of tumour recurrence, RR 1.04 (95% CI, 0.45–2.41), while RCTs also suggested a higher risk, hazard rate (HR) of 1.56 (95% CI, 1.1–2.2).

It is evident that there is no conclusive data on the appropriateness and safety of HRT use in older breast cancer survivors, diagnosed at an age ≥50. The primary outcome of this meta-analysis was the risk of tumour recurrence. Secondary outcomes included the relationship with breast cancer-related mortality.

2. Materials and methods

2.1. Search strategy

The protocol for this review was registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42018106389 [16]. A search of the Medline, CINAHL, Cochrane Library, Google Scholar and EMBASE databases was run from inception through August 2018. The search terms used were: oestrogen replacement therapy, oestrogen-progestin therapy, hormone replacement therapy, tibolone, breast cancer, breast neoplasm, breast tumour, survival, survivor,

recurrence, relapse, menopause and menopausal. An example of the electronic search strategy, as used in the EMBASE database, is illustrated (see Appendix A - Table A1). Additionally, to ensure literature saturation, the reference lists for all included studies were searched for relevant articles.

2.2. Eligibility criteria

Based on the study characteristics, we limited inclusion to studies that were RCTs, quasi-experimental and observational cohort or case-control, had a population of female breast cancer survivors predominantly ≥50 at primary diagnosis (mean age ≥ 50), a reported exposure to either conventional oestrogen-based HRT or the non-conventional synthetic steroid tibolone, a comparator arm on no treatment or on any alternative non-hormonal treatment and reported on breast cancer recurrence in either absolute numbers, proportions, RRs, ORs or HRs. We excluded single-arm studies with no comparator group. Similarly, to prevent population duplication, studies that reported on overlapping or similar participants were excluded in favour of the most recent publication or that with the largest sample size.

Based on the report characteristics, we included all studies regardless of setting. However, due to limitations on language translation, only reports published in English were included. The grey literature was also excluded due to potential for lack of a robust or verifiable peer review process.

2.3. Study selection

The selection of studies was done through a three stage process. In the first stage, a preliminary screening of the titles and abstracts from retrieved articles was performed by one researcher (GHM). Relevant articles from each database were identified and duplicated reports excluded.

In the second stage, full-text screening of all shortlisted studies for eligibility against the established criteria was performed independently by two researchers (GHM and MA) and any conflicts resolved through a common agreement. Finally, a manual search of the references in the eligible studies was done by one researcher (GHM) and relevant articles also screened for eligibility by two researchers (GHM and MA). In studies that did not provide sufficient information for determining eligibility, correspondence was made with the authors via email. If no response was received within six weeks, the studies were deemed ineligible.

2.4. Data extraction

Relevant data were extracted independently by one researcher (GHM) from all eligible studies and verified through a repeat process by the same researcher. Information was obtained on demographic factors (region), disease or prognostic factors (mean age at primary diagnosis, tumour stage, hormone receptor status, nodal status), treatment factors (type of HRT, dosage, treatment duration, type of treatment in comparator group, duration of follow-up) and the outcome measures (counts of recurrent events or deaths and the RRs, ORs or HRs).

2.5. Risk of bias assessment

The risk of bias assessment, based on the main outcome of tumour recurrence, was done at both the individual study level and across all studies by one researcher (GHM) and random studies selected for independent verification by two researchers (MA and KAM). Quality assessment of observational studies was based on the Newcastle-Ottawa Scale (NOS) [17] and that of the RCTs was based on the seven evidence-based domains in the Cochrane's Collaboration risk of bias tool version 1.0 [18].

Using the NOS scale for observational studies, a single score was awarded for each item satisfied in each of the domains, with a maximum of four scores in the selection domain, two scores in the comparability domain and three scores in the exposure, for case-control studies, or outcome, for cohort studies, domain. Overall, the quality of observational studies was grouped into three. The first group comprised poor quality studies which had no score or only one score in the selection domain, no score in the comparability domain and no score or only one score in the exposure or outcome domain. The second group comprised fair quality studies which had a score of two or three in the selection domain, one score in the comparability domain and a score of two or three in the exposure or outcome domain. Finally, the third group comprised good quality studies which had a score of three or four in the selection domain, one score in the comparability domain and a score of two or three in the exposure or outcome domain.

For the purpose of this review, the comparability domain in the NOS scale was modified to have nodal status as the most important confounding factor, based on evidence that nodal involvement is the most significant determinant of breast cancer recurrence and mortality after treatment [19]. Any study which controlled for nodal status, among other factors, received an extra score in the comparability domain. Additionally, in evaluating the adequacy of cohort follow-up, a minimum duration of at least five years (60 months) was considered to be sufficient based on evidence that most cases of breast cancer relapse occur within the first five years [20].

Lastly, to assess the risk of publication bias, the Begg and Mazumdar rank correlation test was performed [21].

2.6. Data analysis

Due to the inherent biases in observational studies of drug use and the methodological differences between RCTs and observational investigations on the effects of treatment [22], this systematic review adopted a thematic approach to discussion based on the study design. The eligible studies were appropriately grouped and assessed on the risk of breast cancer recurrence with HRT use and its associated mortality. Since all data were categorical, the risk ratio (RR) was used as the primary effect measure. Random effects meta-analysis, using the Mantel-Haenszel (M-H) method, were performed for both observational studies and RCTs. This gave a pooled estimate of the risk of breast cancer recurrence or breast cancer-related mortality, the corresponding 95% CI and the p-value.

Heterogeneity was determined using the chi-square test for homogeneity and the I^2 statistic. Where significant heterogeneity was observed, a random effects meta-regression analysis, using the restricted maximum likelihood method (REML), was performed to investigate the relationship between the length of follow-up, study design and study quality with the reported risks. All statistical analysis were done using RevMan version 5.3 (meta-analysis) and the comprehensive meta-analysis software (CMA) version 3 (meta-regression), with a level of significance set at 0.05.

Finally, the overall quality of evidence on the main study outcome, tumour recurrence, was assessed based on the GRADE approach [23] and the results presented in a summary of findings table.

3. Results

In total, 1286 potential articles were identified. After the removal of 501 duplicates, the remaining studies were examined based on the title, abstract and full-text for eligibility (see Fig. 1.). Seven studies fulfilled the eligibility criteria, including four cohort

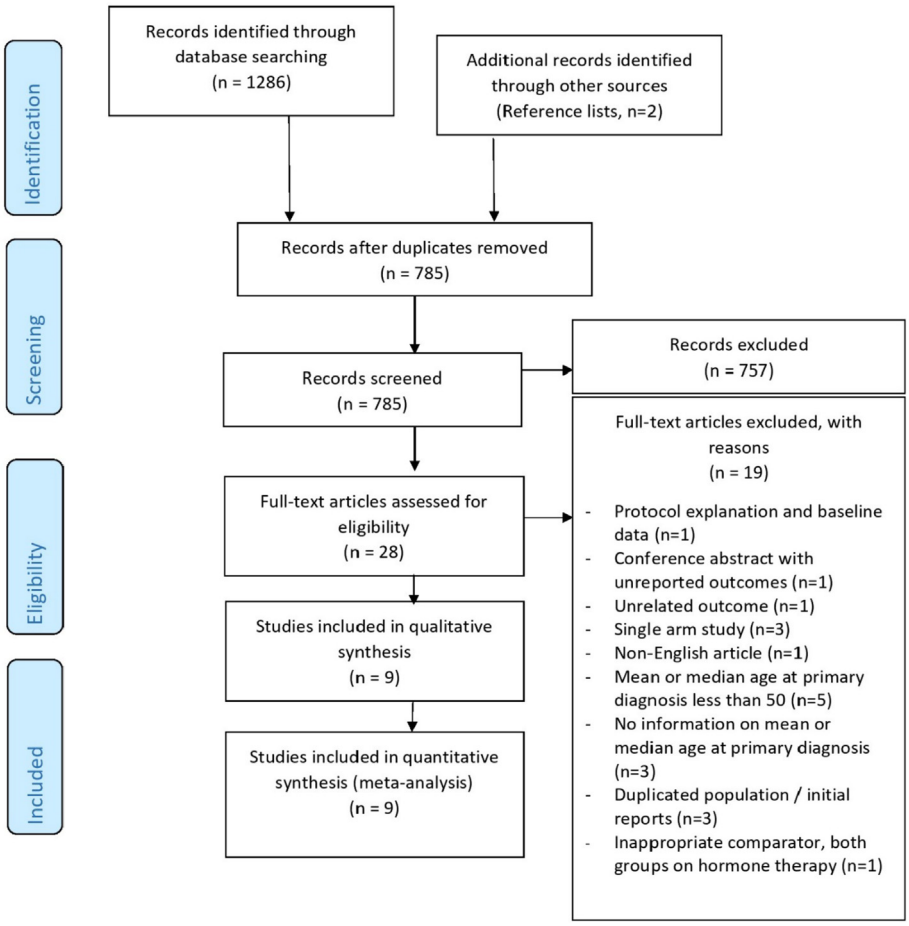

Fig. 1. Flow diagram of the study selection.

studies [24–27], one case-control study [28] and two RCTs [29,30]. A search of the reference lists from these studies identified two additional RCTs that were eligible [31,32]. In total, nine studies were included in the final qualitative and quantitative synthesis.

Nineteen studies were excluded after full-text screening. One study was a protocol with only baseline data, one had no outcome information, one study reported on the prognosis of incident tumours among HRT users, three were single arm studies, one was a non-English publication, three were duplicated populations for which the most recent report or largest sample was included and one had both study groups on HRT (see Appendix B – Table B2). In five studies, the mean age at primary diagnosis of breast cancer was <50 [33–37], whereas three studies did not give the population age at primary diagnosis or any information that would have guided its estimation [12,38,39]. For the latter group, correspondence was made with the authors for relevant age information but no feedback had been received by the time this review was concluded.

A total population of 16,002 female breast cancer survivors were included in this review, drawn mainly from the United States (US) [24–26], the Australasian region [27,31] and the United Kingdom (UK) or Europe [28–32]. The reasons for HRT use varied from the more immediate vasomotor and vaginal symptoms to the prevention of osteoporosis and in one study [25], some women received HRT for cardiovascular disease prevention, an indication that is no longer recommended [40]. The average duration of follow-up for both HRT users and non-users varied from 6 months in the UK pilot trial [32] to 10.8 years in the extended follow-up of the Stockholm trial [30].

3.1. Results and characteristics of observational studies

Observational studies included a total of 11,984 breast cancer survivors, predominantly from the US, UK and Australia. Majority of the women were survivors of an early stage breast cancer diagnosis [24–27].

The characteristics of the studies are shown in Table 1. The mean age at primary diagnosis among HRT users varied from 52 years [26] to 57.6 years [25]. Among the non-users, the age varied from 52.2 years [26] to 64.7 years [25]. One included study did not report the mean age at primary diagnosis [24]. In this study, approximately 70% of both the HRT users and non-users were ≥55 at primary diagnosis and having received no feedback correspondence from the authors, a decision was made to include this population.

3.1.1. Breast cancer recurrence

Tumour recurrence was the main outcome in all studies, assessed through either cancer registries or patient medical records. The definition of recurrence in four studies [25–28] included any second breast cancer event, hence all local, regional, distant metastatic and contralateral disease events. One study [24] did not consider contralateral disease as a recurrent event, including only ipsilateral and distant metastatic events.

Two of the five studies, both American, observed a non-significant higher risk of tumour recurrence with HRT use, RR 2.0 (95% CI 0.69–5.82, $p = 0.203$) [26] and RR 1.44 (95% CI 0.71–2.94, $p = 0.314$) [25]. In the former study [26], an analysis of the 4-year disease free rate further demonstrated an advantage to non-users

Table 1
Results and characteristics of individual studies.

Study	Design	Participants and Setting	Sample size	Age at diagnosis (mean, SD)	Nodal status	Stage	ER/PgR status	Follow-up duration (years, SD)	Treatment		Outcome	
									Type	Duration (years, SD)	Recurrence	Cancer-related mortality
Le Ray et al., 2012 [28]	Case-control	13, 479 women in the United Kingdom.	Cases n = 917	63.1	NR	NR	NR	3.1 (1.8)	Vaginal oestrogen (cream/tablets)	NR	21	NR
			Controls n = 8885	63.1	NR	NR	NR	3.1 (1.8)	None		274	NR
Di Saia et al., 1996 [26]	Cohort	41 patients and 82 matched comparison from a USA cancer registry.	Users n = 41	52.0	NR	Insitu, I, IIA, IIB, IIIA	NR	9	Conjugated oestrogen 0.625 mg with MPA 2.5 mg/day	NR	6	2
			Non-users n = 82	52.2	NR	Insitu, I, IIA, IIB, IIIA	NR	9	None	NR	6	6
Durna et al., 2002 [27]	Cohort	1122 postmenopausal Australian women.	Users n = 286	55.8	Positive (n = 262)	I - IV	NR	5.8 (0–29)	Continuous combined oestrogen (0.625 mg CEE daily) with progestin (10–500 mg MPA/1–5 mg NETA daily); vaginal oestrogen (cream 0.5g/tablets 25 mcg twice weekly); vaginal oestrogen with progestin; oral or transdermal oestrogen alone	1.75 (0–26)	44	13
			Non-users n = 836	63.7	Positive (n = 731)	I - IV	NR	5.1 (0–36)	None	NR	247	122
Natrajan et al., 1999 [25]	Cohort	American women diagnosed with breast cancer on follow-up at a private clinic	Users n = 50	57.6 (3.36)	Positive (n = 3); Negative (n = 47)	I	ER Positive (n = 12); PgR Positive (n = 8)	6.9 (0.7)	Estradiol 25/50 mg and testosterone 75/150/225 mg implants; Oral/transdermal oestrogen and megestrol acetate 20–40 mg for 10–25 days/MPA 10 mg for 10–13 days/NETA 2.5–5 mg	5.5 (2.53)	24	2
			Non-users n = 18	64.7	NR	NR	NR	4.2 (0.5)	None	10	6	5
O'Meara et al., 2001 [24]	Cohort	869 American women enrolled in the Group Health Cooperative and diagnosed with invasive breast cancer between 1977 and 1994	Users n = 174	>50	Positive (n = 31)	I - III	ER Positive (n = 84); PgR Positive (n = 71)	3.7	Unopposed oestrogen (esterified/ethinyl estradiol/dienestrol/estradiol); Combined oestrogen-progestogen	1.25	16	5
			Non-users n = 695	>50	Positive (n = 175)	I - III	ER Positive (n = 409); PgR Positive (n = 311)	NR	None	NR	101	59
Holmberg et al., 2008 [29]	RCT	Scandinavian women (Sweden, Finland, Norway) who had completed primary cancer treatment.	Users n = 221	53.5	Positive (n = 44)	0, I, II	ER positive (n = 139)	4.1 (0.01–7.8)	Continuous or sequential oestradiol hemihydrate with NETA; unopposed medium potency oestradiol	23 m (0–80)	39	6
			Non-users n = 221	52.6	Positive (n = 42)	0, I, II	ER Positive (n = 122)	4.0 (0.27–7.7)	Acupuncture		17	5
Fahlen et al., 2013 [30]	RCT	Postmenop-ausal Swedish women <70 who had undergone primary surgery for breast cancer	Users n = 188	54.4	Positive (n = 31); Negative (n = 127)	NR	ER Positive (n = 113); ER Negative (n = 22)	10.8 (6.2–12.6)	Cyclic oestradiol 2 mg for 21 days and MPA 10 mg for 10 days (women < 55); Spaced out oestradiol 2 mg for 84 days and MPA 20 mg for 14 days (women > 55); Unopposed oestradiol valerate 2 mg/day	2.6 (1.2)	60	10

(*continued on next page*)

Table 1 (*continued*)

Study	Design	Participants and Setting	Sample size	Age at diagnosis (mean, SD)	Nodal status	Stage	ER/PgR status	Follow-up duration (years, SD)	Treatment		Outcome		
									Type	Duration (years, SD)	Recurrence	Cancer-related mortality
			Non-users n = 190	55.2	Positive (n = 37); Negative (n = 112)	NR	ER Positive (n = 103); ER Negative (n = 29)	10.8 (6.2–12.6)	None	NR	48	11
Kenemans et al., 2009 [31]	RCT	Postmenop-ausal women <75 years old at multiple centres in Europe and the Australasia region. Surgically treated within 5 years for T1-3,N0-2,M0 breast cancer	Users n = 1556	50.4	Positive (n = 898)	0, I, IIA, IIB, IIIA, IIIB	ER Positive (n = 1112); PgR Positive (n = 978)	3.07 (0.01 –4.99)	Tibolone 2.5 mg daily	2.74 (0.01 –4.79)	237	54
			Non-users n = 1542	50.8	Positive (n = 894)	0, I, IIA, IIB, IIIA, IIIB	ER Positive (n = 1073); PgR Positive (n = 922)	3.14 (0.01 –4.94)	Placebo	2.76 (0.01 –4.72)	165	49
Marsden et al., 2000 [32]	RCT	Postmenop-ausal women in the UK with early stage breast cancer on follow-up at the Royal Marsden and St. George's Hospitals	Users n = 51	54.7	NR	I, II	NR	0.5	Estradiol valerate 2 mg/d (hysterectomised); Estradiol valerate with levonorgestrel 75mcg/day for 12–28 days (non-hysterectomised)	0.5	2	NR
			Non-users n = 49	52.0	NR	I, II	NR	0.5	None	0.5	1	NR

NETA = norethisterone acetate; NR = not reported; ER = oestrogen receptor; MPA = medroxyprogesterone acetate; CEE = conjugated equine oestrogen; PgR = progesterone receptor.

over HRT users, 86% and 74% respectively. One study reported a non-significant lower risk of tumour recurrence with HRT use, RR 0.74 (95% CI, 0.48–1.15, p = 0.175) [28], adjusting for group differences in obesity, smoking status and use of benzodiazepines did not significantly change the relationship, RR 0.78 (95% CI, 0.48–1.25, p > 0.05). Two studies reported a significant lower risk, adjusted RR 0.62 (95% CI, 0.43–0.87, p < 0.05) [24] and adjusted RR 0.50 (95% CI, 0.30–0.85, p < 0.05) [27]. The number of subjects with tumour recurrence for each study are shown in Table 1.

Hormone use varied from a daily combined regimen of 0.625 mg oestrogen and 2.5 mg medroxyprogesterone [26], varying strengths of oestradiol, with or without progesterone and testosterone implants [24], local vaginal oestrogen, given either as vaginal creams, vaginal tablets or pessaries [28], continuous combined oestrogen-progesterone regimen [27] and unopposed or combined regimen [24] (see Table 1).

Overall, the observational studies provide inconclusive evidence on the safety of HRT use. Individual results suggest that the effect of HRT treatment could be anything between a 50% lower risk of tumour recurrence [24] to a 200% higher risk [26].

3.1.2. Breast cancer-related mortality

Three studies demonstrated a significant lower risk of mortality from tumour recurrence after HRT use, RR 0.14 (95% CI, 0.03–0.68, p = 0.014) [24], adjusted RR 0.34 (95% CI, 0.13–0.91, p = 0.017) [24] and RR 0.40 (95% CI, 0.22–0.72, p < 0.05) [27]. One study [26] demonstrated a non-significant lower risk, RR 0.67 (95% CI, 0.14–3.16, p = 0.614). A comparison of the 4-year survival rate between HRT users and non-users in the latter study further demonstrated an advantage to users, 68.9% (±1.9) and 46.2% (±0.6) respectively. The number of tumour-related deaths for each study are shown in Table 1.

3.2. Results and characteristics of trials

The RCTs included a total of 4018 breast cancer survivors, predominantly from the Scandinavian countries [29,30], Australasian region [31], UK [32] and other parts of Europe [31]. Most of these women had a primary diagnosis of an early stage disease [29,31,32] or small histopathological tumours [30]. The characteristic of the studies are shown in Table 1.

The mean age at primary diagnosis of breast cancer among women randomised to HRT varied from 50.4 years in the LIBERATE (Livial Intervention following Breast Cancer: Efficacy, Recurrence And Tolerability Endpoints) trial [31] to 54.7 years in the UK pilot trial [32]. Similarly, among the non-users, the mean age varied from 50.8 years in the LIBERATE trial [31] to 55.2 years in the extended follow-up of the Stockholm trial [30].

3.2.1. Breast cancer recurrence

Three trials had tumour recurrence as the primary endpoint [29–31], assessed through mammograms, ultrasound, CT scans, X-rays, skeleton scintigraphy and needle aspiration biopsies. In these trials, recurrence included all new loco-regional, distant metastatic and contralateral events. However, in one study [32] the definition of a recurrent event was unclear as this was not the primary endpoint.

All four trials reported a higher risk of tumour recurrence with HRT use. Two studies reported significant results, the extended follow-up of the HABITS (Hormone Replacement After Breast Cancer – Is it safe?) trial [29], HR 2.2 (95% CI, 1.0–5.1) adjusted for group differences in age, receptor status, tamoxifen use, prior use of HRT and nodal status and the LIBERATE trial [31], HR 1.40 (95% CI, 1.14–1.70, p < 0.05). Additionally, in the extended follow-up of the HABITS trial [29], women on HRT had a higher 5-year

cumulative recurrence incidence of 22.2% as compared to 8.0% for non-users, an absolute difference of 14.2% (95% CI, 10.9–17.5). Two studies reported non-significant results, RR 1.92 (95% CI, 0.18–20.52, p = 0.589) in the UK pilot trial [32] and HR 1.3 (95% CI, 0.9–1.9, p > 0.05) in the extended follow-up of the Stockholm trial [30]. The number of recurrent events for each study are shown in Table 1.

Hormone use varied from the conventional agents, that included oestradiol valerate or combined oestradiol with levonorgestrel [32], oestradiol hemihydrate with norethisterone or an unopposed medium potency oestradiol [29] and a cyclic or spaced out regimen of oestradiol followed by medroxyprogesterone acetate [30], to the nonconventional agent tibolone [31]. Only two studies detailed the control group treatment, the HABITS trial that used acupuncture and the placebo-controlled LIBERATE trial.

Overall, evidence from RCTs consistently demonstrate an adverse effect on tumour recurrence with HRT use. Individual results suggest that the effect of treatment is anything between a 30% [30] to a 120% [29] higher risk.

3.2.2. Breast cancer-related mortality

No trial demonstrated any significant adverse effect on mortality from tumour recurrence after HRT use, RR 1.20 (95% CI, 0.37–3.87, p = 0.761) [29], RR 1.09 (95% CI, 0.75–1.60, p = 0.656) [31] and RR 0.92 (95% CI, 0.40–2.11, p = 0.844) [30]. The number of tumour-related deaths for each study are shown in Table 1.

3.3. Risk of bias within studies

The risk of bias assessment for observational studies is summarised in Table 2. In the selection domain, the most frequent risk of bias was the inability to verify the absence of a recurrent event at the start of follow-up, affecting three studies [25–27], and the non-representativeness of HRT users, affecting two studies [25,26]. In the comparability domain, majority of the studies did not control for nodal status, posing an overall high risk of bias from its potential confounding effect. Overall, three observational studies were of good quality [24,27,28], one of fair quality [26] and one of poor quality [25].

The summary risk of bias assessment for RCTs is presented in Table 3. The most frequent risk was that of other biases and reporting bias, with all studies at an unclear risk in the former and two studies at an unclear risk in the latter [29,32]. Overall, all studies were at a low risk of selection, detection, attrition and performance biases.

3.4. Meta-analysis

Breast cancer recurrence

On pooled analysis, there was no evidence of a significant effect on tumour recurrence with HRT use from observational studies (RR 0.80, 95% CI 0.53–1.19; four cohort and one case-control study; 11,984 women) (see Fig. 2). However, trials demonstrated an adverse effect on tumour recurrence with HRT use (RR 1.46, 95% CI

Table 2
Summary risk of bias assessment for observational studies.

	Natrajan et al. [25]	O'Meara et al. [24]	Di Saia et al. [26]	Durna et al. [27]	Le Ray et al. [28]
Selection	✗	✓	✗	✓	✓
Representativeness of exposed cohort */Adequacy of case definition*					
Selection of non-exposed cohort */Representativeness of cases*	✗	✓	✓	✓	✓
Ascertainment of exposure */Selection of controls*	✗	✓	✓	✓	✓
Outcome not present at start */Definition of controls*	✗	✓	✗	✗	✓
Comparability	✗	✗	✗	✓	✗
Nodal status					
Other confounders	✗	✓	✓	✓	✓
Exposure / outcome	✓	✓	✓	✗	✓
Assessment of outcome */Ascertainment of exposure*					
Follow-up long enough (5 years) */Same method for ascertainment for cases and controls*	✓	✗	✓	✓	✓
Adequacy of cohort follow-up */Non-response rate*	✗	✓	✓	✓	✓
Overall score	2	7	6	7	8
Overall quality	Poor	Good	Fair	Good	Good

✓ Low risk of bias
✗ High risk of bias

Table 3
Summary risk of bias assessment for randomised trials.

	Marsden et al. [32]	Kenemans et al. [31]	Holmberg et al. [29]	Fahlen et al. [30]
Selection bias	✓	✓	✓	✓
Random sequence generation				
Allocation concealment	✗	✓	✓	✓
Performance bias	✓	✓	✓	✓
Blinding of participants and personnel				
Detection bias	✓	✓	✓	✓
Blinding of outcome assessment				
Attrition bias	✓	✓	✓	✓
Incomplete outcome data				
Reporting bias	✗	✗	✓	✓
Selective reporting				
Other biases	✗	✗	✗	✗

✓ Low risk of bias
✗ Unclear risk of bias

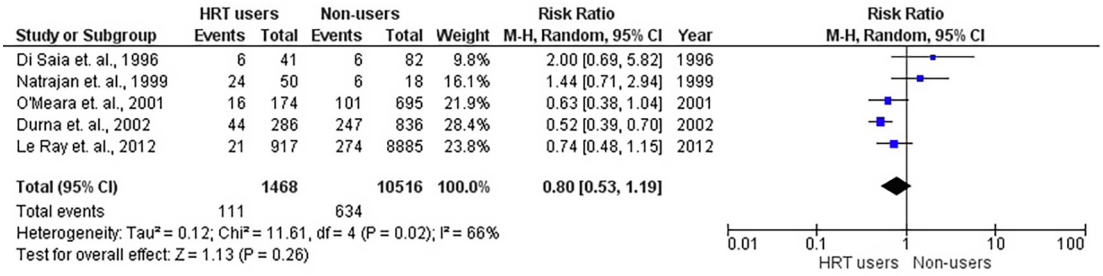

Fig. 2. Forest plot showing the relative risks (RR) of breast cancer recurrence in observational studies and the overall pooled estimate. HRT – hormone replacement therapy; CI – confidence intervals, M-H – mantel haenszel.

1.20–1.77; 4 trials; 4018 women) (see Fig. 3). Substantial heterogeneity was present with observational studies but not with the trials, $I^2 = 66\%$ ($p = 0.02$) and $I^2 = 17\%$ ($p = 0.31$), respectively.

3.4.2. Breast cancer-related mortality. Evidence from observational studies revealed a lower risk of death from tumour recurrence after HRT use (RR 0.32, 95% CI 0.21–0.49; four cohort studies; 2182 women), an absolute effect of 80 fewer deaths per 1000 users (see Figs. 4 and 6). However, there was no evidence of a significant relationship from the trials (RR 1.07, 95% CI 0.77–1.49; three trials; 3918 women), an absolute effect of only 2 more deaths per 1000 users (see Figs. 5 and 6). No significant heterogeneity was present.

3.5. Risk of bias across studies

The Begg and Mazumdar rank correlation test (one-tailed) did not present any evidence of publication bias for both the observational studies and RCTs, $p = 0.11$ and $p = 0.36$ respectively.

3.6. Additional analysis

Sensitivity analysis performed on the pooled estimate of tumour recurrence from observational studies, excluding the lowest quality study [25], demonstrated a change in the initial non-significant lower risk with HRT use to a marginally significant 31% lower risk, RR 0.69 (95% CI, 0.48–0.99; $p = 0.04$). A similar analysis with the RCTs, excluding the study with the highest risk of bias [32], did not significantly change the results.

Results of a meta-regression analysis demonstrated strong evidence that the observed risks of tumour recurrence differ depending on the study design ($p = 0.008$), with the risk likely to be higher with RCTs as compared to observational studies.

Meta-regression results also demonstrated that 97% of the substantial heterogeneity ($I^2 = 66\%$) observed with the pooled estimate from observational studies could be explained by differences in study quality ($r^2 = 0.97$; $p = 0.0092$). A similar analysis on the relationship between the duration of follow-up and the RR of tumour recurrence did not demonstrate any evidence of dependency ($p = 0.1765$) (see Table 4).

3.7. Quality of evidence

The GRADE quality of evidence on the relationship between HRT use and breast cancer recurrence ranged from very low in observational studies to moderate in the RCTs. The very low quality evidence of a non-significant higher risk of tumour recurrence with

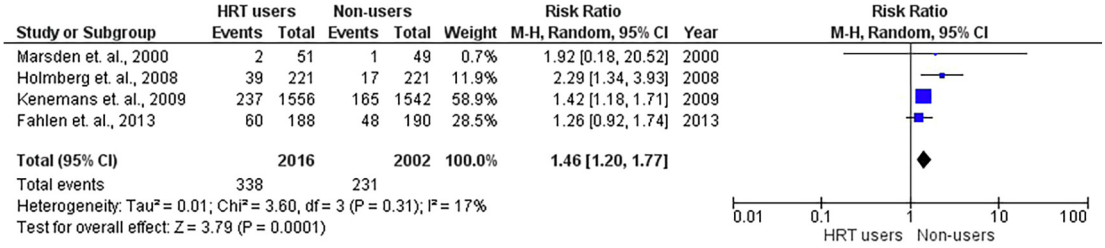

Fig. 3. Forest plot showing the relative risks (RR) of breast cancer recurrence in randomised trials and the overall pooled estimate. CI – confidence intervals; M-H – mantel haenszel.

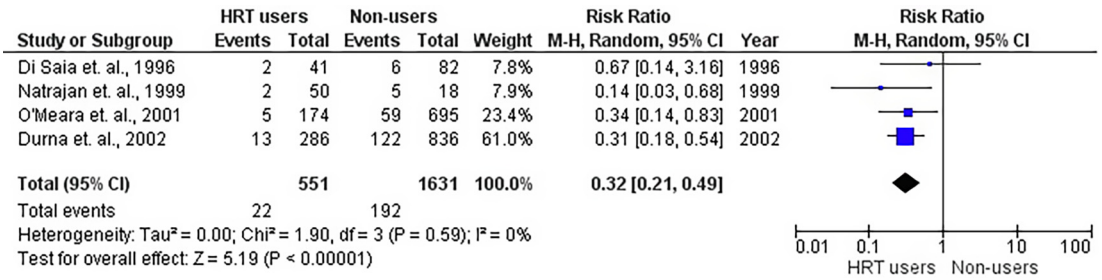

Fig. 4. Forest plot showing the relative risks (RR) of breast cancer-related mortality in observational studies and the overall pooled estimate. HRT – hormone replacement therapy; CI – confidence intervals, M-H – mantel haenszel.

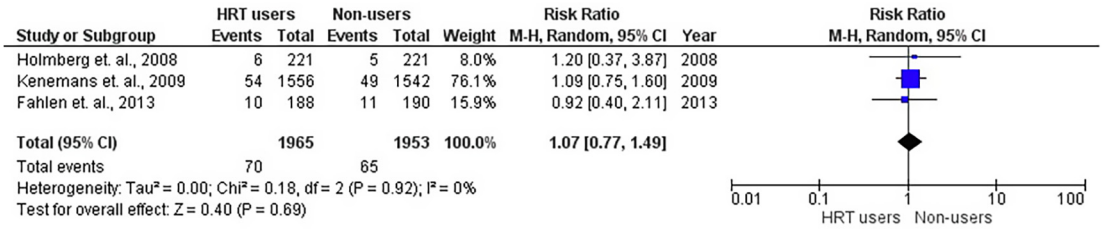

Fig. 5. Forest plot showing the relative risks (RR) of breast cancer-related mortality in randomised trials and the overall pooled estimate. HRT – hormone replacement therapy; CI – confidence intervals, M-H – mantel haenszel.

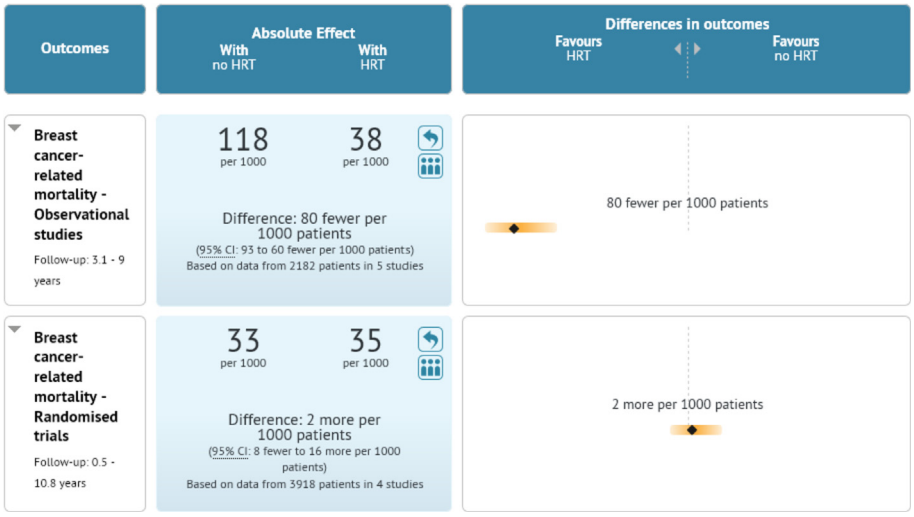

Fig. 6. Absolute effects of HRT use on breast cancer-related mortality.

Table 4
Relationship between study characteristics and relative risk of tumour recurrence.

Explanatory variable	Exponent of slope	95% Confidence Interval	Proportion of heterogeneity explained (R^2)	Interpretation
Duration of follow-up (years)[a]	RR = 1.18	0.93 to 1.49	0.00%	No evidence of dependency (p = 0.1765)
Study quality[a]			97.0%	Strong evidence of dependency (p = 0.0092)
Good	Reference	Reference		
Fair	RR = 3.37	1.12 to 10.12		
Poor	RR = 2.43	1.14 to 5.18		
Study design[b]	RR = 1.99	1.20 to 3.32	64.0%	Strong evidence of dependency (p = 0.0077)

[a] Analysis done only on observational studies, given the limited number of RCTs in the review.
[b] Analysis included all studies.

HRT use demonstrated by the observational studies, RR 0.80 (95% CI, 0.53–1.19), was limited mainly by the risk of bias in the included studies, inconsistency, indirectness and imprecision (see Table 5).

The moderate quality evidence of a significant higher risk of tumour recurrence with HRT demonstrated by the RCTs, RR 1.46 (95% CI, 1.20–1.77), was limited mainly by serious indirectness. This arising from study selection based on the average population age and not individual participant age (see Table 5).

4. Discussion

This study, for the first time, reviewed the available evidence on the relationship between use of HRT and tumour recurrence in breast cancer survivors diagnosed at a post-menopausal age (≥50), a period with a higher incidence of hormone responsive tumours [10].

Observational studies did not report any significant adverse effect on tumour recurrence, with the results of a sensitivity analysis suggesting that HRT use has a significant protective effect. These findings are consistent with observational study results from previous reviews on women across all ages at primary diagnosis [13,14] but inconsistent with findings on younger premenopausal women [8]. It has previously been demonstrated that women who develop primary breast cancer after a period of HRT use have a more favourable prognosis, with significantly less metastasis to the bone, liver and lung, as compared to non-users [41]. However, the extent to which this may apply in this context of recurrent disease is unclear, but there is evidence that the normalization of bone metabolism with HRT use may lower the conditions of tumour cell seeding, impairing bone metastasis [41]. The absolute risk for tumour recurrence with HRT use from the observational studies was 177 cases per 1000 survivors, without treatment the risk was 221 cases per 1000 survivors. This represents an absolute difference of 44 fewer cases of recurrence per 1000 breast cancer survivors with use of HRT. However, this evidence is of very low quality and the true effect of therapy is likely to be substantially different from

Table 5
Summary of Findings.

Menopausal hormone replacement therapy compared to no treatment, acupuncture or placebo in breast cancer survivors diagnosed at a postmenopausal age (population mean age ≥ 50)

Patient or population : Breast cancer survivors diagnosed at a postmenopausal age (population mean age ≥ 50)
Setting: United Kingdom, United States, Australia, Asia, Scandinavian region and other select regions in Europe
Intervention: Conventional oestrogen-based therapies and the non-conventional tibolone treatment
Comparison: No treatment, acupuncture or placebo

Certainty assessment							Summary of findings					
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**		
							With no hormone therapy or acupuncture	**With hormone replacement therapy**		**Risk with no hormone therapy or acupuncture**	**Risk with hormone therapy**	**Risk difference with hormone replacement therapy**
I. Breast cancer recurrence (follow up: range 3.1 years to 9 years; assessed with: Cancer registries and patient medical records)												
917 cases 8885 controls 90/551 exposed 360/1631 unexposed **(5 observational studies)**	serious[a]	serious [b]	serious [c]	serious [d]	undetected	⨁◯◯◯ VERY LOW	917 cases 8885 controls 90/551 exposed 360/1631 unexposed		**RR 0.80** (0.53 to 1.19)	221 per 1,000	177 per 1,000 (117 to 263)	**44 fewer per 1,000** (104 fewer to 42 more)
II. Breast cancer recurrence (follow up: range 0.5 years to 10.8 years; assessed with: Needle aspiration biopsies, mammograms, ultrasound, skeleton scintigraphy, CT-scans and X-rays)												
4018 **(4 RCTs)**	not serious	not serious	serious [e]	not serious	undetected	⨁⨁⨁◯ MODERATE	231/2002 (11.5%)	338/2016 (16.8%)	**RR 1.46** (1.20 to 1.77)	115 per 1,000	168 per 1,000 (138 to 204)	**53 more per 1,000** (23 more to 89 more)

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

[a] Two observational studies which contributed a total weight of 25.9% [25, 26], were at a high risk of selection bias and potential confounding by nodal status. A sensitivity analysis excluding these biased studies changed the non-significant risk decrease to a significant risk decrease. Evidence downgraded one level.

[b] Wide variation in the effect estimate is observed across studies and there is little overlap of the confidence intervals, with the I^2 statistic suggesting substantial heterogeneity (66%). Evidence downgraded one level.

[c] The review aimed to investigate risk of tumour recurrence in women aged ≥ 50 at primary diagnosis but selection of studies was based on the population mean age and not individual participant age, hence a few younger women were included. Evidence downgraded one level.

[d] The effect estimate, RR 0.80 (95% CI, 0.53 - 1.19), includes the null value of no effect and allows for contradictory conclusions of both beneficial and harmful effect of HRT, with the possibility of a > 25% change in the RR. Evidence downgraded one level.

[e] The review aimed to investigate risk of tumour recurrence in women aged ≥ 50 at primary diagnosis but selection of studies was based on the population mean age and not individual participant age, hence a few younger women were included. Evidence downgraded one level.

that estimated by these studies.

The findings from the RCTs suggest a significant adverse effect on tumour recurrence with use of HRT in this population of survivors, an outcome that is consistent with trial results from a previous review on younger premenopausal women [8] and a population of women across all ages at primary diagnosis [13].

Collectively, evidence from RCTs suggest that regardless of the age at primary diagnosis, use of HRT increases the risk of breast cancer relapse. The absolute risk for recurrence as demonstrated by the RCTs was 168 cases per 1000 survivors, without treatment this risk was 115 cases per 1000 survivors. This represents an absolute difference of 53 more cases per 1000 breast cancer survivors with use of HRT. However, this evidence is of moderate quality. The true effect of therapy on tumour recurrence in this population of survivors is thus likely to be close to that estimated by these studies, but a possibility exists that it could be substantially different.

The use of HRT is often part of a broader strategy including lifestyle recommendations regarding exercise, diet, smoking cessation and reduced alcohol consumption [42]. Similarly, therapy use is based on an overall assessment of the associated benefits and risks [43,44]. It is thus likely that majority of the survivors in the observational studies who received prescriptions had less aggressive prognostic factors and adopted healthier lifestyles, a bias by indication that is often present in observational studies of drug use [22]. Hence, the HRT users in these studies may have been at a lower baseline risk of tumour recurrence, which may partly explain the observed protective effect of therapy on recurrence.

The observational studies included in this review were of varying quality and design, majority being retrospective. Statistically significant heterogeneity was evident among these studies, with meta-regression analysis demonstrating that this was mainly attributable to the variations in the risk of bias. The differences in quality of the observational studies was a consequence of both clinical and methodological differences. The methodological heterogeneity may have resulted from the inclusion of both case-control and cohort studies, with different approaches to ascertainment of HRT exposure and tumour recurrence. Clinical heterogeneity may have been the consequence of including study populations from different geographical locations (USA, UK and Australia) and HRT treatments that differed in type, dose and route of administration. However, given the presence of both between study and within study variations in the HRT regimen, a sub-group analysis on specific treatments was not possible.

The RCTS included in this study had a more uniform population of older survivors, drawn mostly from Europe. However, the type and dose of HRT treatment also differed, a possible source of the negligible heterogeneity found. Two of the included studies were extended follow-up reports to the HABITS and Stockholm trials, both of which were terminated prematurely based on an initial joint safety assessment that demonstrated a significant increase in the risk of tumour recurrence with hormone therapy, relative hazard of 1.8 (95% CI, 1.03–3.10) [45]. The initial report of the HABITS trial, at a median follow-up of 2.1 years, demonstrated a hazard rate of 3.5 (95% CI, 1.5–7.4) with use of HRT [46]. This was significantly higher than the risk demonstrated in the extended report included in this review after a median follow-up of 4 years. Similarly, the initial report of the Stockholm trial, after 4.1 years of follow-up, demonstrated no adverse effect of HRT use on tumour recurrence in this population of survivors, HR 0.82 (95%, CI 0.35–1.90) [45]. These findings slightly differ from the non-significant higher risk demonstrated after 10.8 years of extended follow-up in the report included in this review. The main source of the variation between the HABITS and Stockholm trial results, as previously described, arise from differences in the study populations on the nodal status, adjuvant use of tamoxifen and differences in HRT regimen [45]. These also explain the observed differences in the extended follow-up reports in this study.

This systematic review did not present any significant evidence of a relationship between the duration of follow-up and the risk of tumour recurrence. Findings from the Women's Health Initiative (WHI) trial on incident breast cancer demonstrated an increased risk of primary disease with longer duration of therapy [9]. However, given the limited number of studies that reported on the duration of treatment, we did not investigate its relationship with tumour recurrence and we interpret the results on follow-up duration with caution, given the limited number of studies included in the analysis.

The findings from the meta-regression analysis provide strong statistical evidence that the outcome of investigations done on the associated risk of tumour recurrence with HRT use, differ between experimental and observational studies. For evidence of better quality, we recommend future research on this topic to focus on well-designed RCTs.

Overall, despite the contradictory findings between the observational studies and the RCTs, the safety data in this review provides evidence of sufficient quality on a possible adverse effect on tumour recurrence with use of HRT in this population of survivors. The strength in this systematic review, unlike previous reviews which also presented conflicting results between observational studies and RCTs [8,13], was the ability to quantify the associated biases and to appraise the overall quality of evidence. The findings in this study are thus a better guide to clinical decisions on the appropriateness of HRT use in older breast cancer survivors.

4.1. Implications to practice

The most recent consensus statement and recommendations from the International Menopausal Society (IMS) suggests that current safety data do not support the use of systemic HRT in breast cancer survivors [47]. This study further highlights a need for practitioners to exercise caution with the use of HRT in survivors diagnosed at an older postmenopausal age (≥50). However, we are cognisant of the possibility that these women may present with debilitating hot flushes and night sweats and the immediate benefits of HRT on their quality of life may outweigh any potential risks. For such patients, we advise practitioners to make an appropriate judgement, with a primary focus on the overall quality of life.

4.2. Limitations

A major limitation in this review was the selection of studies based on the average population age and not the individual participant age, as this information was unavailable. Therefore, although the included population predominantly comprised of survivors diagnosed at a postmenopausal age (≥50), a fewer younger women were included. The evidence presented is thus indirect.

Secondly, no information was available in the included studies on the mode of management for the primary breast cancer. Information on the type of surgery, either lumpectomy or a mastectomy, the margin status after surgery or the course of chemotherapy is unknown. All these would influence the baseline risk of tumour recurrence. We thus cannot rule out such underlying differences between the HRT users and non-users included in this review.

Finally, generalisability may be limited. The review over-represented survivors of an early stage breast cancer thus applicability to survivors of an advanced stage of disease is unclear. Additionally, we are unsure of the ethnic make-up of the studies hence not certain on its ethnic generalisability.

5. Conclusion

We recommend practice guidelines to further emphasize a more conservative approach to menopausal symptom management in this group of survivors, encouraging the use of alternative and non-hormonal therapies such as selective serotonin reuptake inhibitors,

selective norepinephrine reuptake inhibitors and gabapentin, all of which have been shown to be effective for the relief of vasomotor symptoms in clinical trials [42].

Future research should investigate the risk of recurrence with different HRT regimen, different routes of delivery and different treatment intervals. Such information may guide treatment decisions where the immediate benefits of therapy may outweigh any potential risks.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

Appendix A

Table A1
EMBASE database search strategy.

S1	?estrogen replacement therapy OR ?estrogen-progestin therapy OR hormone replacement therapy OR tibolone	22,803
S2	Breast cancer OR breast neoplasm OR breast tumo?r	499,280
S3	(S1 AND S2)	4691
S4	Surviv*	1,750,809
S5	(S3 AND S4)	514
S6	Recurrence OR relapse	687,930
S7	(S5 AND S6)	173
S8	Menopause OR menopausal	100,999
S9	(S7 AND S8)	107

Appendix B

Table B2
Reasons for study exclusion at full-text screening.

Author (Year)	Title	Journal	Reason for exclusion
Bonnier et al. (1999)	Impact of menopausal hormone-replacement therapy on clinical and laboratory characteristics of breast cancer	International Journal of Cancer; 79 (3): 278 -282	Inappropriate outcome, study does not assess recurrence but prognosis of incident disease in hormone users.
Vassilopoulou-Sellin et al. (2002)	Estrogen replacement therapy for menopausal women with a history of breast carcinoma: Results of a 5-year, prospective study	Cancer; 95 (9): 1817–1826	Mean age at diagnosis <50
Vassilopoulou-Sellin et al. (1999)	Estrogen replacement therapy after localized breast cancer: clinical outcome of 319 women followed prospectively	Journal of Clinical Oncology; 17 (5): 1482-1487	Mean age at diagnosis <50
Kubista et al. (2007)	Safety of tibolone in the treatment of vasomotor symptoms in breast cancer patients—design and baseline data 'LIBERATE'trial	The Breast; 16: 182-189	Protocol explanation and baseline data with no outcome of interest
Durna et al. (2004)	Breast cancer in premenopausal women: Recurrence and survival rates and relationship to hormone replacement therapy	Climacteric; 7 (3): 284-291	Mean age at diagnosis <50
Goutziolis et al. (2007)	Tibolone therapy in breast cancer survivors: A retrospective study	The Journal of Obstetrics and Gynaecology Research; 33 (1): 68-73	Mean age at diagnosis <50
Decker et al. (2003)	Estrogen replacement therapy in breast cancer survivors: A matched-controlled series	Menopause; 10 (4): 277-285	Mean age at diagnosis not reported and no information given that can reflect the population age.
Dew et al. (1998)	A cohort study of hormone replacement therapy given to women previously treated for breast cancer	Climacteric; 1 (2): 137-142	Mean age at diagnosis <50
Gorins et al. (2003)	Hormone replacement therapy in breast cancer patients: a study of 230 patients, with a case-control study	Gynaecology Obstetrics Fertility; 31 (7–8): 614-619	Non-english language
Wile et al. (1993)	Hormone replacement therapy in previously treated breast cancer patient	American Journal of Surgery; 165 (3): 372-375	Wrong comparator, both groups on hormone replacement.
Di Saia et al. (1995)	Replacement therapy for breast cancer survivors. A pilot study	Cancer; 76(S10): 2075–2078	Single-arm study
Vassilopoulou-Sellin et al. (1997)	Estrogen replacement therapy in women with prior diagnosis and treatment for breast cancer	Gynecologic oncology; 65 (1): 89-93	Single-arm study
Guidozzi et al. (1999)	Estrogen replacement therapy in breast cancer survivors	International Journal Of Gynaecology And Obstetrics; 64 (1): 59-63	Single-arm study
Holmberg et al. (2004)	HABITS (hormonal replacement therapy after breast cancer, is it safe?): A randomised comparison trial stopped	Lancet; 363 (9407): 453-455	Duplicate population as Holmberg et al. (2008).Only the most recent extended follow-up report was included.
Von Schoultz et al. (2005)	Menopausal hormone therapy after breast cancer: The Stockholm randomised trial	Journal Of The National Cancer Institute; 97 (7): 533-535	Duplicate population as Fahlen et al. (2013). Only the most recent extended follow-up report was included.

Table B2 (*continued*)

Author (Year)	Title	Journal	Reason for exclusion
Beckmann et al. (2001)	Hormone replacement therapy after treatment of breast cancer: Effects on postmenopausal symptoms, bone mineral density and recurrence rates	Oncology; 60 (3): 199-206	Mean age at diagnosis not reported and no information given that can reflect the population age.
Marsden et al. (2017)	Hormone replacement therapy (HRT) is effective in relieving oestrogen deficiency symptoms (ODS) and improves quality of life in breast cancer patients: The UK randomised HRT trial experience.	Maturitas; 100, 132	Conference abstract, unclear outcomes.
Dew et al. (2002)	Tamoxifen, hormone receptors and hormone replacement therapy in women previously treated for breast cancer: a cohort study	Climacteric: The Journal Of The International Menopause Society; 5 (2): 151-155	Mean age at diagnosis not reported and no information given that can reflect the population age.
Dew et al. (2003)	A cohort study of topical vaginal estrogen therapy in women previously treated for breast cancer	Climacteric: The Journal Of The International Menopause Society, 6 (1), 45-52	Duplicated population.

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