Effect of the use of hormonal replacement therapy on breast cancer prognosis: A systematic review and meta-analysis

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Abstract. Breast cancer is a global health concern. Hormone replacement therapy (HRT) prior to breast cancer diagnosis is of particular interest due to the hormone sensitivity of the breasts. Previous evidence has altered the perception of HRT by highlighting that certain risks could outweigh the benefits. As a result, the popularity of HRT for menopausal symptom relief and disease prevention decreased. To investigate the relationship between pre-diagnosis HRT use and breast cancer survival, a meta-analysis was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A comprehensive search across MEDLINE, Cochrane and Web of Science databases up to August 2025 identified 33 studies. These studies evaluated the impact of HRT on breast cancer survival utilizing various study designs. Quality assessment was performed using the Newcastle Ottawa Scale, while the Risk of Bias in Non-Randomized Studies of Exposures tool was used to evaluate the risk of bias. The pooled analysis revealed that HRT use prior to breast cancer diagnosis was associated with reduced breast cancer mortality (odds ratio, 0.86; 95% CI, 0.79-0.94). Subgroup analyses based on duration and timing of HRT use at diagnosis revealed heterogeneous associations with survival. Shorter duration of use (<5 years) appeared to be associated with lower breast cancer mortality; however, these subgroup analyses were based on a limited number of studies and should be interpreted with caution. Longer duration of use (>10 years) showed no clear association. Studies recruiting after 2000 showed an inverse association between HRT use and breast cancer mortality, a trend more pronounced than in earlier years, although evidence remains limited. In conclusion, pre-diagnosis HRT use was associated with improved breast cancer survival, influenced by treatment duration, timing and temporal factors. It is necessary to note that subgroup findings based on the treatment duration and recruitment period were limited by the low number of contributing studies and should be interpreted with caution. Despite methodological differences among the included studies, the present findings provide valuable insights into the complex relationship between HRT and breast cancer prognosis.

Introduction

Breast cancer has a high mortality and morbidity rate among women and is therefore one of the main concerns in global healthcare (1). In 2020, female breast cancer accounted for 2.3 million new cases (11.7%), surpassing lung cancer as the most commonly diagnosed cancer (2). In the same year, 685,000 women died of breast cancer, making it the leading cause of death in women (3). In terms of 5-year survival, rates in developing countries are lower than in more developed ones (2,4). Given the high survival rates in developed countries (5), emphasizing the identification of prognostic factors for breast cancer is of vital importance.

The main prognostic factors of breast cancer have been recognized for many years. These include hormone receptor status, tumour size, lymph node status, metastasis, tumour grade, progesterone receptor, and HER2 status (6,7). In addition, the use of hormone replacement therapy (HRT) prior to breast cancer diagnosis is particularly relevant, given that breast tissue is sensitive to hormonal stimuli (8).

The use of HRT began in the 1960s and gained widespread popularity for managing premenopausal symptoms (9). In the following decades, several articles were published that not only supported this finding, but also suggested that HRT could prevent chronic diseases such as coronary heart disease (10,11) or osteoporosis (12,13). In contrast, the use of

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Abbreviations: HR, hazard ratio; HRT, hormone replacement therapy; NOS, Newcastle Ottawa Scale; OR, odds ratio; WHI, Women's Health Initiative

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HRT subsequently declined after a study (14) associated its use with an increased risk of endometrial cancer.

The main turning point for this therapy occurred at the beginning of the 21st century. In 2002, the results of the most important study carried out to date were published: WHI (Women's Health Initiative). The conclusions of the study stated that 'Overall health risks exceeded benefits from use of combined oestrogen plus progestin' (15). This was followed by a dramatic decline in HRT use in most countries (16-19), including Spain (20).

After the WHI results and the reduction in HRT use were published, there was a decrease in the incidence of breast cancer in some countries such as Belgium (21), France (22) or New Zealand (23). However, in other countries such as Italy and Spain the incidence remained constant (24). Beyond uncertainty regarding incidence, it is essential to understand how HRT is associated with breast cancer prognosis, a debate that has persisted in the medical and scientific community for years (25,26).

It remains unclear whether the use of HRT prior to diagnosis is associated with a better or worse prognosis, making the evaluation of its role as a prognostic factor necessary (27). There is only one prior meta-analysis aimed at evaluating the association of HRT prescribed before cancer diagnosis (27).

The main objective of this study is to analyze the association between pre-diagnostic HRT use and breast cancer prognosis, while also evaluating the influence of factors potentially modifying this relationship.

Materials and methods

Literature search. The procedures outlined in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement were adhered to in the execution of this meta-analysis (28). The protocol was registered within the PROSPERO database (registration number: CRD42023398582).

The following bibliographic databases were searched: MEDLINE (https://pubmed.ncbi.nlm.nih.gov/), Cochrane (www.cochranelibrary.com) and Web of Science (https://www.webofscience.com/wos/alldb/basic-search). All articles published in English or Spanish up to August 28th, 2025 were included. The search terms included ('menopause hormonal therapy' or 'hormonal replacement therapy' or 'hormone replacement therapy' or 'postmenopausal hormone replacement therapy' or 'estrogen-progestin hormone replacement therapy' or 'combined hormone replacement therapy' or 'estrogen alone hormone replacement therapy' or 'hormone therapy') and ('breast cancer' or 'breast neoplasms' or 'breast tumour' or 'breast tumours' or 'breast carcinoma' or 'breast carcinomas') and ('prognosis' or 'survival' or 'prognostic factor').

Comprehensive search criteria were used to ensure completeness, including cumulative cohort designs, incidence-density cohorts, case-control, and hybrid case-cohort designs that evaluated the possible association between HRT and breast cancer survival. Subsequently, the reference lists of all included articles were screened to identify additional relevant studies.

The screening and selection of articles was carried out by two independent reviewers (JCF and JAM). These reviewers retrieved the reference lists of each article and examined them to identify those studies that met the specified inclusion criteria (see below). This was carried out in multiple stages; firstly, the reviewers identified and removed duplicates across the different databases. Then, they selected studies by title, abstract, and finally, by full text following the inclusion criteria. Discrepancies were resolved by discussion until an agreement was reached and a third researcher intervened to resolve any persisting conflicts.

Inclusion and exclusion criteria. The studies incorporated in this analysis adhered to the following criteria: i) Hormone Replacement Therapy (HRT) served as the primary exposure under investigation; ii) the study design encompassed cumulative cohort designs, incidence-density cohorts, case-control, or hybrid case-cohort structures; iii) the key outcomes encompassed breast cancer mortality or survival, accompanied by risk estimates and 95% confidence intervals (CI) (or data facilitating their computation).

Exclusion criteria comprised commentaries, conference communications, systematic reviews, reviews, book chapters, and letters to the editor. Additionally, articles not written in English or Spanish and those that lacked the requisite data for analysis and studies involving non-human samples were excluded from consideration.

Data extraction. From the pool of eligible articles, two researchers (JCF and JAM) systematically extracted the following information: year of publication, authorship details, title, recruitment start and end dates, follow-up conclusion date, interquartile range, country of origin of the study, subpopulations examined, Hormone Replacement Therapy use, sample size, strength of association (risk ratio, hazard ratio or odds ratio) with its 95% confidence intervals (CI), and the set of adjusted covariates employed in the multivariate analysis. In instances where a study presented multiple risk estimates, the one adjusted for the most extensive array of confounding factors was chosen.

Study quality assessment and risk of bias. After the study selection, methodological quality was evaluated by two researchers (JCF and PRC) using the Newcastle Ottawa Scale (NOS) (29). For this evaluation, eight items were reviewed for each study. These items were classified into three categories: selection, comparability and outcome or exposure, depending on whether it was a cohort or a case-control study. Studies scoring 7 or higher were deemed high quality. Discrepancies were resolved by discussion.

Following Cochrane recommendations, we also used the Risk of Bias in Non-randomized Studies of Exposures (ROBINS-E) tool to assess the risk of exposure bias in each study included in our meta-analysis (30).

Statistical analysis. Because the included studies reported different measures of association (Hazard ratios, risk ratios and odds ratios), all estimates were treated as generic relative effect measures on the log scale and pooled using inverse-variance weighting. A random-effects model was applied. Results are presented as effect estimates accompanied by a 95% confidence interval (CI), visually represented through Forest plots.

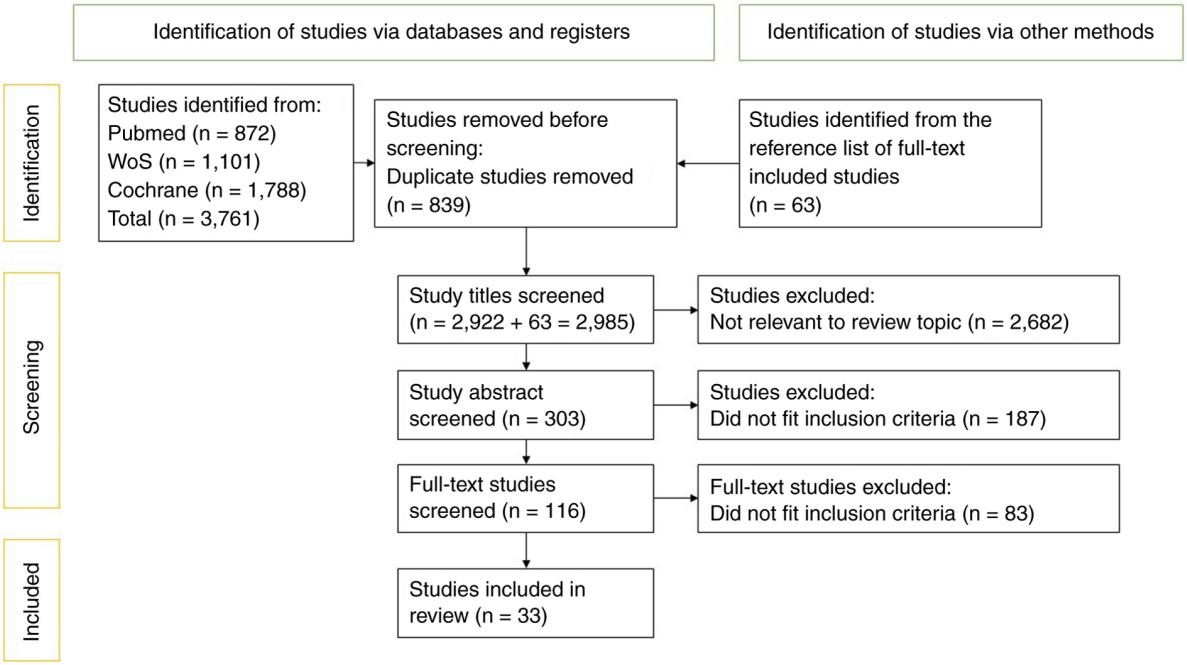

Figure 1. Flowchart.

The assessment of heterogeneity was executed using Q and I^2 statistics. Publication bias was evaluated using Begg's and Egger's tests and by examining funnel plots (31). In addition, to account for potential differences between time-to-event and binary effect measures, an additional sensitivity analysis stratified by type of effect measure (hazard ratio vs. odds ratio) was performed.

The analyses were performed considering HRT use (yes/no), and also based on the duration of use (<5 years; 5 to 10 years; >=10 years), HRT use at the time of diagnosis (current; past; not indicated), article quality (as per the NOS) risk of bias (ROBINS-E tools), and year of participant recruitment. For the latter, participants were segregated into groups: recruited before and after 2000, due to the pivotal alteration in hormone concentrations during treatment at that juncture (15). In all analyses, adjusted estimates were used when available; otherwise, raw data were used.

Because the included studies used different definitions of HRT exposure (e.g. months vs years of use, varying cut-offs, and differing definitions of current and past use), categories were harmonised where possible.

Data were analysed using STATA 16.0 software. Given that the confidence intervals specified in the articles are not totally symmetric around the effect size for all studies, the 'civartolerance' in STATA (defined as Confidence Interval upper limit-effect size=effect size-Confidence Interval lower limit) was set at 0.15. Since generic effect sizes with confidence intervals require approximate symmetry around the effect estimate on the appropriate scale, CI symmetry was checked using the civartolerance option in Stata's meta suite. Two studies (32,33) showed confidence intervals that remained markedly asymmetric even after relaxing this tolerance, suggesting potential reporting or calculation errors. These studies were therefore excluded from the pooled quantitative synthesis, while their findings are qualitatively described in the Discussion.

Results

Study characteristics. After conducting the search based on the criteria outlined above, a total of 3,761 articles were initially identified. Subsequently, an additional 63 articles were incorporated through supplementary search methods. The next step involved the removal of duplicate articles (n=839), followed by a sequential process of filtering and exclusion guided by title assessment (n=2,682), abstract review (n=187), and thorough evaluation of the full articles (n=83) by the reviewers. Finally, this meta-analysis includes 33 studies: 30 retrospective cohort studies (8,10,32-59), 1 hybrid case-cohort study (15), 1 nested case-control study (60) and 1 prospective cohort study (61).

Given that Persson *et al* (32) and Hunt *et al* (33) reported effect sizes with asymmetric confidence intervals, they were excluded from the quantitative synthesis. Similarly, Christante *et al* (37) did not provide sufficient data for inclusion in the meta-analysis, and was also excluded. A visual representation of the bibliographic search process is shown in Fig. 1. Table I summarizes the main characteristics of the included articles, while Table SI provides information detailing the factors included in the multivariate analysis of each article.

Quality and bias analysis. The results of the quality analysis conducted using the NOS revealed that 21 of the included studies were classified as of good or fair quality (NOS>=7) (8,10,15, 34-36,38,39,42,44,46-48,50-53,56,58,60,61), while 8 studies were identified as poor quality (NOS<7) (40,41,43,45,49, 54,55,57).

On the other hand, the application of the ROBINS-E tool determined that 5 articles had a low risk of bias (36,39,40,48,60), while 9 articles were identified as having some concerns (10, 34,42,45,47,50,55,56,58). In the remaining 19 studies, a high risk of bias was found (8,15,32,33,35,37,38,41,43,44,46,49, 51-54,57,59,61) (Fig. 2).

Table I. Main characteristics of the included articles.

First author/s, year	Follow up-period	Country	Study design	Sample size	Stratum	HRT exposure	Outcome measure (95% CI)[a]	Covariate adjustment	NOS	(Refs.)
Manson *et al*, 2018	1993-2014	USA	Cohort	26,897	-	-	0.55 (0.33-0.92)[b]	No	>7	(38)
Sener *et al*, 2009	1994-2002	USA	Cohort	1,055	-	-	0.44 (0.26-0.73)[b]	Yes	<7	(43)
Fletcher *et al*, 2005	1993-2003	Australia	Cohort	4,022	-	Current use	0.64 (0.41-1.00)[b]	Yes	>7	(39)
Schuetz *et al*, 2007	1990-1999	Germany	Cohort	1,072	-	Current use	0.37 (0.24-0.57)[c]	No	<7	(40)
							0.62 (0.39-1.00)[c]	Yes		
Alonso-Molero *et al*, 2022	2007-2017	Spain	Cohort	1,685	Born 1940-1959	-	0.77 (0.38-1.55)[b]	Yes	>7	(58)
					<5 years of use	-	0.71 (0.28-1.79)[b]			
					≥5 years of use	-	0.85 (0.31-2.39)[b]			
Rossouw *et al*, 2002	1993-2002	USA	Clinical trial	16,608	-	Past use	1.26 (1.00-1.59)[b]	No	>7	(15)
					-	Past use	1.26 (0.83-1.92)[b]	Yes		
					<5 years of use	Past use	2.13 (1.15-3.94)[b]	No		
					5-10 years of use	Past use	4.61 (1.01-21.02)[b]	No		
					≥10 years of use	Past use	1.81 (0.60-5.43)[b]	No		
Godina *et al*, 2020	2002-2016	Sweden	Cohort	814	-	-	0.68 (0.48-0.99)[b]	No	>7	(8)
					-	-	0.81 (0.55-1.19)[b]	Yes		
Grodstein *et al*, 1997	1976-1994	USA	Cohort	121,700	-	Current use	0.77 (0.59-1.00)[c]	No	>7	(10)
					-	Current use	0.76 (0.56-1.02)[c]	Yes		
Ettinger *et al*, 1996	1969-1992	USA	Cohort	454	-	Current use	1.89 (0.43-8.36)[c]	Yes	<7	(41)
Jernström *et al*, 1999	1978-1997	Sweden	Cohort	984	-	-	0.78 (0.65-0.93)[c]	Yes	>7	(61)
					>5 years of use	-	0.77 (0.56-1.08)[c]	Yes		
					<5 years of use	-	0.78 (0.63-0.96)[c]	Yes		
Schairer *et al*, 1999	1973-1995	USA	Cohort	280,000	LNN; <5 years of use	Past use	0.8 (0.40-1.40)[b]	Yes	>7	(42)
					LNN; <5 years of use	Current use	0.60 (0.30-1.20)[b]			
					LNN; 5-10 years of use	Past use	0.70 (0.40-1.20)[b]			
					LNN; 5-10 years of use	Current use	0.40 (0.20-0.80)[b]			
					LNN; ≥10 years of use	Past use	1.20 (0.60-2.50)[b]			
					LNN; ≥10 years of use	Current use	0.60 (0.20-1.50)[b]			
					LNP; <5 years of use	Past use	0.50 (0.30-0.90)[b]			
					LNP; <5 years of use	Current use	0.50 (0.30-0.80)[b]			
					LNP; 5-10 years of use	Past use	1.60 (0.90-2.80)[b]			
					LNP; 5-10 years of use	Current use	1.20 (0.60-2.20)[b]			
					LNP; ≥10 years of use	Past use	1.20 (0.60-2.40)[b]			
					LNP; ≥10 years of use	Current use	0.80 (0.30-1.70)[b]			

Table I. Continued.

First author/s, year	Follow up-period	Country	Study design	Sample size	Stratum	HRT exposure	Outcome measure (95% CI)[a]	Covariate adjustment	NOS	(Refs.)
Hellmann *et al*, 2010	1976-2007	Denmark	Cohort	12,617	-	-	0.64 (0.43-0.96)[b]	Yes	>7	(35)
Newcomb *et al*, 2008	1988-2005	USA	Cohort	12,269	-	-	0.87 (0.78-0.98)[b]	Yes	>7	(36)
					-	Past use	0.92 (0.78-1.08)[b]			
					-	Current use	0.85 (0.73-0.98)[b]			
					<5 years of use	-	0.89 (0.73-1.08)[b]			
					>5 years of use	-	0.89 (0.75-1.06)[b]			
Rosenberg *et al*, 2008	1993-2003	Sweden	Cohort	2,660	-	Current use	0.63 (0.42-0.95)[b]	Yes	>7	(34)
					-	Past use	1.03 (0.68-1.54)[b]			
					<5 years of use	Current use	0.76 (0.45-1.27)[b]	Yes		
					<5 years of use	Past use	1.02 (0.64-1.63)[b]			
					>5 years of use	Current use	0.52 (0.29-0.93)[b]			
					>5 years of use	Past use	1.02 (0.48-2.17)[b]			
Magnusson *et al*, 1996	1977-1991	Sweden	Cohort	1,589	-	-	0.74 (0.49-1.14)[d]	No	<7	(57)
Willis *et al*, 1996	1982-1991	USA	Cohort	422,373	-	-	0.84 (0.75-0.94)[c]	Yes	>7	(56)
					2-5 years of use	-	0.78 (0.65-0.93)[c]			
					6-10 years of use	-	0.78 (0.62-0.98)[c]			
					>11 years of use	-	0.93 (0.75-1.15)[c]			
Sturgeon *et al*, 1995	1979-1989	USA	Cohort	49,000	-	-	0.70 (0.70-0.80)[c]	Yes	<7	(55)
Bonnier *et al*, 1998	1985-1995	France	Cohort	426	-	-	0.49 (0.24-0.98)[c]	No	<7	(54)
Sourander *et al*, 1998	1987-1995	Finland	Cohort	7,317	-	Past use	0.94 (0.47-1.90)[c]	No	>7	(59)
					-	Current use	0.57 (0.27-1.20)[c]			
Sellers *et al*, 1997	1996-2002	USA	Cohort	41,837	<5 years of use	-	1.91 (0.64-5.69)[c]	Yes	>7	(53)
					>5 years of use	-	0.92 (0.55-1.54)[c]			
Beral *et al*, 2003	1996-2002	UK	Cohort	1,084,110	-	Current use	1.22 (1.00-1.48)[c]	Yes	>7	(52)
					-	Past use	1.05 (0.85-1.29)[c]			
Stahlberg *et al*, 2005	1993-2004	Denmark	Cohort	10,874	-	Current use	1.97 (1.14-3.42)[b]	Yes	<7	(45)
					-	Past use	1.31 (0.68-2.52)[b]			
Norman *et al*, 2010	1994-2004	USA	Cohort	2,502	<3 years of use	Past use	0.79 (0.52-1.21)[d]	Yes	>7	(51)
					<3 years of use	Current use	0.86 (0.54-1.36)[d]			
					>3 years of use	Past use	0.96 (0.50-1.86)[d]			
					>3 years of use	Current use	0.81 (0.57-1.15)[d]			
Pentti *et al*, 2006	1994-2001	Finland	Cohort	11,667	<5 years of use	-	0.96 (0.32-2.82)[b]	Yes	>7	(50)
					>5 years of use	-	2.62 (0.98-7.00)[b]			

Table I. Continued.

First author/s, year	Follow up-period	Country	Study design	Sample size	Stratum	HRT exposure	Outcome measure (95% CI)[a]	Covariate adjustment	NOS	(Refs.)
Chen *et al*, 2005	1993-2000	USA	Cohort	7,436	HRT use in stage I	-	1.23 (0.72-2.10)[b]	Yes	<7	(49)
					HRT use in stage II	-	1.01 (0.72-1.41)[b]			
Obi *et al*, 2016	2002-2009	Germany	Cohort	3,321	-	Past use	1.19 (0.87-1.62)[b]	Yes	>7	(48)
					-	Current use	0.72 (0.53-0.97)[b]			
Holm *et al*, 2014	1993-2008	Denmark	Cohort	1,064	-	Current use	0.55 (0.37-0.84)[b]	Yes	>7	(47)
					<5 years of use	Current use	0.64 (0.36-1.12)[b]			
					>5 years of use	Current use	0.51 (0.31-0.86)[b]			
Chlebowski *et al*, 2013	1993-2011	USA	Cohort	41,449	-	-	1.32 (0.90-1.93)[b]	Yes	>7	(46)
Reding *et al*, 2011	1993-2009	USA	Cohort	1,911	-	-	0.93 (0.68-1.27)[b]	Yes	>7	(44)
Pocobelli *et al*, 2014	1990-2008	Canada	Nested case-control	13,823	-	-	1.00 (0.80-1.20)[d]	Yes	>7	(60)

[a]The outcome measure is used as a generic label for relative effects ([b]hazard ratio/[c]risk ratio/[d]odds ratio). HRT, hormone replacement therapy; LNN, lymph node negative; LNP, lymph node positive; NOS, Newcastle Ottawa Scale; -, not applicable or not reported.

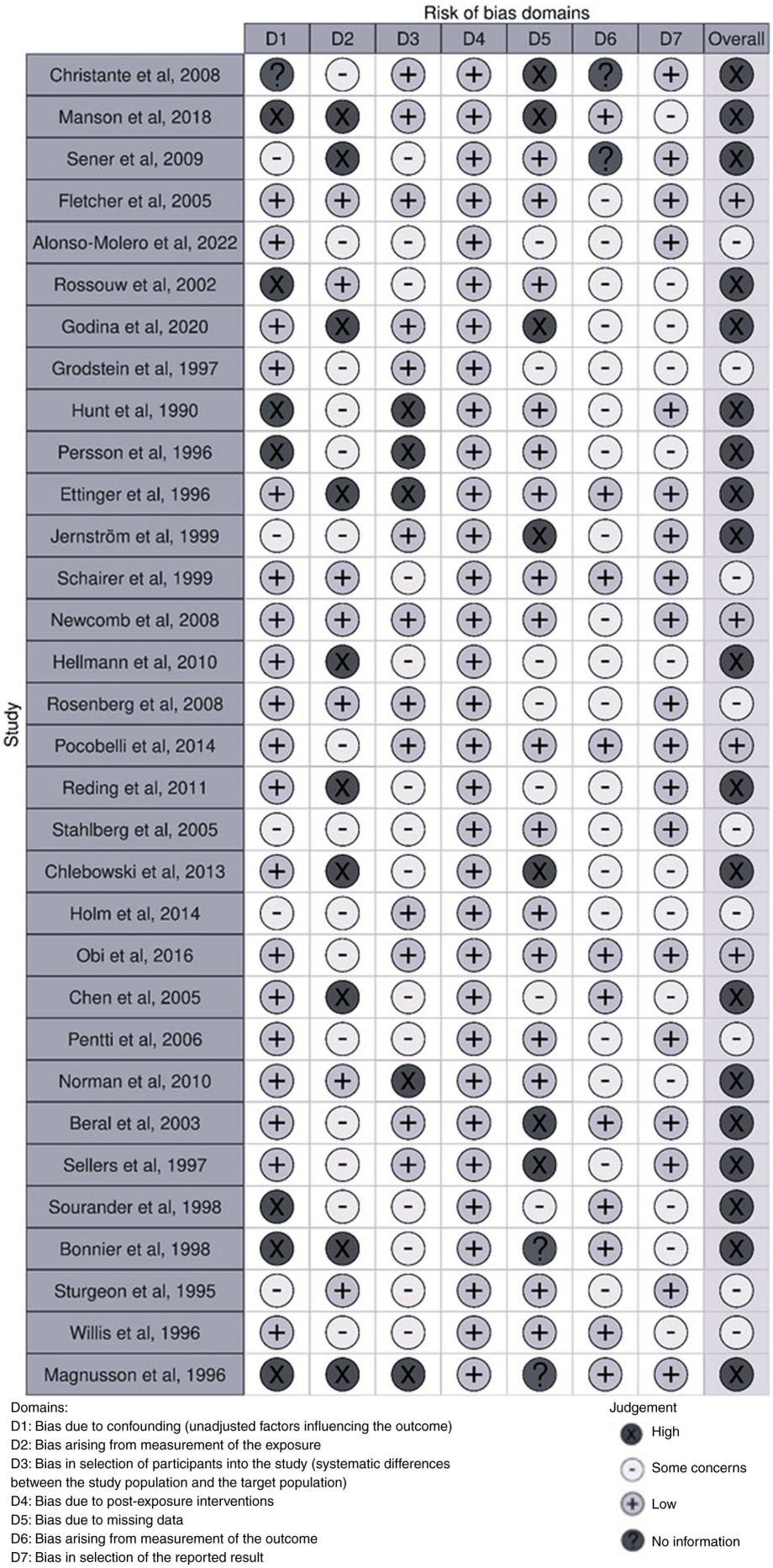

Figure 2. Risk of bias in non-randomized studies.

Data analysis

Use of hormone replacement therapy vs. non-use. First, we aggregated the findings from a total of 29 studies (8,10,15,34-36,38-58,60,61) that comprehensively compared survival outcomes between women who had used HRT prior to breast cancer diagnosis and those who had not (Fig. 3).

These analyses underscored that patients using HRT had a 14% lower risk of breast cancer mortality compared to those who did not [OR=0.86; 95% CI: 0.79-0.94]. Heterogeneity among the included studies was moderate (I^2=57.49%, P=0.001). Inspection of funnel plots revealed asymmetry, indicating a notable potential for publication bias, which was further supported by statistical testing (Egger's test: z=-3.20 P=0.001) (Fig. S1).

As a sensitivity analysis, the overall association was re-estimated after stratifying studies by type of effect measure. When only hazard ratios were pooled, the combined estimate (HR 0.88, 95% CI 0.77-1.01) was very similar to the main result, although the confidence interval was wider and crossed the null (Fig. S2). When only risk ratios were considered, the pooled association remained statistically significant (RR 0.84, 95% CI 0.72-0.99) and closely aligned with the overall estimate (Fig. S3). Analyses restricted to the small subset of studies reporting odds ratios (OR 0.90, 95% CI 0.78-1.03) yielded a pooled estimate (Fig. S4) that was again of similar magnitude but less precise. These findings indicate that the inverse association between pre-diagnostic HRT use and breast cancer mortality is robust across different effect measures, and that mixing hazard ratios, risk ratios and odds ratios as generic relative effects in the main analysis in unlikely to have materially altered the direction or approximate size of the association.

Next, we conducted a separate analysis comparing crude and adjusted estimates (Figs. S5 and S6). We observed disparities between these two analyses: crude (OR=0.67, 95% CI: 0.49-0.93) and adjusted (OR= 0.88, 95% CI: 0.80-0.97). The strength of the association attenuated after adjustment. Regarding heterogeneity, the studies in the raw analysis showed high heterogeneity (I^2=81.21%, P=0.001), while the adjusted results indicated a moderate degree (I^2=57.82%, P=0.001).

Impact of duration of HRT use. To stratify the mortality risk according to treatment duration, two types of analyses were conducted: the first one included the Women's Health Initiative (WHI) study (15) (Table II), while the second excluded the Women's Health Initiative (WHI) study, given that it specifically reported on invasive breast cancer (Table SII).

HRT use was categorized into three groups based on duration of use: less than 5 years (15,34,36,42,47,50,53,56,58,61), between 5 and 10 years (15,34,36,42,47,50,53,56,58,61), and more than 10 years (15,42,56).

When including the WHI study (15), the analysis for duration of use of less than 5 years showed an association with lower breast cancer mortality (Fig. 4). This association persisted after removing the WHI study from the analysis (Fig. S7), although both estimates relied on a relatively low number of contributing studies and should be interpreted with caution.

For a 5 to 10-year period, the initial analysis (Fig. 4) established a non-significant association with breast cancer mortality, whereas the second analysis, which excluded the WHI study, reached statistical significance. Again, the WHI study (15) presented the most pronounced association, with a Hazard Ratio (HR) of 4.61 (95% CI 1.01-21.03). Heterogeneity was moderate in both analyses.

Finally, for treatment which exceeded 10 years, there was virtually no difference in the odds ratio (OR) whether including the WHI study or not (15), showing no clear association. A distinction was noted when comparing these results with the Schairer study (42), where participants were treated for more than 12 years (Table II; Figs. 4 and S7).

Use at the time of diagnosis. When conducting the analysis based on HRT status at the time of diagnosis, two distinct groups emerged: those actively using HRT (defined as 'Current') (10,34,36,39-42,45,47,48,51,52,59,60) and those who had previously used it (defined as 'Past') (10,15,34,36,42,45,48,51,52,59,60); (Fig. 5; Table II).

In this analysis, current users had a lower risk of breast cancer mortality, whereas past users did not differ from those who had never used HRT (Table II; Fig. 5). Removing the WHI study did not materially change the estimates for past users (Fig. S8).

Significant heterogeneity was observed among the included studies, which remained similar even when the WHI Study (15) was excluded.

Year of recruitment. For this analysis, we categorized studies based on the year of recruitment. On the one hand, studies with participant recruitment before the year 2000 (10,15,34-36,38-47,49-57,60,61); on the other, studies with participant recruitment after the year 2000 (8,48,58) (Fig. 6; Table II). That year marked a turning point in the use of HRT following the publication of the WHI trial results (15).

When the recruitment occurred after the year 2000, HRT use was significantly associated with lower breast cancer mortality, without heterogeneity across combined studies. Conversely, when examining studies with earlier recruitment, a decrease in the strength of the association was noted, with moderate heterogeneity (Table II; Fig. 6).

Exploring the influence of article quality and risk of bias. Finally, we evaluated the impact of study quality (Fig. S9; Table II). Separating studies by their NOS score revealed only minor differences. In high-quality studies (NOS≥7) (8,10,15,34-36,38,39,42,44,46-48,50-53,56,58,60,61), the strength of the association was slightly weaker than in moderate-quality studies (NOS<7) (40,41,43,45,49,54,55,57). Furthermore, heterogeneity was higher in the lower-quality group. However, the test for subgroup differences was not statistically significant (P=0.76).

We also stratified the analyses by ROBINS-E risk of bias (Fig. S10), classifying studies as having low (36,39,40,48,60), moderate (34,41,42,45,47,50,55,56,58), or high risk (8,15,35,38,43,44,46,49,51-54,57,61). We found a statistically significant association in both low-risk studies and in high-risk studies, whereas the association did not reach statistical significance in studies with moderate risk of bias. Across all three risk-of-bias strata, heterogeneity was moderate and the overall test for subgroup differences was insignificant. Taken together, these findings indicate that the results are broadly consistent across levels of study quality and risk of bias, although estimates are less precise in studies with lower-quality or moderate-risk.

Meta-regression analysis. We conducted a meta-regression to assess potential sources of heterogeneity in our analyses.

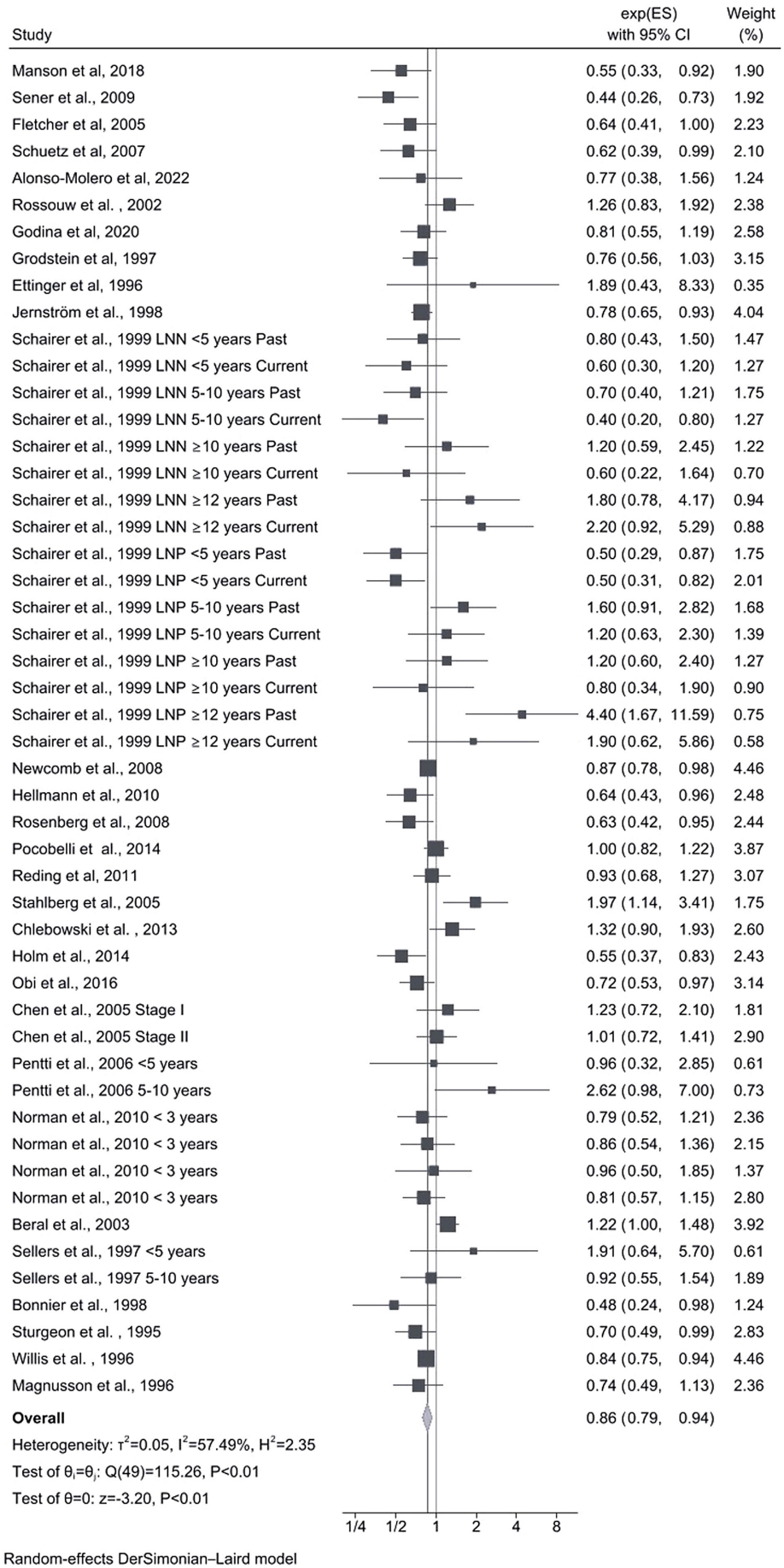

Figure 3. Forest plot of the association between hormone replacement therapy use and breast cancer mortality. exp(ES), exponentiated effect size (expressed as odds ratio); LNN, lymph node negative; LNP, lymph node positive.

Table II. Results from the present meta-analysis.

Subgroup	Number of studies	Number of patients	exp(ES) (95% CI)	I^2 (%)
HRT duration[a]				
<5 years	10	791,147	0.80 (0.69-0.94)	41.55
5-10 years	10	791,147	0.85 (0.70-1.03)	54.54
>10 years	3	718,981	1.33 (0.96-1.85)	49.01
HRT use status at the time of diagnosis[a]				
Current	14	1,545,188	0.82 (0.70-0.96)	63.70
Past	11	1,555,184	1.01 (0.90-1.13)	38.90
Year of recruitment				
Women recruited in 2000 or later	3	5,820	0.75 (0.60-0.95)	0.00
Women recruited before 2000	26	2,170,399	0.87 (0.79-0.96)	59.51
Article quality				
High-quality studies (NOS ≥7)	21	2,104,313	0.87 (0.79-0.96)	66.43
Moderate-quality (NOS ≤6)	8	71,906	0.83 (0.62-1.11)	68.02
Risk of bias (ROBINS-E tool evaluation)				
Low	5	34,507	0.83 (0.71-0.96)	43.12
Moderate	9	901,023	0.93 (0.77-1.12)	63.51
High	18	1,275,147	0.87 (0.76-0.98)	54.37

[a]Including the WHI study. The same analysis without the WHI study is shown in Table SII. exp(ES), exponentiated effect size (expressed as odds ratio); HRT, hormone replacement therapy; NOS, Newcastle Ottawa Scale; OR, odds ratio; ROBINS-E, Risk of Bias in Non-Randomized Studies of Exposures; WHI, Women's Health Initiative.

Predictors such as the quality of included articles, publication year, and recruitment year were evaluated. In none of these analyses did any of the variables appear to influence the heterogeneity shown, as the R^2 value was always zero (Table III). Given the limited number of studies relative to the number of potential predictors, these analyses were likely underpowered and should be interpreted with caution.

Discussion

Our study has highlighted several key findings that contribute to the current understanding of the relationship between HRT and breast cancer prognosis. The results indicate that HRT use prior to breast cancer diagnosis is associated with improved survival in breast cancer patients, consistent with findings reported in a previous meta-analysis (27).

The potential mechanisms that may underlie the observed association with a better prognosis include the following factors: 1) women taking HRT tend to adopt healthier lifestyles and maintain a lower BMI [8], and 2) women using HRT often undergo more frequent gynecological and breast cancer screenings, leading to earlier detection of less aggressive (more hormone-dependent) cancers (62).

Interestingly, our analysis also revealed potential disparities in the impact of HRT use on breast cancer survival based on the year of participant recruitment. Studies with participant recruitment before the year 2000 (10,15,38-41,43,61) showed lower odds of breast cancer mortality among HRT users than non-users, whereas studies recruiting after 2000 showed an attenuated difference (8,58). This temporal difference could be attributed to changes in HRT prescription practices, formulations, or population characteristics over time. Although an inverse association was observed for shorter treatment durations in some analyses, current use at diagnosis was associated with lower mortality compared with never having taken HRT, these findings were not fully consistent across all subgroup analyses. In addition, the statistical power of the duration of use and use-at-diagnosis subgroups is limited because these subgroups rely on a relatively small number of studies. Consequently, these results should be considered exploratory and interpreted with caution rather than as definitive evidence of effect modification. Furthermore, to the best of our knowledge, only three articles included women recruited after the year 2000, which further restricts the precision of these estimates and highlights the need for further research in this field.

Although our pooled analysis suggests that pre-diagnostic HRT use is associated with improved breast cancer survival, several lines of evidence indicate that this association may be at least partially attributable to confounding by health behaviors, screening intensity, and selective prescribing patterns rather than reflecting a direct causal protective effect. Multiple observational studies included in our meta-analysis document substantial baseline differences between HRT users and non-users. For example, cohorts with detailed baseline information such as Newcomb *et al* (36), Rosenberg *et al* (34), Godina *et al* (8), Alonso-Molero *et al* (58), Pocobelli *et al* (60), and others (42,46-48,50,53-55,57) consistently show that women using HRT tend to have a lower body mass index, healthier lifestyle profiles (including lower smoking rates and more moderate alcohol consumption), higher educational attainment, and more frequent engagement with preventive

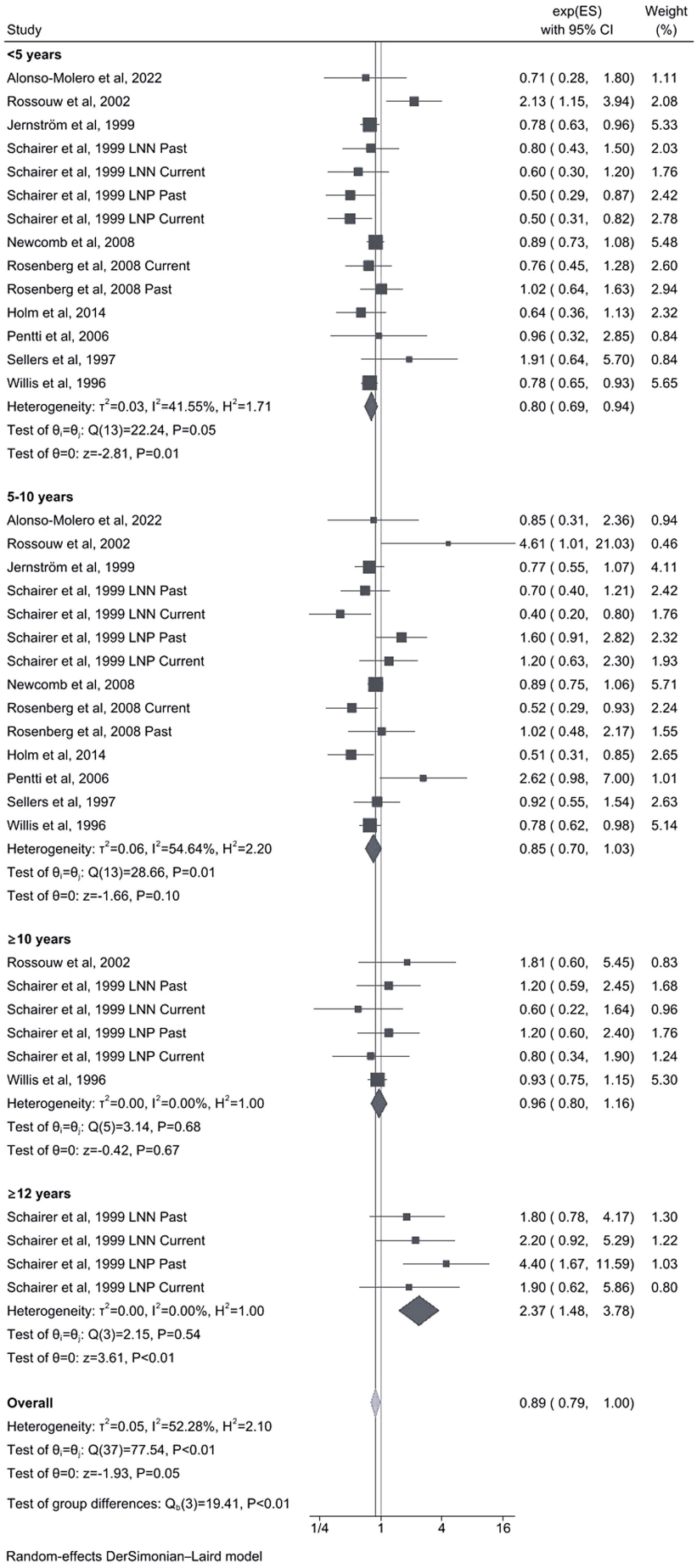

Figure 4. Forest plot of the association between HRT use and breast cancer mortality based on HRT duration. exp(ES), exponentiated effect size (expressed as odds ratio); HRT, hormone replacement therapy; LNN, lymph node negative; LNP, lymph node positive.

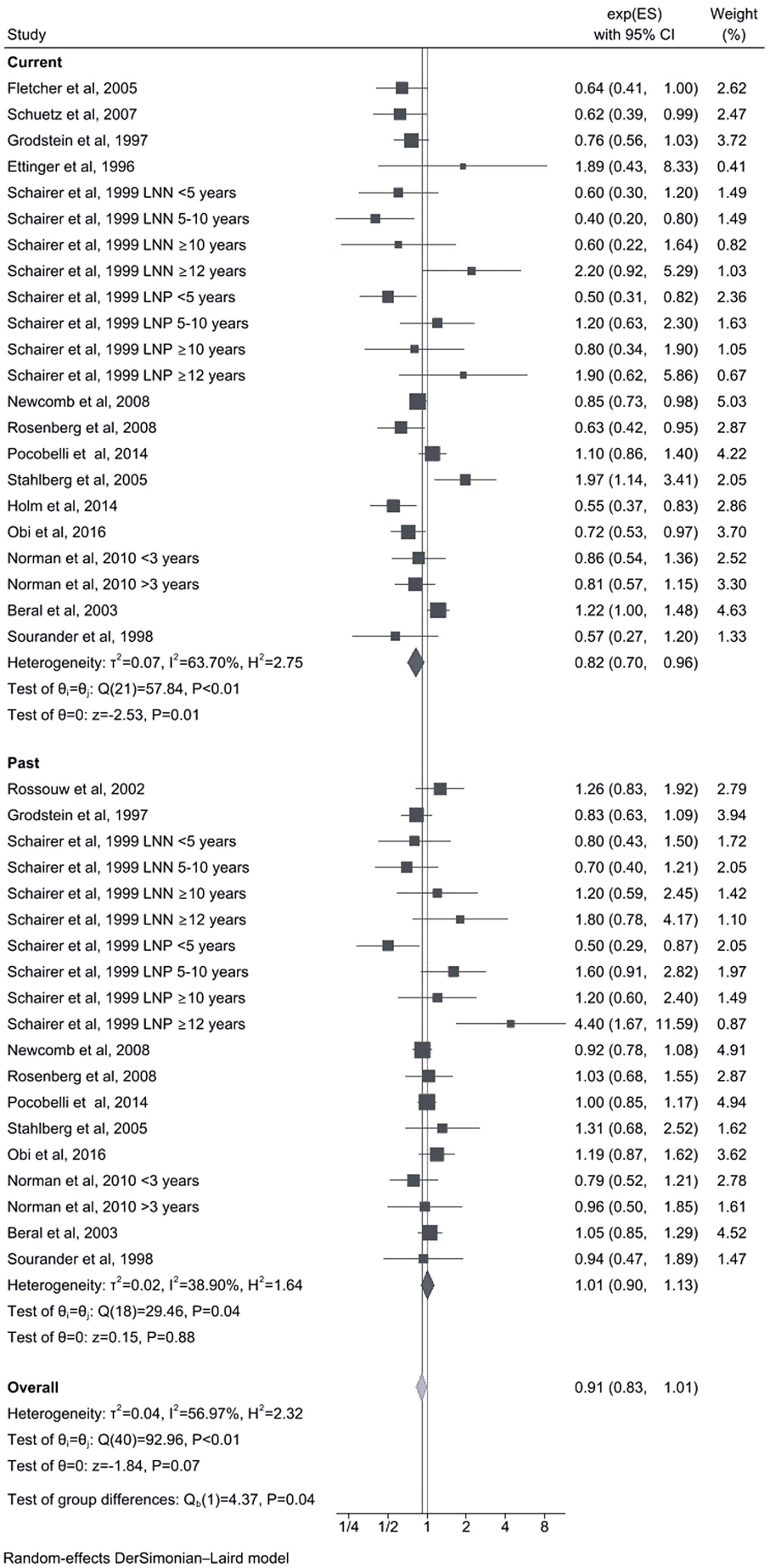

Figure 5. Forest plot of the association between HRT use and breast cancer mortality based on the status of HRT use at the time of diagnosis. exp(ES), exponentiated effect size (expressed as odds ratio); HRT, hormone replacement therapy; LNN, lymph node negative; LNP, lymph node positive.

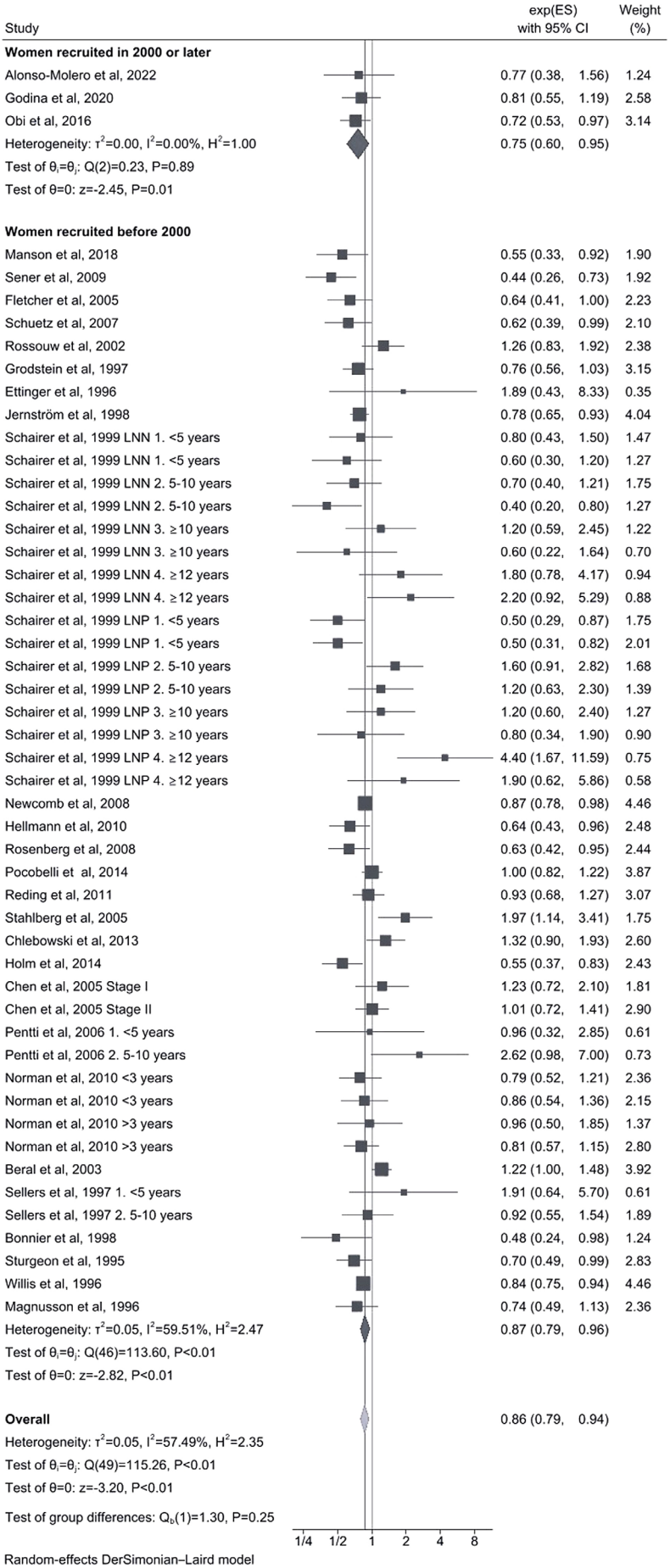

Figure 6. Forest plot of the association between hormone replacement therapy use and breast cancer mortality categorized by recruitment period. exp(ES), exponentiated effect size (expressed as odds ratio); LNN, lymph node negative; LNP, lymph node positive.

Table III. Meta-regression analysis.

Subgroup	Coefficient (95% CI)	τ^2	I^2, %
Model	Not applicable	0.045	57.49
Period of recruitment before 2000	-0.136 (-0.260 to 0.530)	0.065	65.95
Year of publication	-0.006 (-0.020 to 0.008)	0.067	65.29
High quality (NOS ≥7)	0.061 (-0.200 to 0.330)	0.066	66.23

NOS, Newcastle Ottawa Scale.

health care, including regular mammography and gynecological check-ups. These women are also more likely to be diagnosed with earlier-stage tumours and more favourable prognostic profiles at breast cancer diagnosis. This pattern is consistent with a 'healthy estrogen user' profile and suggests that residual confounding by unmeasured or incompletely adjusted lifestyle, comorbidity, and socioeconomic factors may persist even in studies that performed multivariable adjustment.

In addition, several studies (8,34,36,42,48) with detailed information on pre-diagnostic mammographic history and mode of tumour detection report that HRT users are significantly more likely to have screen-detected breast cancers, and their tumours tend to be smaller and less advanced at diagnosis compared to non-users. This raises the possibility that lead-time bias and detection bias contribute to the observed survival advantage, as earlier detection among HRT users may inflate survival estimates without necessarily altering the underlying disease course. In this context, the apparently lower breast cancer mortality among current HRT users should be interpreted with particular caution, as it is highly susceptible to healthy-user and survivor biases and may not reflect a direct protective effect of HRT.

Furthermore, evidence from the Breast Cancer Detection Demonstration Project (42) and related cohorts indicates that HRT is selectively prescribed to, and maintained in, healthier women, and is often discontinued when women develop symptoms of serious illness. This creates a 'healthy estrogen user survivor effect' whereby current users appear to have lower mortality rates not because HRT confers protection, but because women who remain on HRT are systematically healthier than those who stop or never start therapy. In contrast to these observational findings, the randomised Women's Health Initiative trial (15) which, by design minimizes healthy-user bias and differential screening, did not demonstrate a survival benefit from combined oestrogen-plus-progestin therapy. Taken together, these considerations suggest that while our meta-analysis demonstrates a consistent inverse association between pre-diagnostic HRT use and breast cancer mortality across multiple observational studies, this association should be interpreted cautiously and may not reflect a true causal protective effect.

Our comprehensive evaluation of study quality and potential biases using the NOS (29) and the ROBINS-E tool (30) enhances the robustness of our findings. A substantial proportion of the included studies were judged to have suboptimal quality or a high risk of bias according to the NOS and ROBINS-E assessments. However, stratified analyses showed that the direction and magnitude of the association between HRT use and breast cancer prognosis were broadly similar across NOS and ROBINS-E strata, and tests for subgroup differences were not statistically significant. These findings support the robustness of the overall association but also indicate that the high prevalence of bias and the imprecision observed in some subgroups should temper confidence in the exact magnitude of the association.

Furthermore, it is noteworthy that our analyses revealed the influence of specific studies on heterogeneity. When the WHI study (15) was removed from the analysis of HRT use at the 'Time of Diagnosis', the heterogeneity between studies decreased even further, with an I^2 of 1.05% (P=0.43). The WHI Study (15) itself demonstrated the most pronounced association in the subgroup analysis of HRT duration of use analysis for the period of less than 5 years, reporting an RR of 2.13 (95% CI 1.15-3.94). However, the remaining evaluated studies indicated an association between HRT use and breast cancer survival. A moderate-to-high degree of heterogeneity was initially observed, with an I^2 of 63.28% (P=0.01). Nevertheless, when the WHI study was excluded, the heterogeneity disappeared (I^2=0% and P=0.46). These observations accentuate the potential influence of specific studies on the overall heterogeneity of the results. One of the possible explanations that could justify the discordant results from the WHI study could be the advanced age of the participants or the inclusion of only those who showed no signs of cancer on a previous mammogram (63).

The strengths of our study compared to previous meta-analyses, include the incorporation of the ROBINS-E tool (30), which enables the systematic evaluation of potential biases, ensuring methodological rigor in observational research. Additional strengths include stratification by publication years and the inclusion of three articles published after 2017 (8,38,58), the publication year of the aforementioned meta-analysis. These articles all feature follow-up periods exceeding 10 years and are high-quality studies with NOS scores of 7 or higher.

Despite the valuable insights gained from this meta-analysis, several limitations warrant consideration. First, the observed heterogeneity among studies could be influenced by differences in study design, patient populations, treatment regimens, and methodological approaches. A longer follow-up period and a more precise assessment of HRT use would be necessary to provide a more accurate estimation of breast cancer survival with HRT.

Second, the potential for publication bias, as suggested by funnel plot asymmetry, indicates that smaller studies with non-significant findings might be underrepresented.

Third, there could be heterogeneity in the combined odds ratios (ORs) due to variations in study methodologies; some studies utilized raw data without controlling for confounding factors, whereas others adjusted for relevant confounders. However, the sensitivity analysis restricted to adjusted estimates showed an association (OR=0.88) very similar to the overall result (OR=0.86), which supports the robustness of the main finding.

Fourth, the definition of HRT exposure varied across studies, and the necessity to harmonize different exposure categories may have introduced non-differential misclassification. This could attenuate differences between subgroups and bias the corresponding estimates towards the null.

Fifth, different effect measures (HRs, RRs and ORs) were combined as generic relative effects, even though these measures are not strictly interchangeable for time-to-event outcomes. Nevertheless, sensitivity analyses restricted to each effect measure separately yielded pooled estimates that were very similar in magnitude and direction to the main analysis, suggesting that this approximation is unlikely to have substantially biased the overall findings.

Sixth, there is a lack of information regarding HRT dosage, and substantial variations exist in the methods used to group regimens across studies.

Finally, several subgroup analyses were based on a limited number of studies in some strata, so these findings should be interpreted with caution. From a clinical perspective, these observational findings should not be interpreted as evidence to initiate or continue HRT use with the aim of improving breast cancer prognosis.

In conclusion, our systematic review and meta-analysis suggest that HRT use prior to breast cancer diagnosis is associated with improved breast cancer survival, although the statistical power of some subgroup analyses is limited by the low number of available studies. The observed association with better survival appears to be influenced by factors such as treatment duration, timing of discontinuing HRT use, and the year of participant recruitment. These findings underscore the complexity of the relationship between HRT use and breast cancer prognosis and emphasize the need for personalized assessment of HRT use in the context of breast cancer management. Further research is warranted to clarify the underlying mechanisms and potential clinical implications of these observed associations. Importantly, these observational data do not support the use of HRT as a therapeutic strategy to enhance breast cancer prognosis.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

JACF contributed substantially to the conceptualization and design of the study, conducted an independent bibliographic search, created the database with the relevant information extracted from each article, contributed to the analysis and interpretation of the data, and wrote the paper. JAM conducted an independent bibliographic search and data extraction as part of the double-blind review process of the meta-analysis. JACF and JAM confirm the authenticity of all the raw data, performed the statistical analysis and participated in the critical revision of the manuscript. JACF and PRC contributed to the evaluation of the quality by applying the Newcastle Ottawa Scale and the interpretation of the data. JL supervised the analysis and interpretation of the data. IGA contributed to the conceptualization and design of the study and participated in the critical revision of the manuscript. TDS contributed to the conceptualization and design of the study, performed the analysis and contributed to the interpretation of the data, and wrote the paper. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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