



Systematic Review Impact of Hormone Replacement Therapy on the Overall Survival and Progression Free Survival of Ovarian Cancer Patients: A Systematic Review and Meta-Analysis

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Simple Summary: The standard treatment course for ovarian cancer virtually always induces menopause with subsequent symptoms. This systematic review and meta-analysis strived to further elucidate the safety of Hormone Replacement Therapy in the setting of ovarian cancer treatments by investigating its effect on Overall Survival and Progression-Free Survival. The results highlighted a slight benefit in terms of survival and recurrence rates in favour of the hormone replacement therapy groups, pooling respective Hazard Ratios (HR) of 0.66 and 0.73. However, detailed subgroup analyses revealed no statistically significant results in terms of recurrence for the treated groups, while data were sequenced based on stages, grade of differentiation, the radicality of surgery, and the age of participants. Even so, in null outcomes regarding progression-free survival, hormone replacement therapy remains advantageous in lessening menopausal symptoms and improving the quality of life for these patients.

Abstract: Background: Frequently, patients treated for Ovarian Cancer (OC) undergo menopause with subsequent symptoms. This review scrutinised the impact of Hormone Replacement Therapy (HRT) on the Overall Survival (OS) and Progression-Free Survival (PFS) of patients diagnosed with OC. Methods: A systematic literature search was conducted in the most popular English databases. Inclusion and exclusion criteria were applied to select publications that evaluate OS and PFS in these patients. End-point analysis targeted values of log(HR) and its Standard Error (SE). Results: Up to 1 September 2022, 11 studies were included in the qualitative synthesis. Eight publications, totalling 4191 patients, were included in the meta-analyses. Eight studies were considered for the OS analysis and pooled an HR of 0.66 with respective 95% CI between 0.57 and 0.76, with a *p*-value < 0.00001 at a Z value of 5.7, in favour of the HRT group. Results for PFS showed an overall HR of 0.73 in favour of the HRT group; CI between 0.57 and 0.95, *p* = 0.02 at a Z value of 2.36. Further subgroup analyses highlighted the non-inferiority of this treatment. Conclusions: Patients treated for OC that receive HRT for menopausal symptoms after various treatments appeared to have better OS than never-users.

Keywords: ovarian cancer; hormone replacement therapy; overall survival; progression-free survival; menopause; gynecological cancers; quality of life

1. Introduction

The vast majority of ovarian cancers (OC) are diagnosed at stages FIGO (The International Federation of Gynecology and Obstetrics) III and IV [1]. This makes OC one of the most lethal gynaecological neoplasias, with very high mortality rates compared to its relatively low incidence [2]. This is because most cases produce little to no symptoms or have very unspecific manifestations [3]. Moreover, no advantage has been ascertained from



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Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). a systematic population screening using miscellaneous markers and scores or imaging findings [4]. Although most recent breakthroughs in ovarian cancer treatments regarding either BRCA (Breast Cancer gene)-positive cases [5] or Homologous Recombination Deficiency (HRD) mutations [6] have pivoted the paradigm in systemic maintenance strategies, the golden-standard first-line therapy for these patients remains platinum-based chemotherapy or surgery or a combination of the above [7]. These therapeutic approaches virtually always induce menopause with ensuing symptoms.

Climax morbidity has been intensely investigated over the past decades [8]. Multifarious strategies have been deployed to mitigate symptoms, such as vasomotor reactions, loss of bone density, increased risk of cardiovascular events and problems regarding sexual health [9]. One of the most compelling and well-known strategies consists of using Hormone Replacement Therapies (HRTs) based on either Estrogen or Progesterones, or a combination of both. These therapies have increased in popularity since the FDA (Food and Drug Administration) approved Premarin, a mixture of over 50 estrogens used to treat hot flushes. Shortly after, studies demonstrated an increased risk of endometrial neoplasia [10] in patients using conjugated estrogens, while prospective investigations deemed HRT detrimental [11]. Although methods have been deployed to mitigate some of these issues, such as restricting the use of unopposed estrogens, developing combined estrogen and progesterone therapies and some studies being reinterpreted [12], HRT remains a contentious matter. Moreover, recent studies even unveiled a decreased risk for developing OC that was associated with oral contraceptive use [13].

The use of HRT, although highly efficacious in lessening postmenopausal symptoms, positively correlated with the onset of malignancy. The existence of estrogen and progesterone receptors in Epithelial Ovarian Cancer (EOC) cells has been well documented [14]; hence, the safety of HRT use in patients diagnosed with OC remains pending. However, more contemporary publications explored the safety of such treatments in the setting of OC. They even found a positive correlation between the use of HRT and the OS of these patients [15]. Consequently, investigating these relationships is of utmost importance, and such analyses might further clarify conflicting results. Even in null outcomes on the Overall Survival (OS) or Progression-Free Survival (PFS) of OC patients, HRT would still be advantageous in relieving menopausal symptoms and improving Quality of Life (QoL). Therefore, this systematic review and meta-analysis were undertaken to explore the influence of HRT on the OS and PFS of patients diagnosed with OC.

2. Materials and Methods

A systematic literature search was completed in the most popular English language databases: PubMed, SCOPUS, EMBASE and Web of Science. Duplicates were excluded manually and by using the automatisation softwares EndNote [16] and Zotero [17]. Data were exported into a workflow Excel spreadsheet in Supplementary Materials (Microsoft Excel 2016, Microsoft Corporation, Redmond, WA, USA) [18]. Title and abstract screening excluded irrelevant publications. The remaining articles were refined through inclusion and exclusion criteria before being included in the final analysis. Crucial data were pooled from primary publications, while the end-point analysis was based on log Hazard Ratios log(HR) and its Standard Error (SE). This review heeded The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [19].

2.1. Eligibility Criteria

2.1.1. Inclusion Criteria

Inclusion criteria were acquired based on the PICO strategy:

Population: patients diagnosed with and treated for ovarian cancer and, therefore, at surgically or medically induced menopause. Any age, grade, histological type and treatment was considered.

Intervention: patients that receive HRT in any type and form (estrogens, progesterones or combinations).

Control: similar control groups encompassing never-users of HRT.

Outcomes: studies that evaluate the OS and PFS of the experimental and control groups. Data might be reported as unadjusted HR from univariate analyses and respective Confidence Intervals (CI), number of expected and observed events and log-rank testing *p*-values, or simply providing the analysed number of patients and total events and respective log-rank *p*-values.

Type of Study: Randomised or non-randomised Controlled Trials (RCTs and non-RCTs), good quality prospective or retrospective cohort studies, good quality case-control studies.

2.1.2. Exclusion Criteria

Language:	articles in languages other than English
Different study designs:	case reports, case series, other reviews and meta-analyses,
	umbrella reviews
Full-text:	articles with no full-text available
Missing data:	no OS or PFS analyses; missing CI for respective HR;
missing data that did r	ot allow the pooling of log(HR) and SE; studies that only

present multivariate Cox regression HRs adjusted for various aspects.

2.2. Information Sources

The search formula was used in the most popular English databases: PubMed, SCO-PUS, EMBASE and Web of Science.

2.3. Search

A predefined search formula was used as follows: "((hormone replacement therapy) OR (estrogen replacement therapy) OR (progestin replacement therapy) OR (estrogenprogestin combination therapy)) AND ((ovarian cancer) OR (ovarian neoplasm))". Correct terms were indexed using Medical Subject Headings (MeSh); however, the final search strategy was composed of unrestrained words to ensure the maximum pooling of publications.

2.4. Data Collection Process

Search results were screened for duplicates using automatisation software (End-Note [16] and Zotero [17]). The remaining articles were considered based on Title and Abstract to exclude irrelevant publications. Relevant studies were filtered through inclusion and exclusion criteria. The selection process was conducted by two independent reviewers (AP and DLP), while a third one resolved dissimilarities (PAAC).

2.5. Data Items

Elemental data were extracted from included studies: primary author, year of publication, study design, population characteristics (age, type of OC, type and duration of treatment), HRT course, regimen and moment of inception, side effects, efficacy measures, OS and PFS in HR with 95% CI. For studies that did not include unadjusted HR values, data regarding the number of analysed patients, observed events and log-rank *p*-values were also used.

2.6. Risk of Bias within Studies

Risk of Bias Assessment Tool 2 (RoB2) [20] was used for the quality assessment of RCTs. Quality appraisal for non-RCTs, cohorts (both prospective and retrospective) and case-control studies was evaluated using the Newcastle-Ottawa Scale (NOS) [21] and the NOS for case-control studies, a variation of the original NOS.

2.7. Summary Measures

There are many ways to express time-to-event data in publications. Although dichotomous data can always be used, and consequently, risk ratio measures are analysed, the ratio

effect measure of HR was used, as per Cochrane's recommendations [22]. The ratio summary statistics can take the lowest value of 0 and go up to infinite values, while one is usually thought to be the null effect. Accordingly, the log transformation is usually undertaken. This will render confidence intervals appearing symmetric and is the preferred method for analysing data [23]. Peto's method [24] is acceptable for fixed effects meta-analyses, and the $\left[\frac{\sum logrank(O-E)}{\sum logrank(V)}\right]$, where O - E represents the Observed minus Expected pooled $\ln HR =$ and V stands for Variance. For this meta-analysis, however, the inverse variance approach was used—the pooled lnHR = $\left[\frac{\sum \frac{\ln HR}{V}}{\sum \frac{1}{V}}\right]$, where V represents the variance of lnHR. Cox proportional hazard models usually provide InHRs and SE and, therefore, are compatible with the inverse variance pathway. Sometimes, studies might provide HRs and respective $\left[\frac{\text{UppCI-LowCI}}{2 \times \phi^{-1}(1-\frac{\alpha}{2})}\right]^2$. The UppCI 95% CI. In this case, V can be obtained by the formula V =and LowCI are the upper and lower 95% CI, and ϕ stands for the cumulative distribution function of the normal distribution. Hence, $\phi^{-1}(1-\frac{\alpha}{2}) = 1.96$ for 95% CI. Regardless, the most suitable statistics are not always presented in primary publications; therefore, transformations need to be done to obtain the lnHRs and their variance [25]. Tierney et al.'s paper accurately depicts 10 ways to obtain the desired summary measures from individual trials, while Cochrane's handbook depicts 3 main derived reliable methods. While the first was discussed above, another possibility is obtaining HR estimates from the log-rank analysis, a direct method. Here, Simmonds [26] describes the $\ln HR = \frac{(O-E)}{V}$, where O stands for the observed events in the research groups, E is the log-rank expected number of events and V stands for the variance of the test. However, sometimes data are presented as just the number of analysed patients, events in both groups and perhaps a *p*-value from the log-rank test [27]. For these instances, the following were used: in the case of equal randomisation in both arms of the trial, the $(O - E) = \frac{1}{2} \times \sqrt{O \times \phi^{-1}(1 - \frac{p}{2})}$. Here, the O is the number of observed events, and *p* is the *p*-value derived from the Mantel-Haenszel version of the log-rank statistics. Variance is roughly estimated by the formula $V \approx \frac{O}{4}$. A formula for variance is given when the number of observed events is reported for both the experimental and control groups: $(O - E) = \sqrt{\frac{O_r \times O_c}{O} \times \phi^{-1}(1 - \frac{p}{2})}$. Here, O_r stands for the number of observed events in the research group, the O_c represents the number of observed events in the control group, while O is the total number of observed events. In this scenario, the variance will be estimated by $V \approx \frac{O_r \times O_c}{O}$. If the randomisation is not equal in both groups, another formula was employed: $(O - E) = \frac{\sqrt{O \times R_r \times R_c}}{(R_r + R_c)} \times \phi^{-1} (1 - \frac{p}{2}).$ Here, the Rc stand for the number of patients. The variance will be estimated accordingly to $V \approx \frac{O \times R_r \times R_c}{(R_r + R_c)^2}$. Regardless of the method used, the (O – E) and V values were imputed in $\ln HR = \frac{O-E}{V}$, and the var(ln(HR)) is easily deduced by var(ln(HR)) = $\frac{1}{V}$. These values were finally used in the inverse variance method for obtaining pooled HRs. The third option will be to reconstruct data from the Kaplan-Meier survival curves [28] if neither of the above is presented in the original papers.

2.8. Planned Analysis Method

Data were computed into the Fixed or Random Effects model depending on the levels of heterogeneity. Heterogeneity was assessed using the Chi-squared (Chi²) test. The cut-off values for p were set at 0.10. I² values of 25, 50 and 75% were considered low, medium and high heterogeneity.

2.9. Publication Attrition

Publication bias was highlighted using Funnel Plots.

2.10. Additional Analyses

Subgroup analyses were planned where possible. Data sequencing was based on types of OC and HRT type, disease stage, participants' age, resectability status and duration of treatment. Sensitivity analyses were achieved by excluding one study at a time from the meta-analyses. The analysis had robust sensitivity if the overall HR remained in the initial CI. All statistical analyses were performed using Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020 [29].

3. Results

3.1. Study Selection

The final database search was performed on 1 September 2022, and retrieved 7814 results. Automatisation software eliminated 2656 duplicates, while the rest were eliminated manually (429). Title and abstract screening excluded a total of 4688 irrelevant studies. The remaining publications were filtered through inclusion and exclusion criteria. Thirty studies were excluded as follows: eight studies [30–37] were conference papers, case reports or other reviews; six [38–43] did not concentrate on OC; six [44–49] did not asses OS, PFS or the effects of HRT; another six [50–55] did not provide a complete text; three publications [56–58] only evaluated the pre-diagnosis effect of HRT in OC; while one study [59] presented in-vitro results. Finally, 11 studies [15,60–69] were included in the qualitative synthesis. Due to a lack of data in these publications, only eight [15,61–63,66–69] were part of the quantitative meta-analyses, as the other three did not present adequate summary statistics measures to estimate respective logHR and SEs. A PRISMA study selection flowchart [19] can be consulted in Figure 1.



Figure 1. PRISMA flow diagram of included studies.

3.2. Study Characteristics

Essential data extracted from primary publications are shown in Table 1. Two RCTs [15,62] and one non-RCT [60] were included, alongside seven cohort studies and one retrospective case-control study. Only five publications reported adverse side effects of HRT [15,60,61,63,68], and two reported second primary malignancies [15,63].

Study ID	Year	Study Design	Age (Years)	Type of OC	Figo Stages	Type of Tx	Type of HRT	Duration of HRT	Moment of Inception	Follow-Up	Side Effects
Eeles [64]	1991	Retrospective case-control	<20-50	Serous, mucinous, endometrioid, adenocarcinoma, clear cell	I–IV	Surgery	E, E + P, P, testosterone	Median (range): 28 (<1-200) months	-	Median (range): 42 (<1–216) months	-
Malfetano [60]	1993	Non- randomised phase II Clinical Trial	median (ranges): 58.5 (42–76)	Epithelial carcinoma	Advanced or recurrent, including metastatic	Patients previously treated with chemotherapy and failed or progressed under first-line	Medroxyprogesterone acetate (P)	Median (ranges): 2 (1–8) months	-	-	Gastrointestinal = 1, anemia = 1 (grade 2) and 1 of each: renal, pulmonary, dermatologic and gastrointestinal (grade 1)
Guidozzi [62]	1999	RCT	27–59	Serous, mucinous, endometrioid, clear cell	I–IV	Surgery and chemotherapy	E (Premarin)	-	6–8 weeks after surgery	-	-
Uršič-Vršaj [63]	2001	Retrospective cohort	mean (range): HRT group 41 (27–51) and control 43 (23–59)	Serous cystade- nocarcinoma	I–III	Surgery or surgery followed by chemotherapy and/or radiation therapy	E, E + P	Mean (ranges): 24 (1–70) months	Mean (ranges): 21 (1–25) months after diagnosis	Mean (ranges): 49 (11–141) months	Breast carcinoma
Mascarenhas [69]	2006	Cohort	mean (SD): HRT group 58.81 (7.75) and control 63.72 (7.02)	Serous, mucinous, endometrioid, others, unclassified histology	I–IV	-	E, E + P (P added cyclically or continuous), Estriol (vaginally and orally)	Variable	-	5 years	-
Li [65]	2012	Cohort	mean (ranges): HRT group 40.3 (20–45) and control 42.9 (20–45)	Serous adenocarcinoma, mucinous adenocarcinoma	I–111	Surgery and chemotherapy	E, E + P	-	20 days after cytoreductive surgery	-	-
Wen [68]	2013	Retrospective cohort	mean (range): HRT group 39 (16, 54) and control 38 (19, 53)	Serous, mucinous, endometrioid, clear cell, other	I–IV	Surgery and/or chemotherapy	Estrogen-tibolone, tibolone	Median (ranges): 12 (1, 140) months	-	At least 1 year	Mammary gland hyperplasia = 3
Bęević [67]	2015	Cohort	median (range): 61 (34, 98)	Serous, mucinous, endometrioid, clear cell, NOS, other	I–IV	-	E, E + P, other	Variable between <1 year and >10 years	-	Mean (SD): 3.6 (3.2) years	-

Table 1. Key data from the included publications. E = Estrogen-based therapy. P = Progesterone based therapy.

Tal	ble	1.	Con	t.

Study ID	Year	Study Design	Age (Years)	Type of OC	Figo Stages	Type of Tx	Type of HRT	Duration of HRT	Moment of Inception	Follow-Up	Side Effects
Eeles [15]	2015	RCT	median (range): 58.7 (29.3, 89.6)	Serous, mucinous, endometrioid, clear cell, undifferentiated, other, unknown	I–IV	Chemotherapy: single agent platinum, platinum-based doublet or triplet regimen, other. Surgery	conjugated estrogens, conjugated estrogens and norgestrel, estradiol patch, estradiol implant	5 years	Median (IQR): 4.1 (1.6, 6.3) years after diagnosis	Median (IQR): 19.1 (18.2, 20.2) years	Transient ischemic attack, cerebrovascular accident, myocardial infarction, fracture, second primary malignancy (breast = 2, colon = 1, jejunum = 1)
Zhang [61]	2016	Retrospective cohort	mean (range): HRT group 33.5 (21, 50) and control 31.2 (22, 50)	Serous	I–III	Surgery and/or chemotherapy	Estrogen, estrogen-tibolone, tibolone	Median: 20 months	Mean (ranges): 7 (2, 19) months after completing chemotherapy	At least 1 year	Mammary gland hyperplasia = 2
Ji [66]	2022	Retrospective cohort	mean (SD): 41 (11); HRT group 41.5 (8.5) and control 41 (11.4)	-	-	Primary surgery, surgery and neoadjuvant and/or adjuvant chemotherapy	Oral and transdermal: E, E + P, tibolone	Mean (SD): 3.48 (2.91) years	Mean (SD): 127.2 (93.7) days after primary surgery	Mean (SD): 5.6 (2.9) years	-

3.3. Risk of Bias within Studies

The NOS [21] was used for the included cohort studies [61,63,65–69], case-control studies [60] and non-randomised trials [60] to assess bias. All studies received good to excellent ratings, ranging between 6 [60,64], 8 [65–67,69] and 9 [61,63,68] out of 9 overall stars, showing the sound quality of the included studies (Table 2).

Study ID	Year	Selection (Number of *)	Comparability (Number of *)	Exposure (Number of *)	Total (Number of *)
Eeles [64]	1991	2	2	2	6
Malfetano [60]	1993	3	0	3	6
Uršič-Vršaj [63]	2001	4	2	3	9
Mascarenhas [69]	2006	3	2	3	8
Li [65]	2012	4	2	2	8
Wen [68]	2013	4	2	3	9
Beević [67]	2015	3	2	3	8
Zhang [61]	2016	4	2	3	9
Ji [66]	2022	4	2	2	8

Table 2. NOS scores for the included cohort studies.

* = stars.

Eeles et al.' s [15] and Guidozzi's [62] RCTs were evaluated using the latest version of the RoB2 program [20] for parallel RCTs. Eeles et al.' s [15] study had a low risk of bias, while the other RCT presented some concerns. These were primarily due to the deviations from the intended interventions, as some participants in the experimental group stopped taking the HRT. Results are highlighted in Table 3.

Table 3. Rob scores for the included RCT.

Study ID	Year	Randomisation Process	Deviations from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall
Guidozzi [62]	1999	+	!	+	+	+	!
Eeles [15]	2015	+	+	+	+	+	+
		+					

Low concerns Some concerns.

3.4. Overall Survival Results

3.4.1. Results of Individual Studies

Eight studies totalling 3578 patients were included in the OS quantitative analysis. Four studies [15,66,67,69] provided unadjusted HRs with corresponding 95% CI; therefore, the direct method for extracting corresponding logHRs and SEs was used. Three other studies [61–63] provided observed events numbers in both groups; consequently, the indirect transformation formula using the provided log-rank *p*-values was used to determine logHRs and SEs. One study [68] presented both options; hence, the direct method was used again. Detailed results can be found in the supplementary material, the Summary Statistics sheet.

3.4.2. Synthesis of Results

The meta-analysis investigating the effect of HRT on OS of OC patients included 3578 patients, out of which 912 received HRT. The fixed effects model pooled an overall

			HRT	NO-HRT		Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% CI	Year	IV, Fixed, 95% Cl
Guidozzi (62)	-0.22	0.23	59	66	10.3%	0.80 [0.51, 1.26]	1999	
Ursic-Vrsaj (63)	-0.13	0.57	24	48	1.7%	0.88 [0.29, 2.68]	2001	
Mascarenhas (69)	-0.7765	0.1542	150	499	23.0%	0.46 [0.34, 0.62]	2006	_
Wen [68]	-0.3993	0.6712	- 77	77	1.2%	0.67 [0.18, 2.50]	2013	
Beevic [67]	-0.2242	0.1295	233	299	32.5%	0.80 [0.62, 1.03]	2015	
Eeles [15]	-0.4632	0.1826	75	75	16.4%	0.63 [0.44, 0.90]	2015	_
Zhang (61)	-0.07	0.51	31	81	2.1%	0.93 [0.34, 2.53]	2016	
Ji [66]	-0.4875	0.2062	263	1521	12.8%	0.61 [0.41, 0.92]	2022	- _
Total (95% CI)			912	2666	100.0%	0.66 [0.57, 0.76]		•
Heterogeneity: Chi ² =	9.28, df = 7 (P = 0.23 7 = 5 70 (P ≤ 0.0000	3); I ² = 25	%					0.1 0.2 0.5 1 2 5 10
restion overall effect.	2 - 5.10 (1 - 0.0000							Favours HRT Favours NO-HRT

HR of 0.66, with a 95% CI of 0.57 to 0.76, showing statistical significance (p < 0.00001) at a Z value of 5.70 in favour of the HRT group. Heterogeneity was 25%. The results are shown in Figure 2.

Figure 2. Forrest plots for the HRT vs. no-HRT groups' OS analysis.

3.4.3. Publication Bias

Publication attrition was assessed using funnel plots. The graphic in Figure 3 shows a slight tendency to asymmetry. No significant bias was detected.



Figure 3. Funnel plot for the OS analysis [15,61–63,66–69].

3.4.4. Result of Additional Analyses

Sensitivity analyses were achieved by excluding one study at a time from the quantitative synthesis, and results can be conferred in Table 4. All results remained in the initial 95% CI, and the overall effect was kept throughout, showing robust sensitivity.

None of the included studies reported results for the OS based on staging, resectability, differentiation or histological subtypes of the disease or age of the participants. Moreover, none of the publications reported results based on type, inception timing or HRT duration. Therefore, the only feasible subgroup analysis was based on the type of included publications, RCTs vs other types. As expected, sequencing results from RCTs only lessened the heterogeneity to 0%. The overall effect was kept at an HR of 0.69. Nevertheless, the other

types of studies pooled a higher 41% I² value. Even so, the effect carried over at an HR of 0.64. No subgroup differences were highlighted. Results can be consulted in Figure 4.

Excluded Study	Year	HR [95% CI]	Pooled HR [95% CI]	Pooled I ²	Pooled <i>p</i> -Value
Guidozzi [62]	1999	0.80 [0.51, 1.26]	0.64 [0.55, 0.75]	29%	< 0.00001
Ursic-Vrsaj [63]	2001	0.88 [0.29, 2.68]	0.65 [0.56, 0.76]	33%	< 0.00001
Mascarenhas [69]	2006	0.46 [0.34, 0.62]	0.73 [0.62, 0.86]	0%	0.0002
Wen [68]	2013	0.67 [0.18, 2.50]	0.66 [0.57, 0.76]	35%	< 0.00001
Beevic [67]	2015	0.80 [0.62, 1.03]	0.60 [0.50, 0.71]	0%	< 0.00001
Eeles [15]	2015	0.63 [0.44, 0.90]	0.66 [0.57, 0.78]	35%	< 0.00001
Zhang [61]	2016	0.93 [0.34, 2.53]	0.65 [0.56, 0.75]	32%	< 0.00001
Ji [66]	2022	0.61 [0.41, 0.92]	0.66 [0.57, 0.77]	35%	< 0.00001

Table 4. Sensitivity analysis for the OS statistics.



Figure 4. Forrest plot for the OS subgroup analysis based on the type of included studies.

Unremarkable findings were observed in the corresponding funnel plot for this analysis, which is shown in Figure 5.

3.5. Progression-Free Survival Results

3.5.1. Results of Individual Studies

Five studies totalling 613 patients were included in the PFS quantitative analysis. A summary of the results is shown in the Supplementary Material, in the Summary Statistics sheet. One publication [15] provided unadjusted HRs with corresponding 95% CI; therefore, the direct method for extracting corresponding logHRs and SEs was used. Two other studies [62,63] provided observed events numbers in both groups; thus, the indirect transformation formula using the provided log-rank *p*-values was used to determine logHRs and SEs. One study [68] presented both options, and the direct method was preferred.

Interestingly, one study [61] presented an unadjusted HR outside the 95% CI. However, the publication also provided the number of observed events in each group and log-rank statistics. Hence, the indirect method was used again. Details are provided in the supplementary material, in the Summary Statistics sheet.





3.5.2. Synthesis of Results

The meta-analysis examining the effect of HRT on the PFS of OC patients included 613 patients, out of which 266 received HRT. The fixed effects model pooled an overall HR of 0.73, with a 95% CI of 0.57 to 0.95, showing statistical significance (p = 0.002) at a Z value of 2.36 in favour of the HRT group. Heterogeneity was trivial at 0%. The results are shown in Figure 6.



Figure 6. Forrest plots for the HRT vs. No-HRT groups' PFS analysis.

3.5.3. Publication Bias

Publication attrition was assessed using funnel plots. The graphic in Figure 7 shows a slight tendency to asymmetry again. No significant bias was detected.



Figure 7. Funnel plot for the PFS analysis [15,61-63,68].

3.5.4. Result of Additional Analyses

Sensitivity analyses were achieved by excluding one study at a time from the quantitative synthesis, and the results can be conferred in Table 5. All results remained in the initial 95% CI, and the overall effect was kept throughout, showing robust sensitivity.

Excluded Study	Year	HR [95% CI]	Pooled HR [95% CI]	Pooled I ²	Pooled <i>p</i> -Value
Guidozzi [62]	1999	0.94 [0.50, 1.76]	0.70 [0.53, 0.93]	0%	0.01
Ursic-vrsaj [63]	2001	0.64 [0.26, 1.62]	0.74 [0.57, 0.97]	0%	0.03
Wen [68]	2013	0.73 [0.39, 1.35]	0.74 [0.55, 0.98]	0%	0.03
Eeles [15]	2015	0.68 [0.47, 0.97]	0.80 [0.55, 1.15]	0%	0.23
Zhang [61]	2016	0.86 [0.34, 2.16]	0.72 [0.55, 0.95]	0%	0.02

Table 5. Sensitivity analysis for the PFS statistics.

Multiple subgroup analyses were feasible. The first subgroup analysis was based on the type of included publications, RCTs vs other types. Heterogeneity remained trivial, and no subgroup differences were highlighted. At a closer look, results based on RCTs did not seem to carry over the effect, pooling an HR of 0.73, showing no statistically significant effect at a *p*-value of 0.05. Other studies failed to highlight any differences. Results can be consulted in Figure 8.

			HRT	NO-HRT		Hazard Ratio			Hazard Ra	tio	
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% CI	Year		IV, Fixed, 95	% CI	
1.8.1 ONLY RCTs											
Guidozzi [62]	-0.06	0.32	59	66	16.8%	0.94 [0.50, 1.76]	1999			_	
Eeles (15)	-0.3927	0.1848	75	75	50.4%	0.68 [0.47, 0.97]	2015				
Subtotal (95% CI)			134	141	67.2%	0.73 [0.54, 1.00]					
Heterogeneity: Chi ² =	0.81, df = 1 (P = 0.3)	7); I ^z = 0%	6								
Test for overall effect:	Z = 1.93 (P = 0.05)										
1.8.2 OTHER STUDIES	5										
Hrein-Vreai (63)	-0.44	0.47	24	48	7.8%	0.64 (0.26, 1.62)	2001			_	
Wen (68)	-0.3208	0.3168	77	77	17.2%	0.73 [0.39, 1.35]	2013				
Zhang [61]	-0.15	0.47	31	81	7.8%	0.86 [0.34, 2.16]	2016	-			
Subtotal (95% CI)			132	206	32.8%	0.73 [0.47, 1.15]	2010				
Heterogeneity: Chi ² =	0.19 , df = 2 (P = 0.9°	1); I ^z = 0%	5								
Test for overall effect:	Z = 1.35 (P = 0.18)										
Total (05% CI)			266	347	100.0%	0 73 [0 57 0 05]					
10(a) (95% CI)			200	347	100.0%	0.75[0.57, 0.95]					
Heterogeneity: Chif=	1.00, dt = 4 (P = 0.9)	1); F= 09	þ					0.1 0.2	0.5 1	2 5	10
Test for overall effect:	Z = 2.36 (P = 0.02)							Fav	ours HRT Fav	ours NO-HRT	
Test for subaroup diff	'erences: Chi² = 0.00), df = 1 (F	r = 1.0	U), F= 0%,							

Figure 8. Forrest plot for the PFS subgroup analysis based on the type of included studies.

The corresponding funnel plot for this analysis, shown in Figure 9, did not highlight publication attrition.



Figure 9. Funnel plot for the PFS subgroup analysis based on the type of included studies.

Four studies [61–63,68] presented results based on the stages of the disease. A subgroup analysis was carried out, and data were split into stages from I to IV. While HRT carried over a tendency to improve recurrences, it was not statistically significant at any stage of the disease. Results are shown in Figure 10. Two studies, however, failed to include any stage IV patients [61,63].

Study or Subgroup	lon[Hazard Ratio]	SE	HRT Total	NO-HRT Total	Woight	Hazard Ratio	Voar	Hazard Ratio
1.3.11	log[nazaru Nacio]	31	Total	Total	weight	IV, TIACU, 55% CI	rear	IV, TIXED, 55% CI
Guidozzi (stage l) (62)	-0.32	1.16	7	9	2.0%	0.73 (0.07, 7.05)	1999	
Ursic-Vrsaj (stage I) [63]	-0.48	2.12	10	20	0.6%	0.62 [0.01, 39.45]	2001	←
Wen (stage I) [68]	-0.17	0.55	40	42	8.8%	0.84 [0.29, 2.48]	2013	
Zhang (stage I) [61] Subtotal (95% CI)	0	0	23 80	58 129	11.4%	Not estimable 0.81 [0.31, 2.09]	2016	-
Heterogeneity: Chi ² = 0.03, Test for overall effect: Z = 0.	df = 2 (P = 0.98); I ^z = 44 (P = 0.66)	0%						
1.3.2								
Guidozzi (stage II) [62]	-0.34	1.25	9	4	1.7%	0.71 [0.06, 8.25]	1999	
Ursic-Vrsaj (stage II) [63]	-0.28	1.22	3	6	1.8%	0.76 [0.07, 8.26]	2001	
Wen (stage II) [68]	-0.22	0.71	11	10	5.3%	0.80 [0.20, 3.23]	2013	
Zhang (stage II) [61]	-0.88	0.88	3	12	3.4%	0.41 [0.07, 2.33]	2016	
Subtotal (95% CI)			26	32	12.2%	0.65 [0.26, 1.62]		
Heterogeneity: Chi ² = 0.37, Test for overall effect: Z = 0.	df = 3 (P = 0.95); I ^z = 92 (P = 0.36)	0%						
1.3.3 III								
Guidozzi (stage III) [62]	-0.07	0.26	38	46	39.4%	0.93 [0.56, 1.55]	1999	
Ursic-Vrsaj (stage III) [63]	-0.12	0.53	11	22	9.5%	0.89 [0.31, 2.51]	2001	
Wen (stage III) [68]	-0.15	0.5	22	23	10.6%	0.86 [0.32, 2.29]	2013	
Zhang (stage III) [61]	-0.54	0.54	5	11	9.1%	0.58 [0.20, 1.68]	2016	
Subtotal (95% CI)			76	102	68.6%	0.86 [0.58, 1.26]		-
Heterogeneity: Chi ² = 0.62, Test for overall effect: Z = 0.	df = 3 (P = 0.89); P = 77 (P = 0.44)	0%						
1.3.4 Ⅳ								
Guidozzi (stage IV) [62]	-0.18	0.68	5	7	5.8%	0.84 [0.22, 3.17]	1999	
Wen (stage IV) [68]	-0.35	1.15	2	2	2.0%	0.70 [0.07, 6.71]	2013	
Subtotal (95% CI)			7	9	7.8%	0.80 [0.25, 2.52]		
Heterogeneity: Chi ² = 0.02, Test for overall effect: Z = 0.	df = 1 (P = 0.90); I ² = 38 (P = 0.70)	0%						
Total (95% CI)			189	272	100.0%	0.82 [0.60, 1.13]		•
Heterogeneity: Chi ² = 1.34,	df = 12 (P = 1.00); I ² :	= 0%						
Test for overall effect: Z = 1.	22 (P = 0.22) es: Chiř = 0.31 df = 1	3 (P =	0.06) 1	Z = 0%				Favours HRT Favours NO-HRT

Figure 10. Forrest plot for the PFS subgroup analysis based on stages of the disease.

Figure 11 shows the funnel plot for the age subgroup analysis.



Figure 11. Funnel plot for the PFS subgroup analysis based on stages of the disease.

Differentiation grade subgroup analysis included 429 patients. Neither well-moderated nor poorly differentiated subtypes showed any benefit in recurrence rates from HRT. One

			HRT	NO-HRT		Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% CI	Year	IV, Fixed, 95% Cl
1.4.1 WELL								
Guidozzi (well) [62]	-0.32	1.16	25	28	3.0%	0.73 [0.07, 7.05]	1999	· · · · · · · · · · · · · · · · · · ·
Ursic-Vrsaj (well) [63]	-0.73	0.87	13	26	5.3%	0.48 [0.09, 2.65]	2001	
Wen (well) [68]	-0.55	0.61	38	27	10.7%	0.58 [0.17, 1.91]	2013	
Zhang (well) [61]	0	0	24	53		Not estimable	2016	_
Subtotal (95% CI)			100	134	18.9 %	0.57 [0.23, 1.40]		
Heterogeneity: Chi ² = 0.08,	df = 2 (P = 0.96); I^2 =	= 0%						
Test for overall effect: Z = 1	.23 (P = 0.22)							
1.4.2 MODERATED								
Guidozzi (moderate) [62]	-0.31	0.49	15	11	16.6%	0.73 [0.28, 1.92]	1999	· · · · · · · · · · · · · · · · · · ·
Wen (moderate) [68]	-0.44	0.49	25	31	16.6%	0.64 [0.25, 1.68]	2013	
Zhang (moderate) [61]	-0.17	0.73	4	19	7.5%	0.84 [0.20, 3.53]	2016	
Subtotal (95% CI)			44	61	40.6%	0.71 [0.39, 1.32]		
Heterogeneity: Chi ² = 0.10,	df = 2 (P = 0.95); I^2 =	= 0%						
Test for overall effect: Z = 1	.08 (P = 0.28)							
1.4.3 POOR								
Guidozzi (poor) [62]	-0.28	0.44	19	27	20.5%	0.76 [0.32, 1.79]	1999	· · · · · · · · · · · · · · · · · · ·
Wen (poor) [68]	-0.52	0.58	14	19	11.8%	0.59 [0.19, 1.85]	2013	
Zhang (poor) [61]	-0.16	0.7	3	8	8.1%	0.85 [0.22, 3.36]	2016	
Subtotal (95% CI)			36	54	40.5%	0.72 [0.39, 1.33]		-
Heterogeneity: Chi ² = 0.18,	df = 2 (P = 0.91); I^2 =	= 0%						
Test for overall effect: Z = 1	.04 (P = 0.30)							
			400	240	400.0%			
10tal (95% CI)			180	249	100.0%	0.69 [0.46, 1.02]		🕶
Heterogeneity: Chi ² = 0.57,	df = 8 (P = 1.00); I ² =	= 0%						0.01 0.1 1 10 100
Test for overall effect: Z = 1	.88 (P = 0.06)							Favours HRT Favours NO-HRT
Test for subaroup difference	es: Chi ² = 0.21, df =	2 (P =	: 0.90),	I ² = 0%				

publication failed to report data for moderated and poorly differentiated disease, but mixed the results [63]. Numbers can be consulted in Figure 12.

Figure 12. Forrest plot for the PFS subgroup analysis based on differentiation grade.

Trivial publication bias is found in the funnel plots shown in Figure 13.



Figure 13. Funnel plot for the PFS subgroup analysis based on differentiation grade.

Exploring whether HRT would affect recurrences based on the resectability of the disease yielded no statistically significant results either. The comparison between optimally debulked and suboptimally debulked patients is presented in Figure 14.

			HRT	NO-HRT		Hazard Ratio			Hazard	Ratio	
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% Cl	Year	P	V, Fixed,	95% CI	
1.5.1 OPTIMAL											
Guidozzi (optimally) [62]	-0.28	0.31	44	46	28.0%	0.76 [0.41, 1.39]	1999			-	
Ursic-Vrsaj (optimally) [63]	-0.61	0.95	14	28	3.0%	0.54 [0.08, 3.50]	2001				
Wen (optimally) [68]	0	0.43	59	64	14.5%	1.00 [0.43, 2.32]	2013		+		
Zhang (optimally) [61]	-0.48	0.68	27	72	5.8%	0.62 [0.16, 2.35]	2016	_			
Subtotal (95% CI)			144	210	51.3%	0.78 [0.50, 1.23]			-		
Heterogeneity: Chi ² = 0.60, df =	3 (P = 0.90); $I^2 = 0\%$										
Test for overall effect: Z = 1.06 (P = 0.29)										
1.5.2 SUBOPTIMAL											
Guidozzi (unoptimally) [62]	-0.32	0.36	15	20	20.7%	0.73 [0.36, 1.47]	1999			-	
Ursic-Vrsaj (unoptimally) [63]	-0.35	0.55	10	20	8.9%	0.70 [0.24, 2.07]	2001			_	
Wen (unoptimally) [68]	0	0.48	18	13	11.7%	1.00 [0.39, 2.56]	2013				
Zhang (unoptimally) [61]	-0.43	0.6	4	9	7.5%	0.65 [0.20, 2.11]	2016	-			
Subtotal (95% CI)			47	62	48.7%	0.77 [0.48, 1.21]			-		
Heterogeneity: Chi ² = 0.43, df =	3 (P = 0.93); I ² = 0%										
Test for overall effect: Z = 1.13 (P = 0.26)										
Total (95% CI)			191	272	100.0%	0 78 [0 56 1 07]					
Heterservite Obi? 4.04 df	7 (D 0.00), 17 00(151	212	100.070	0.70 [0.50, 1.07]			•		
Helerogenerity: chi = 1.04, di = 7 (r = 0.99), r = 0%								1'0	100		
Test for overall energy 2 = 1.55 (P = 0.12) Favours NO Favours NO Favours NO								avours NO-HRT			
Test for subgroup differences: Chi ² = 0.01, df = 1 (P = 0.94), l ² = 0%											



The funnel plot presented in Figure 15 is unremarkable.



Figure 15. Funnel plot for the PFS subgroup analysis based on resectability.

Finally, two studies presented PFS results based on the participants' age. The analysis proved no benefit in terms of PFS for any age categories, as shown in Figure 16.

			HRT	NO-HRT		Hazard Ratio		Hazard Ratio	
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% Cl	Year	IV, Fixed, 95% CI	
1.6.1 <29									
Ursic-Vrsaj (sub-29) [63]	-1.54	1.42	4	5	3.6%	0.21 [0.01, 3.47]	2001	•	
Wen (sub-29) [68]	-0.36	1	6	6	7.4%	0.70 [0.10, 4.95]	2013		
Subtotal (95% CI)			10	11	11.0%	0.47 [0.10, 2.34]			
Heterogeneity: Chi ² = 0.46,	at = 1 (P = 0.50); F =	:0%							
Test for overall effect: $Z = 0$.92 (P = 0.36)								
1.6.2 30-39									
Ursic-Vrsaj (30-39) [63]	-1.25	1.16	5	6	5.5%	0.29 [0.03, 2.78]	2001		
Wen (30-39) [68]	-0.16	0.45	37	38	36.3%	0.85 [0.35, 2.06]	2013	_ _	
Subtotal (95% CI)			42	44	41.8 %	0.74 [0.32, 1.68]			
Heterogeneity: Chi ² = 0.77,	df = 1 (P = 0.38); I^2 =	:0%							
Test for overall effect: Z = 0	.72 (P = 0.47)								
1.6.3 40-49									
Ursic-Vrsaj (40-49) [63]	-0.84	0.78	14	22	12.1%	0.43 [0.09, 1.99]	2001		
Wen (40-49) [68]	-0.19	0.52	29	28	27.2%	0.83 [0.30, 2.29]	2013		
Subtotal (95% CI)	-16 4 (D 0 40) - 17	~~	43	50	39.3%	0.08 [0.29, 1.38]			
Heterogeneity: Chi ² = 0.48, df = 1 (P = 0.49); l ² = 0%									
Test for overall effect: $Z = 0$.90 (P = 0.37)								
1.6.4 50-59									
Ursic-Vrsaj (50-59) [63]	-1.19	1.1	2	15	6.1%	0.30 [0.04, 2.63]	2001		
Wen (50-59) [68]	-0.72	2	5	5	1.8%	0.49 [0.01, 24.53]	2013	←	
Subtotal (95% CI)			7	20	7.9%	0.34 [0.05, 2.24]			
Heterogeneity: Chi ² = 0.04,	df = 1 (P = 0.84); I ² =	:0%							
Test for overall effect: Z = 1	.12 (P = 0.26)								
Total (95% CI)			102	125	100.0%	0.64 [0.38, 1.09]		•	
Heterogeneity: Chi ² = 2.46,	df = 7 (P = 0.93); l ² =	:0%							
Test for overall effect: Z = 1	.65 (P = 0.10)							U.UI U.I I 10 100 Eavours HRT Eavours NO-HRT	
Test for subgroup difference	es: Chi ^z = 0.71, df =	3 (P =	0.87),	I² = 0%					

Figure 16. Forrest plot for the PFS subgroup analysis based on age categories.

The corresponding funnel plot can be consulted in Figure 17.



Figure 17. Funnel plot for the PFS subgroup analysis based on age categories.

Results from individual studies based on respective subgroup categories can be further consulted in the Supplementary Material, in the PFS Subgroups sheet, alongside the detailed workflow. All subgroup analyses were based on the indirect method for pooling logHRs and SEs due to the nature of the data presented in the original publications. Fixed effect methods were employed, given the trivial heterogeneity in all the analyses.

4. Discussion

4.1. Summary of Evidence

The results of the current meta-analyses align with those presented in the primary included publications [15,61-63,66-69] and emphasise a benefit in the OS of OC patients receiving HRT compared to never-users. The overall pooled HR of 0.66 showed statistical significance with a p-value < 0.00001, while the analyses pooled a trivial 25% heterogeneity and used a fixed effects model. The relatively low number of publications was mitigated by a robust population size of 3578 patients, of which 912 received HRT. No substantial publication attrition was disclosed while performing the funnel plots for the included publications. Results align with previous spottings that exhibit an OS benefit for the HRT groups. To the best of our knowledge, up to this date, there are only three other metaanalyses published in the literature that investigate the subject of HRT in the setting of OC. Li et al.'s meta-analysis [70], published in 2015, included 1448 patients and pooled an HR = 0.69 (95% CI: 0.61-0.79), also statistically significant. However, their study did not investigate the PFS in these settings, but analysed the RR (Relative Risk) of occurrence. Pergialiotis' meta-analysis [71], published in 2016, based their statistics on the OR of cancerrelated deaths and recurrences in 1521 women. Their study found no statistically significant discrepancies for these groups regarding OS and recurrence. Finally, the 2020 Cochrane systematic review [72] focused on the QoL indicators. Nevertheless, the study did enclose 350 patients in an OS analysis that pooled a favourable HR of 0.71 for the HRT group. The present meta-analysis included 4191 OC patients in two analyses regarding the OS and PFS (measured by HRs) of patients treated or not with HRT, the largest to date. Adding to the novelty, comprehensive subgroup analyses were undertaken to evaluate the actual effect size of HRT treatment. Interestingly, when analysing HRT based on the age of participants and the stage, differentiation and resectability of the disease, all analyses were deemed insignificant in terms of recurrences. It is worth mentioning that all included studies were cohorts [61–63,68], as the only RCT [15] investigating the PFS only provided overall PFS, rather than results based on the categories above. Thus, the results must be interpreted with caution. Regardless, even in the context of a null effect on the recurrence rates, HRT can still be deemed a viable option for these patients in terms of improving QoL and lessening climacteric symptoms.

Mixing RCTs, cohort studies or other studies might introduce bias and potentially become problematic. However, due to the limited number of identified publications, this was performed as a necessity. Accordingly, a subgroup analysis was undertaken to sequence the data from RCTs [15,62] and other types of studies. This was possible for both the OS and the PFS analyses. The analysis proved helpful, as it diminished the heterogeneity from 25% down to 0% in OS analysis when only considering RCTs, proving that mixing the results was the cause of the heterogeneity in the initial analysis. Cochrane also states that when pooling the desired effect measures from non-randomised studies, HR can be obtained from adjusted analyses, such as Cox multivariate regression analyses [73]. This will indeed lessen the risk of bias pooled from such publications; yet, some might consider these HRs incompatible for meta-analyses with the unadjusted HRs or those extracted directly from (O - E) events [27]. The present meta-analyses only used HRs pooled from unadjusted univariate analyses or obtained via a direct method described in the materials and methods subsection.

While there is still some disagreement regarding the risk-to-benefit ratios of HRT in treating menopausal symptoms [11], the advantages are well documented in selected patients and scenarios [12]. However, there is still apprehension as to the mechanism of

action of HRT in OC. Interestingly, the primary included publications and the present meta-analyses showed a benefit in OS and PFS for the patients treated with HRT. Although E and P are known for reducing overall mortality and morbidity in general menopause, the mechanism of action in OC might be more complex; otherwise, the effect would not have carried over in the PFS analysis. One might argue that clinicians are more inclined to prescribe HRT for OC patients who are younger, fitter and have an earlier-stage disease and, therefore, a better prognosis. However, most studies controlled for such variables and provided measures of dissimilarities between groups. This was also marked in the quality assessment of cohorts and RCTs that yielded promising results, potentially mitigating the selection bias for the treatment and control groups. Consequently, a mechanism of action needs to be elucidated for HRT in OC, and perhaps future molecular models and studies will strive to explain.

Multifarious treatments were applied in the primary included publications, ranging from E only or P only to various combinations and doses. Some differences were also highlighted in the moment of inception for the HRT relative to the treatment of OC and the duration. Hence, sound conclusions cannot be outlined regarding the exact dosage, drug, moment of inception and course of treatment necessary for HRT to have a positive effect. Even so, it appears from these primary included publications that most regimens begin within the first year of oncologic treatments and last for at least one year. Although side effects reporting was scarce in the included studies [15,60,61,63,68], mammary gland hyperplasia seemed to be one of the most common side effects [61,68] of the treatment that demanded treatment to be halted. More concerning were the secondary primary malignancies reported in two studies [15,63]. Eeles' publication [15] disclosed two breast malignancies, alongside one colon and one jejunum malignant tumour, while an older study highlighted breast carcinoma [63].

4.2. Limitations and Strengths

The relatively low number of included publications for the meta-analyses can be an intrinsic limitation. However, it is partially mitigated by the more significant population sizes derived from these studies. The limited number of databases can also influence the outcomes through missing potentially eligible reports. However, a large number of 7814 studies were initially identified, while no publication attrition was detected. A slight warping in the funnel plots can also be attributed to the smaller studies that tend to magnify the effect. While no language criteria were applied for the search formula, articles that did not present an English full-text were excluded from this review, potentially marking language as a limiting factor. I² was used for heterogeneity assessment. Although this is not an absolute measurement of heterogeneity, I² is a valuable tool for highlighting the proportion between variances in true effect size or sampling errors. Chi² and *p*-values were also added. Trivial heterogeneity was regarded in all meta-analyses with satisfactory Chi² and *p* values for I². This must also be interpreted with caution, as it can also highlight an over-selection of studies.

HRs were the choice parameters, and analyses were based on the logHR values and their respective variance measures, SEs. Cochrane advises against using continuous data outcomes for time-to-event measures (mean or median time of survival or until recurrence), as they usually exclude the censored data and produce bias [22]. One study reported the outcomes in this manner [65] and was not included in the present meta-analyses. HR is continuously changing; however, for the time-to-event analyses, most publications will assume a constant HR for participants through their contribution time. This is called a simplified HR, and this assumption will, nevertheless, be carried over in the pooling of data when performing a meta-analysis [73]. It is virtually impossible to overcome, but must be stated as a potential limitation to the present analyses.

5. Conclusions

The current systematic review and meta-analysis indicated that HRT could be safely and efficiently administered to patients treated for OC, who invariably experience menopause and subsequent symptoms. Furthermore, a statistically significant advantage in the OS and PFS has been marked in the HRT-treated groups compared to never-users, potentially implying a role of the HRT in managing OC patients with menopause-related manifestations. More detailed analyses based on the age of participants and the stage, grade of differentiation and resectability of the disease failed to disclose any benefit in terms of PFS for HRT users. However, even in this setting of non-inferiority, HRT can be safely considered for lessening symptoms and improving QoL for these patients.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cancers15020356/s1, Workflow Excel Spreadsheet [15,60–69].

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