

# The use of menopausal hormone therapy in women survivors of gynecological cancer: safety report based on systematic reviews and meta-analysis

Iñaki Lete<sup>1</sup>, Gabriel Fiol<sup>1</sup>, Laura Nieto<sup>1</sup>, Ana Santaballa<sup>2</sup>, María Jesús Plá<sup>3</sup>, Nicolás Mendoza<sup>1,\*</sup>, on behalf of the HMT Eligibility Criteria Group<sup>§</sup>

<sup>1</sup>Spanish Menopause Society, 28036 Madrid, Spain

<sup>2</sup>Spanish Society of Medical Oncology, 28011 Madrid, Spain

<sup>3</sup>Spanish Society of Gynaecology and Obstetrics, 28036 Madrid, Spain

\*Correspondence: [nicomendoza@telefonica.net](mailto:nicomendoza@telefonica.net) (Nicolás Mendoza)

<sup>§</sup>HMT Eligibility Criteria Group: Laura Baquedano, Joaquín Calaf, María Jesús Cancelo, Antonio Cano, Camil Castelo Branco, Rafael Comino, Pluvio Coronado, Ester de la Viuda, José Luis Doval, María Fasero, Javier Ferrer, Gabriel Fiol, Ana Gómez, María Ángeles Gómez, Silvia González, Misericordia Guinot, Eva Iglesias, Ana Rosa Jurado, Plácido Llaneza, Iñaki Lete, Paloma Lobo, Dani Lubián, Montserrat Manubens, Milagros Martínez, Marina Mazheika, Nicolás Mendoza, Aníbal Nieto, Laura Nieto, Borja Otero, Santiago Palacios, María Jesús Plá, Ezequiel Pérez-Campos, Jesús Presa, Francisco Quereda, Isabel Ramírez, Miriam Ribes, Beatriz Roca, Sonia Sánchez, Rafael Sánchez-Borrego, Ana Santaballa.

DOI: [10.31083/j.ejgo4205155](https://doi.org/10.31083/j.ejgo4205155)

This is an open access article under the CC BY 4.0 license (<https://creativecommons.org/licenses/by/4.0/>).

Submitted: 10 February 2021 Revised: 22 March 2021 Accepted: 31 March 2021 Published: 15 October 2021

The data collected during the last two decades on the effects of Hormonal menopause treatment (HMT) could help to provide a safer and more effective long term-treatment of menopause symptoms and possible complications such as osteoporotic fractures, cognitive impairment, or cardiovascular conditions, as well as an improved quality of life. Having a history of suffering from gynecological cancer (endometrial, cervical or ovarian) is one of the conditions that most strongly determines the use of any form of HMT due to the concerns associated with a possible recurrence of the disease. *Objective:* To create a set of eligibility criteria for the use of HMT in gynecological cancer patients. *Methods:* The study was registered in PROSPERO (registration number CRD42020166658). *Results:* Ovarian cancer survivors who use HMT have better overall survival, disease-free survival, and lower recurrence rates than women survivors who do not use HMT. Endometrial cancer survivors who use HMT do not have a higher rate of disease recurrence than those survivors who do not use HMT. Cervical cancer survivors who use HMT do not have a higher rate of disease recurrence than those survivors who do not use HMT. *Conclusion:* HMT is safe in women who have suffered from most of non-advanced gynecological cancers.

## Keywords

Menopausal hormone therapy; Gynecological cancer survivors

## 1. Introduction

The data collected during the last two decades on the effects of Hormonal menopause treatment (HMT) could help to provide a safer and more effective long term-treatment of menopause symptoms and possible complications such as osteoporotic fractures, cognitive impairment, or cardiovascular conditions, as well as an improved quality of life [1–4]. Based on all of this information, international societies have con-

cluded that the benefits of HMT outweigh the risks in healthy symptomatic postmenopausal women when HMT is initiated within 10 years of the menopause or when younger than 60 years of age [5, 6].

However, there are currently no guidelines available that provide recommendations on the prescription of HMT in postmenopausal women with any medical condition that could compromise its use. In the case of contraceptive methods, there is a globally available document that provides information for this purpose. Thus, the “WHO Medical Eligibility Criteria” classifies the various medical conditions of women into four categories, providing the scientific community with recommendations for the safe use of any contraceptive method [7].

Having a history of suffering from gynecological cancer (endometrial, cervical or ovarian) is one of the conditions that most strongly determines the use of any form of HMT due to the concerns associated with a possible recurrence of the disease. Moreover, the majority of women survivors of these cancers have received treatments that have sharply increased their menopausal symptoms, due to oophorectomy or the effects of QT and RT, which further increases the need to treat them with effective remedies, one of the most notable being HMT [8].

The objective of this report is to create a set of eligibility criteria for the use of HMT in gynecological cancer patients, similar to those established for contraceptive methods. A consortium of scientific societies coordinated by the Spanish Menopause Society met to develop guidelines for the use of HMT in patients with medical conditions, based on the best available evidence.

## 2. Methods

The study was registered in PROSPERO (registration number CRD42020166658) and is part of the “Eligibility criteria for HMT project” (**Supplementary material 1**).

### 2.1 Selection of studies

We conducted an exhaustive literature searches in the following databases: MEDLINE (via PubMed), The Cochrane Library (CENTRAL), and EMBASE (via [embase.com](http://embase.com)), from their inception until the most recent date. We will design a search strategy that is tailored to the requirements of each database, which will include a combination of controlled vocabulary and search terms related to each gynecological cancer. Appendix displays an exploratory search strategy for MEDLINE. When necessary, we will use validated filters to retrieve the appropriate study designs.

Two independent researchers screened the references yielded by the search to reach an agreement on the inclusion of studies.

The PICOS (Population, Intervention, Comparators, Outcomes, Study Design) criteria are developed *a priori* to guide the scope of the review, along with the procedures, selection, and synthesis of the literature search. The selection criteria were as follows:

(Population) menopausal women of any age with gynecological cancer receiving HMT; (Intervention) any HMT preparation (oestrogens alone or combined with a progestogen, tibolone or tissue selective oestrogen complex) or any route of administration (oral, transdermal, vaginal or intranasal); (Outcome) recurrence and mortality; (Study Design) randomized controlled trials, and related extension studies or follow-up reports. Any complete article that met the inclusion criteria was reviewed in detail.

### 2.2 Data extraction and risk of bias assessment

We described the synthesis of the evidence following the PRISMA guidelines [9]. We assessed the risk of bias of the eligible studies using the Cochrane tool for clinical trials, which takes into account the evaluation of five possible sources of bias (selection, performance, detection, attrition and report bias) [10]. For observational studies, we adapted the ROBINS I tool, focusing on the evaluation of the impact of the confounding variables, selection bias, outcome measures, and attrition [11]. Pooled analyses were conducted using the Mantel-Haenszel method and the random effects model included within the RevMan software statistical package (v 5.3.5) [12].

We made explicit judgements on the certainty of the evidence for each outcome of interest according to GRADE criteria [13]. Quality will be classified as high, moderate, low or very low, based on several factors (including risk of bias, inaccuracy, inconsistency, lack of directionality and publication bias).

## 3. Results

The quality of the studies is described in Tables 1,2,3 (Ref. [14–32]) and in the **Supplementary material** provided.

### 3.1 Ovarian cancer

Three randomized clinical trials (RCTs) were included on the impact of HMT on ovarian cancer recurrence and mortality [14–16]. Six retrospective observational studies were also considered [17–22]. Most patients received combined oral HMT, primarily with equine conjugated estrogens (ECE) 0.625–1.25 mg/day plus medroxyprogesterone 4 mg/day.

There were no differences in overall survival when all studies were pooled (RR 0.90, 95% CI: 0.73 to 1.10; Fig. 1a), but differences emerged when only RCTs were analyzed [14–16] indicating improvement after HMT (HR 0.71, 95% CI: 0.54 to 0.93; Fig. 1b).

One of the cohort studies [21] presented the results according to the age of the participants. Survival in women under 55 years was higher when using HMT, according to a univariate analysis (HR 0.41, 95% CI: 0.19 to 0.89,  $p = 0.023$ ), but not in the multivariate model (according to disease stage and chemotherapy administration; HR 0.49, 95% CI: 0.23 to 1.09,  $p = 0.08$ ). For patients over 55 years old, HMT did not affect survival.

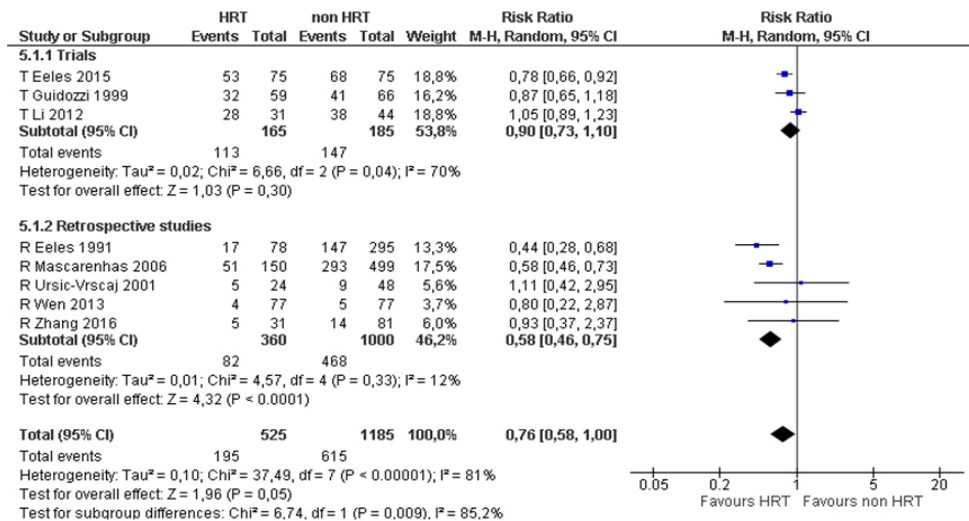
Combined data from two RCTs [14, 16] showed an increase in recurrence-free survival with HMT (HR 0.72, 95% CI: 0.58 to 0.90; Fig. 1c), and a reduction in the risk of recurrence (RR 0.81, 95% CI: 0.70 to 0.93; Fig. 1d). These results were maintained when data from retrospective studies were added (RR 0.81, 95% CI: 0.71 to 0.92; Fig. 1d).

Disease-free survival was also higher for HMT users younger than 55 years in the Power 2016 study [21], both in the univariate (HR 0.34, 95% CI: 0.17 to 0.69;  $p = 0.003$ ) and multivariate models (adjusted HR 0.35, 95% CI: 0.17 to 0.74;  $p = 0.006$ ). For women over 55 years of age, the use of HMT was not associated with increased disease-free survival.

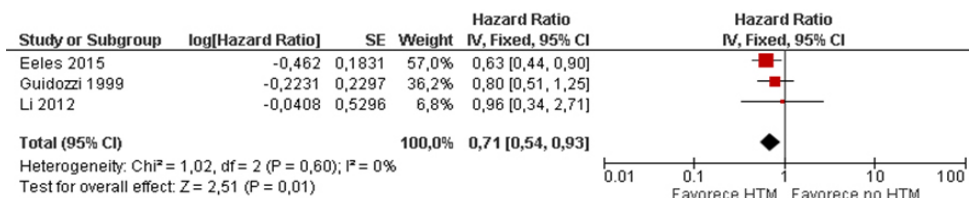
### 3.2 Endometrial cancer

One RCT was identified [23] with 1236 participants where neither the dose nor the route of administration of HMT is described, with a mean follow-up of 35.7 months. Eight observational studies were also included, one prospective [24] and seven retrospective studies [25–31] with a total of 1801 endometrial cancer survivors who received HMT and 6015 who did not. Almost all were limited to patients with early stages of the disease.

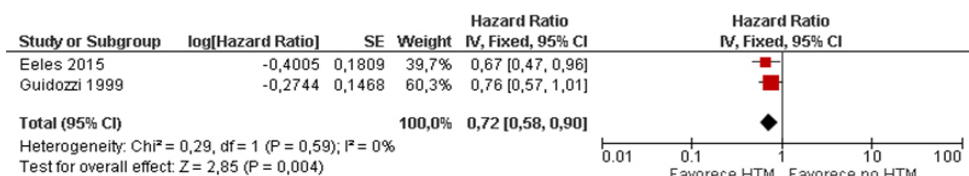
The RCT [23] found no difference in recurrence according to HMT use (RR 1.17, 95% CI: 0.54 to 2.50), the same being true for the combined analysis of the RCT and the prospective study (RR 1.08, 95% CI: 0.52 to 2.24; Fig. 2a). However, when adding the results of the retrospective studies, a significant reduction in recurrence was observed with the use of HMT (RR 0.64, 95% CI: 0.50 to 0.82; Fig. 2b). In particular, recurrence was reduced with combined HMT (RR 0.31, 95% CI: 0.13 to 0.73; Fig. 2c) but not with estrogen alone



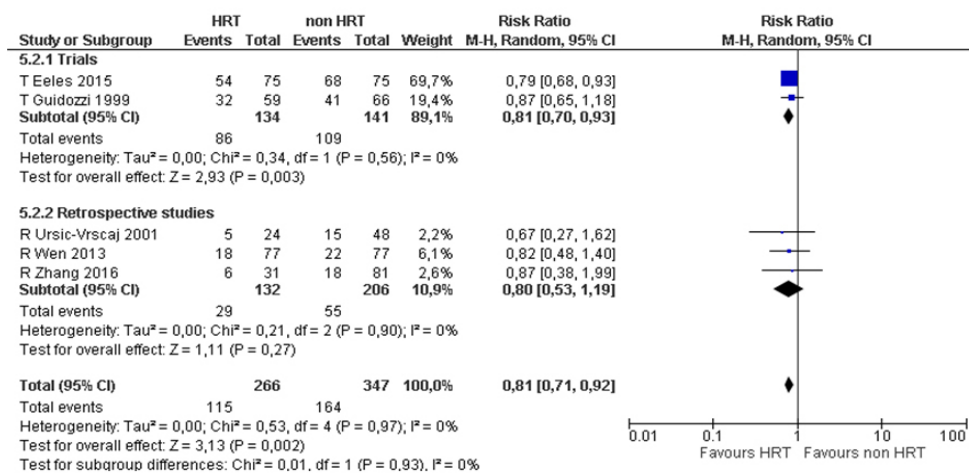
a



b

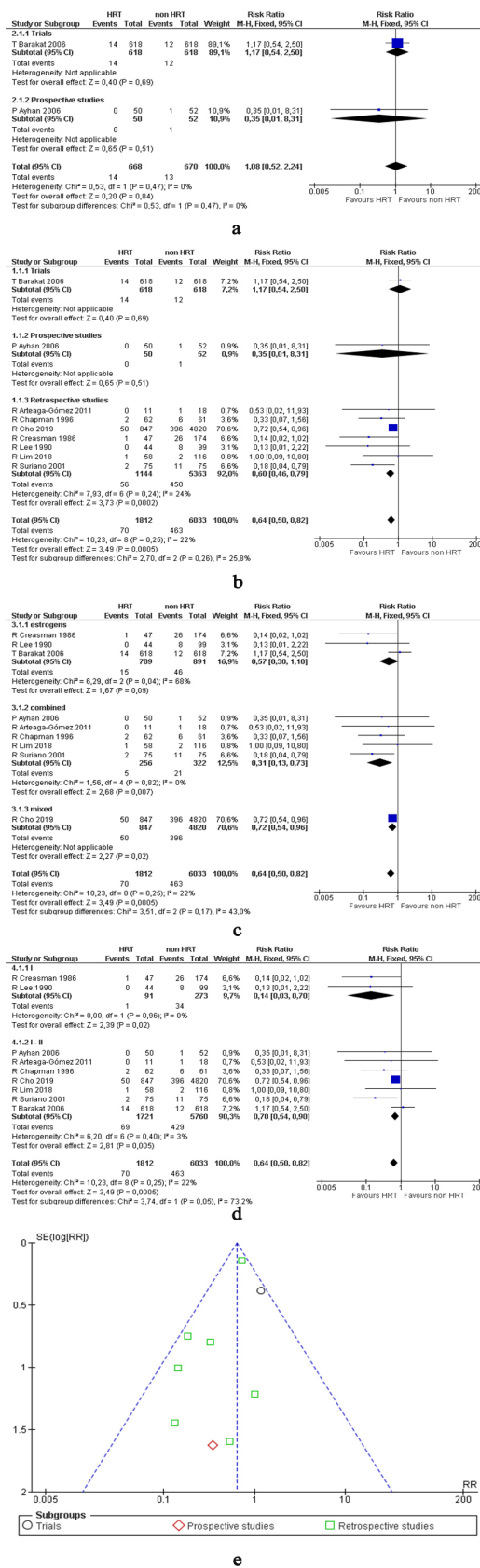


c



d

**Fig. 1. Ovarian cancer.** (a) Mortality (data from clinical trials and retrospective studies). (b) Overall survival (data from clinical trials). (c) Recurrence-free survival (data from clinical trials). (d) Recurrence (data from clinical trials and retrospective studies).



**Fig. 2. Endometrial cancer.** (a) Recurrence (data from clinical trials and prospective studies). (b) Recurrence (data from clinical trials and prospective and retrospective studies). (c) Recurrence (by type of treatment). (d) Recurrence (by stage of disease). (e) Recurrence (analysis of publication bias).

**Table 1. Ovarian cancer. Summary of findings.**

No of studies	Study design	Certainty evaluation					Impact	Certainty
		Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations		
Mortality								
3	Randomized trials [14–16]	Serious <sup>a</sup>	Not serious	Not serious	Not serious	None	RR 0.90, 95% CI: 0.73 to 1.10	⊕⊕⊕○ MODERATE
Mortality								
9	Randomized trials [14–16] and retrospective cohorts [17–22]	Very serious <sup>b</sup>	Serious <sup>c</sup>	Not serious	Not serious	None	RR 0.76, 95% CI: 0.58 to 1.00	⊕○○○ VERY LOW
Overall survival								
3	Randomized trials [14–16]	Serious <sup>a</sup>	Serious <sup>c</sup>	Not serious	Not serious	None	HR 0.71, 95% CI: 0.54 to 0.93 120 less per 1000 (84 to 220 less) <sup>d</sup>	⊕⊕○○ LOW
Recurrence-free survival								
2	Randomized trials [14, 15]	Serious <sup>a</sup>	Not serious	Not serious	Not serious	None	HR 0.72, 95% CI: 0.58 to 0.90	⊕⊕⊕○ MODERATE
Recurrence of ovarian cancer								
2	Randomized trials [14, 16]	Serious <sup>a</sup>	Not serious	Not serious	Not serious	None	RR 0.81, 95% CI: 0.70 to 0.93 147 less per 1000 (54 to 232 less)	⊕⊕⊕○ MODERATE
Recurrence of ovarian cancer								
8	Randomized trials [14, 16] and retrospective cohorts [18, 20, 22]	Very serious <sup>b</sup>	Not serious	Not serious	Not serious	None	RR 0.81, 95% CI: 0.71 to 0.92	⊕⊕○○ LOW

<sup>a</sup> Lack of blinding, with an impact on the loss of participants.

<sup>b</sup> Retrospective studies with selection and confounding bias.

<sup>c</sup> Inconsistency (presence of notable statistical heterogeneity not explained by the characteristics of the studies).

<sup>d</sup> Data taken from the Cochrane review by Saeai [34].

**Table 2. Endometrial cancer. Summary of findings.**

No of studies	Study design	Certainty evaluation					Impact	Certainty
		Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations		
Recurrence								
1	Randomized trial [23]	Serious <sup>a</sup>	Not serious	Not serious	Serious <sup>b</sup>	None	RR 1.17, 95% CI: 0.54 to 2.50 <sup>c</sup>	⊕⊕○○ LOW
Recurrence								
9	Randomized trial [23], prospective [24] and retrospective [25–31] cohorts	Very serious <sup>d</sup>	Not serious	Not serious	Not serious	Publication bias <sup>e</sup>	RR 0.64, 95% CI: 0.50 to 0.82  28 less for every 1000 women treated rather than untreated (38 to 14 less)	⊕○○○  VERY LOW

<sup>a</sup> Limitations in study design and execution: lack of information on sequence generation and allocation masking; in addition, the trial was stopped early without completion of recruitment.

<sup>b</sup> Interruption of the trial before completion of planned recruitment affects the accuracy of the effect estimator.

<sup>c</sup> Median follow-up of 37.5 months.

<sup>d</sup> Most retrospective cohort studies showed a high risk of confounding bias.

<sup>e</sup> Publication bias of retrospective studies with negative results (analysis 02.05 in Annex 2).

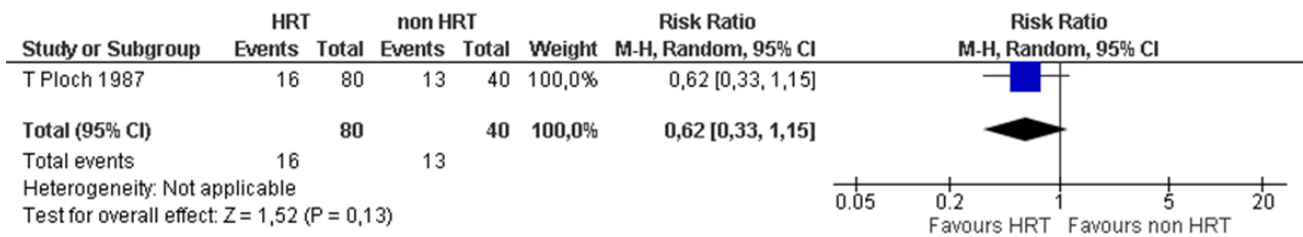
**Table 3. Cervico-uterine cancer. Summary of findings.**

No of studies	Study design	Certainty evaluation					Impact	Certainty
		Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations		
Cervical-uterine cancer. Mortality (Hormonal replacement therapy versus symptomatic management without hormonal treatment)								
1	Randomized trial [32]	Very serious <sup>a</sup>	No	Not serious	Serious <sup>b</sup>	None	OR 0.46, 95% CI: 0.20 to 1.09 <sup>c</sup>	⊕○○○ VERY LOW
Cervical-uterine cancer. Recurrence (Hormonal replacement therapy versus symptomatic management without hormonal treatment)								
1	Randomized trial [32]	Very serious <sup>a</sup>	No	Not serious	Serious <sup>b</sup>	None	OR 0.52, 95% CI: 0.22 to 1.23 <sup>c</sup>	⊕○○○ VERY LOW

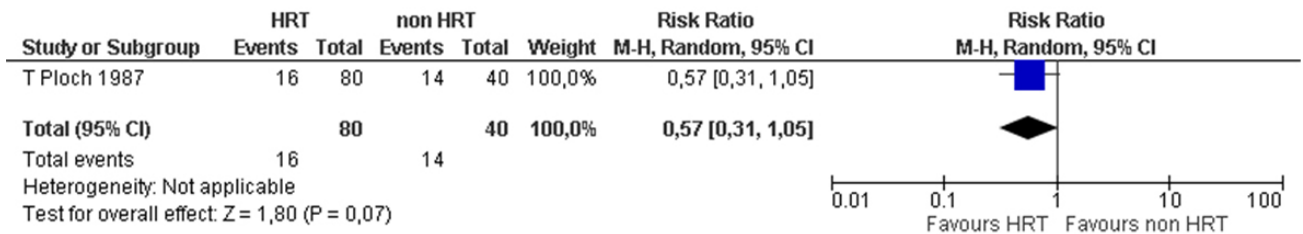
<sup>a</sup> Lack of information on sequence generation, allocation masking, blinding, selective reporting of results, failure to specify the role of industry.

<sup>b</sup> A single clinical trial of low methodological quality.

<sup>c</sup> Follow-up at least 5 years.



**a**



**b**

**Fig. 3. Cervical cancer.** (a) Mortality. (b) Recurrence.

(RR 0.57, 95% CI: 0.30 to 1.10). These results were found to be independent of the stage of the disease (RR for Stage I 0.14, 95% CI: 0.03 to 0.70; RR for Stage I–II 0.70, 95% CI: 0.54 to 0.90; Fig. 2d).

### 3.3 Cervical cancer

One RCT was identified [32] with 120 patients under 45 years of age with Stage I and II cancer. Oral HMT was combined with different formulations over an observation period of more than 5 years. This RCT found no significant differences in either mortality (RR 0.62, 95% CI: 0.33 to 1.15; Fig. 3a) or recurrence (RR 0.57, 95% CI: 0.31 to 1.15; Fig. 3b).

## 4. Discussion

Taken together, analysis of the researched literature leads to the conclusion that HMT is probably safe in terms of recurrence and/or mortality, in patients who have suffered from non-advanced gynecological cancer, but this affirmation should be interpreted with caution mostly after ovarian cancer.

### 4.1 Why is this report important?

There is considerable confusion regarding the appropriateness of prescribing HMT in women with gynecological cancer, particularly because of the fear of recurrence or increased mortality that may occur with its use.

Women who have suffered from gynecological cancer often present earlier and more intense menopausal symptoms due to ovarian surgery or the effects of certain treatments (RT, QT), which have a severe impact on their quality of life. These long-term risks often overlap with those suffered by women with premature ovarian failure (POF), thus extending the suitability of HMT [8].

This report complements the recommendations contained in a recent position paper published by EMAS and IGCS [33].

### 4.2 Strengths

This is the first published work where several systematic reviews and meta-analyses are gathered to analyze the recurrence and mortality associated with HMT use in women survivors of gynecological cancer (endometrial, ovarian, or cervical).

This is also the first time that categories of evidence (eligibility criteria) have been distinguished for the use of HMT in these patients, using the strictest methodological tools.

Other systematic reviews have been included [34, 40, 41] as sources of studies relevant to this report.

### 4.3 Limitations

The quality of evidence is low overall. Many studies include the generic use of HMT without distinguishing between dose, formulation, or route of administration.

### 4.4 Special considerations

#### 4.4.1 Ovarian cancer

The recommendation is based on the analysis of three RCTs and six retrospective observational studies. One of the major limitations of these studies is the use of different compounds, guidelines, and routes of administration of HMT. Most ovarian cancer survivors in these studies used oral equine conjugated estrogens, alone if they had been hysterectomized, and in combination with a progestogen (usually medroxyprogesterone acetate) when the women retained their uterus. In addition, no conclusions can be drawn about the different types of ovarian carcinomas. HMT may slightly improve overall survival in women who have undergone sur-

gical treatment for epithelial ovarian cancer, but the certainty of the evidence is low. Respecting other types of ovarian cancer, the evidence in this review is limited by imprecision and incompleteness of reported relevant outcomes and therefore the results should be interpreted with caution.

#### 4.4.2 Endometrial cancer

The recommendation is based on the analysis of one RCT and eight observational studies (one prospective cohort study and seven retrospective studies). The studies included only patients in the early stages of endometrial cancer (I and II) and the treatments used differed in terms of composition, pattern, and route of administration.

The advantage of administering HMT to these patients is the improvement of their quality of life without compromising their survival. No recommendations can be made on the use of HMT in patients with stage III and IV.

Analysis of these studies, however, suggests the existence of a publication bias in retrospective studies with negative results (Fig. 2e).

#### 4.4.3 Cervical cancer

This recommendation is based on a single RCT with several biases and limitations. The advantage of administering HMT to these patients is the improvement of their quality of life without compromising their survival.

#### 4.4.4 Vulval and vaginal cancer

Regarding cancers of the vulva and vagina, although we have not found studies that measure the safety of HMT, most of them are squamous cell carcinomas not hormone-dependent, so we agree that there should be no contraindication to the use of HMT, whether systemic or local, when is indicated [38, 39, 41].

### 4.5 Cancer risk in healthy HMT users

#### 4.5.1 Ovarian cancer

The literature review has revealed an increased risk of ovarian cancer in case-control and cohort studies with both estrogen therapy alone and combined with progestogen.

The global RR is between 1.29 (95% CI: 1.19 to 1.40,  $I^2 = 57.4%$ ) [42] and 1.37 (95% CI: 1.29 to 1.46;  $p < 0.0001$ ) [43]. This difference is maintained regardless of the time of administration of the treatment and is similar in both Europe and North America, whilst the results obtained in Australia were not significant [42]. Evidence for an increased risk was found only for serous and endometrioid tumors, but not for other histological subtypes. It is not established if there are differences according to guidelines and types of treatment.

#### 4.5.2 Endometrial cancer

Exposure of the endometrium to estrogen has been associated with an increased risk of developing endometrial cancer, which is why progestogen is recommended as opposed to estrogenic treatment.

The Women Health Initiative study showed a non-significant risk reduction with continuous in comparison

with cyclic HMT [44]. The Million Women Study reported the protective effect of continuous combination treatment (RR 0.71, 95% CI: 0.56 to 0.90), while the use of tibolone and estrogen alone was associated with an increased risk [45, 46]. Other studies have pointed to an increased risk in combination therapy with synthetic progestogens, and even micronized progesterone [47].

These differences in the effects of using estrogens alone and those combined with progestogens appear to be more marked in obese women, where the risk of estrogen treatment is higher and progestogen protection seems to be increased [46].

#### 4.5.3 Cervical cancer

The literature provides little information regarding the effect of HMT on the development of cervical cancer. The EPIC study (European Prospective Investigation into Cancer and Nutrition), on 308,036 women revealed a significant risk reduction (RR 0.5, 95% CI: 0.4 to 0.8), particularly if the treatment duration exceeds five years. While it has been suggested that estrogens may promote cervical carcinogenesis with a protective effect of progestogens, risk reduction seems to be evident in both estrogenic treatment and the combined use of estrogens [48].

#### 4.6 Future research

Our report, however, has identified some important areas of improvement for future research. It is expected that the results will contribute to the development of studies that further examine the safety and efficacy of HMT for treating menopausal symptoms in gynecological cancer survivors. Larger RCTs should be conducted, and over a longer follow-up period, to evaluate the various HMT strategies.

## 5. Conclusions

Non-advanced ovarian cancer survivors who use HMT have better overall survival, disease-free survival, and lower recurrence rates than women survivors who do not use HMT.

Endometrial cancer survivors who use HMT do not have a higher rate of disease recurrence than those survivors who do not use HMT.

Cervical cancer survivors who use HMT do not have a higher rate of disease recurrence than those survivors who do not use HMT.

## Author contributions

IL, GF, NM—conception and design of the idea. IL, GF, NM—preparation of manuscript. LN, AS, MJP—review of information, selection of valuable articles, critical reading of articles. All authors participated in data interpretation, statement and approved the final version of the manuscript.

## Ethics approval and consent to participate

Not applicable.



## Acknowledgment

This article has been translated and edited by Your English Lab.

## Funding

This research received no external funding.

## Conflict of interest

The authors declare no conflict of interest.

## Supplementary material

Supplementary material associated with this article can be found, in the online version, at <https://ejgo.imrpess.com/EN/10.31083/j.ejgo4205155>.

## Appendix

Search strategy:

“Hormone Replacement Therapy”[Mesh] OR hormone replacement[tiab] OR hormonal replacement[tiab] OR estrogen replacement[tiab] OR hormone therapy[tiab] OR hormonal therapy[tiab]) AND (prognos\*[ti] OR survivor\*[ti] OR postoperative[ti] OR adjuvant[ti] OR after[ti] OR (after[tiab] AND diagnos\*[tiab]) OR following[ti]) AND (endometrial[ti] OR “Endometrial Neoplasms”[Majr] OR ovarian[ti] OR “Uterine Cervical Neoplasms”[Mesh] OR cervical[ti]).

## References

- [1] de Villiers TJ, Hall JE, Pinkerton JV, Pérez SC, Rees M, Yang C, *et al*. Revised global consensus statement on menopausal hormone therapy. *Maturitas*. 2016; 91: 153–155.
- [2] Davey DA. Menopausal hormone therapy: a better and safer future. *Climacteric*. 2018; 21: 454–461.
- [3] Chester RC, Kling JM, Manson JE. What the Women’s Health Initiative has taught us about menopausal hormone therapy. *Clinical Cardiology*. 2018; 41: 247–252.
- [4] Stepan JJ, Hruskova H, Kverka M. Update on Menopausal Hormone Therapy for Fracture prevention. *Current Osteoporosis Reports*. 2019; 17: 465–473.
- [5] Baber RJ, Panay N, Fenton A. 2016 IMS Recommendations on women’s midlife health and menopause hormone therapy. *Climacteric*. 2016; 19: 109–150.
- [6] The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2018; 25: 1362–1387.
- [7] Gaffield ML, Kiarie J. Who medical eligibility criteria update. *Contraception*. 2016; 94: 193–194.
- [8] Mendoza N, Juliá MD, Galliano D, Coronado P, Díaz B, Fontes J, *et al*. Spanish consensus on premature menopause. *Maturitas*. 2015; 80: 220–225.
- [9] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of Clinical Epidemiology*. 2009; 62: e1–e34.
- [10] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd edn. Chichester: John Wiley & Sons. 2019.
- [11] Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, *et al*. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *British Medical Journal*. 2016; 355: i4919.
- [12] Manager (RevMan) (Version 5.4.) [Computer program]. The Cochrane Collaboration. 2020. Available at: <https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman> (Accessed: 10 February 2021).
- [13] Schünemann H, Brożek J, Guyatt G, Oxman A. *Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach*. 2013. Available at: <https://gdt.gradeapro.org/app/handbook/handbook.html> (Accessed: 10 February 2021).
- [14] Eeles RA, Morden JP, Gore M, Mansi J, Glees J, Wenzl M, *et al*. Adjuvant hormone therapy may improve survival in epithelial ovarian cancer: results of the AHT randomized trial. *Journal of Clinical Oncology*. 2015; 33: 4138–4144.
- [15] Li L, Pan Z, Gao K, Zhang W, Luo Y, Yao Z, *et al*. Impact of post-operative hormone replacement therapy on life quality and prognosis in patients with ovarian malignancy. *Oncology Letters*. 2012; 3: 244–249.
- [16] Guidozi F, Daponte A. Estrogen replacement therapy for ovarian carcinoma survivors: a randomized controlled trial. *Cancer*. 1999; 86: 1013–1018.
- [17] Eeles RA, Tan S, Wiltshaw E, Fryatt I, A’Hern RP, Shepherd JH, *et al*. Hormone replacement therapy and survival after surgery for ovarian cancer. *British Medical Journal*. 1991; 302: 259–262.
- [18] Ursic-Vrscaj M, Bebar S, Zakelj MP. Hormone replacement therapy after invasive ovarian serous cystadenocarcinoma treatment: the effect on survival. *Menopause*. 2001; 8: 70–75.
- [19] Mascarenhas C, Lambe M, Bellocco R, Bergfeldt K, Rimán T, Persson I, *et al*. Use of hormone replacement therapy before and after ovarian cancer diagnosis and ovarian cancer survival. *International Journal of Cancer*. 2006; 119: 2907–2915.
- [20] Wen Y, Huang H, Huang H, Wu M, Shen K, Pan L. The safety of postoperative hormone replacement therapy in epithelial ovarian cancer patients in China. *Climacteric*. 2013; 16: 673–681.
- [21] Power L, Lefas G, Lambert P, Kim D, Evaniuk D, Lotocki R, *et al*. Hormone use after nonserous epithelial ovarian cancer: overall and disease-free survival. *Obstetrics and Gynecology*. 2016; 127: 837–847.
- [22] Zhang Y, Chen J, Lu W, Li B, Zhu Q, Wan X. Efficacy of post-operative hormone replacement therapy on prognosis of patients with serous ovarian carcinoma. *Chinese Medical Journal*. 2016; 129: 1316–1321.
- [23] Barakat RR, Bundy BN, Spirtos NM, Bell J, Mannel RS. Randomized double-blind trial of estrogen replacement therapy versus placebo in stage I or II endometrial cancer: a Gynecologic Oncology Group Study. *Journal of Clinical Oncology*. 2006; 24: 587–592.
- [24] Ayhan A, Taskiran C, Simsek S, Sever A. Does immediate hormone replacement therapy affect the oncologic outcome in endometrial cancer survivors? *International Journal of Gynecological Cancer*. 2006; 16: 805–808.
- [25] Suriano KA, McHale M, McLaren CE, Li KT, Re A, DiSaia PJ. Estrogen replacement therapy in endometrial cancer patients: a matched control study. *Obstetrics and Gynecology*. 2001; 97: 555–560.
- [26] Arteaga-Gómez AC, Castellanos-Barroso G, Colín-Valenzuela A, García-Vargas J, Márquez-Acosta G, Reyes-Muñoz E. Hormone therapy effect in postmenopausal women with history of endometrial cancer. *Ginecología Y Obstetricia de México*. 2011; 79: 11–17.
- [27] Creasman WT, Henderson D, Hinshaw W, Clarke-Pearson DL. Estrogen replacement therapy in the patient treated for endometrial cancer. *Obstetrics and Gynecology*. 1986; 67: 326–330.
- [28] Lee RB, Burke TW, Park RC. Estrogen replacement therapy following treatment for stage I endometrial carcinoma. *Gynecologic Oncology*. 1990; 36: 189–191.
- [29] Chapman JA, DiSaia PJ, Osann K, Roth PD, Gillotte DL, Berman ML. Estrogen replacement in surgical stage I and II endometrial cancer survivors. *American Journal of Obstetrics and Gynecology*. 1996; 175: 1195–1200.

- [30] Lim S, Kim YH, Lee KB, Lee JM. The influence of hormone therapy with drospirenone-estradiol on endometrioid type endometrial cancer patients. *Journal of Gynecologic Oncology*. 2018; 29: e72.
- [31] Cho HW, Ouh YT, Lee JK, Hong JH. Effects of hormone therapy on recurrence in endometrial cancer survivors: a nationwide study using the Korean Health Insurance Review and Assessment Service database. *Journal of Gynecologic Oncology*. 2019; 30: e51.
- [32] Ploch E. Hormone replacement therapy in patients after cervical cancer treatment. *Gynecologic Oncology*. 1987; 26: 169–177.
- [33] Rees M, Angioli R, Coleman RL, Glasspool R, Plotti F, Simoncini T, *et al*. European Menopause and Andropause Society (EMAS) and International Gynecologic Cancer Society (IGCS) position statement on managing the menopause after gynecological cancer: focus on menopausal symptoms and osteoporosis. *Maturitas*. 2020; 134: 56–61.
- [34] Saeib N, Peeyananjarasri K, Liabsuetrakul T, Buhachat R, Myriokefalitaki E. Hormone replacement therapy after surgery for epithelial ovarian cancer. *Cochrane Database of Systematic Reviews*. 2020; 1: CD012559.
- [35] Pergialiotis V, Pitsouni E, Prodromidou A, Frountzas M, Perrea DN, Vlachos GD. Hormone therapy for ovarian cancer survivors: systematic review and meta-analysis. *Menopause*. 2016; 23: 335–342.
- [36] Edey KA, Rundle S, Hickey M. Hormone replacement therapy for women previously treated for endometrial cancer. *The Cochrane Database of Systematic Reviews*. 2018; 5: CD008830.
- [37] Shim S, Lee SJ, Kim S. Effects of hormone replacement therapy on the rate of recurrence in endometrial cancer survivors: a meta-analysis. *European Journal of Cancer*. 2014; 50: 1628–1637.
- [38] O'Donnell RL, Clement KM, Edmondson RJ. Hormone replacement therapy after treatment for a gynaecological malignancy. *Current Opinion in Obstetrics & Gynecology*. 2016; 28: 32–41.
- [39] Di Donato V, Palaia I, D'Aniello D, Musacchio L, Santangelo G, Di mauro F, *et al*. Does hormone replacement therapy impact the prognosis in endometrial cancer survivors? A systematic review. *Oncology*. 2020; 98: 195–201.
- [40] Angioli R, Luvero D, Armento G, Capriglione S, Plotti F, Scaletta G, *et al*. Hormone replacement therapy in cancer survivors: utopia? *Critical Reviews in Oncology/Hematology*. 2018; 124: 51–60.
- [41] Deli T, Orosz M, Jakab A. Hormone replacement therapy in cancer survivors – review of the literature. *Pathology & Oncology Research*. 2019; 26: 63–78.
- [42] Liu Y, Ma L, Yang X, Bie J, Li D, Sun C, *et al*. Menopausal hormone replacement therapy and the risk of ovarian cancer: a meta-analysis. *Frontiers in Endocrinology*. 2019; 10: 801.
- [43] Collaborative Group On Epidemiological Studies Of Ovarian Cancer, Beral V, Gaitskell K, Hermon C, Moser K, Reeves G, *et al*. Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. *Lancet*. 2015; 385: 1835–1842.
- [44] Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, *et al*. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *Journal of the American Medical Association*. 2013; 310: 1353–1568.
- [45] Beral V, Bull D, Reeves G. Endometrial cancer and hormone-replacement therapy in the Million Women Study. *Lancet*. 2005; 365: 1543–1551.
- [46] Sjögren LL, Mørch LS, Løkkegaard E. Hormone replacement therapy and the risk of endometrial cancer: a systematic review. *Maturitas*. 2016; 91: 25–35.
- [47] Tempfer CB, Hilal Z, Juhasz-Boess, Reznicek GA. *Cancers (Basel)* menopausal hormone therapy and risk of endometrial cancer: a systematic review. *Cancers*. 2020; 12: 2195.
- [48] Roura E, Travier N, Waterboer T, de Sanjosé S, Bosch FX, Pawlita M, *et al*. The influence of hormonal factors on the risk of developing cervical cancer and pre-cancer: results from the EPIC cohort. *PLoS ONE*. 2016; 11: e0147029.