Does Hormone Replacement Therapy Impact the Prognosis in Endometrial Cancer Survivors? A Systematic Review

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Abstract

Purpose: The objective of this study was to evaluate the impact of hormone replacement therapy (HRT) on the prognosis in endometrial cancer (EC) survivors. **Methods:** The research was conducted using the following electronic databases: MEDLINE (PubMed), Web of Science, ClinicalTrials.gov, and Cochrane Library. We performed a review of studies published from January 1986 to January 2019. We selected studies that included EC patients submitted to surgery with curative intent and postoperative use of HRT. **Result:** Seven of 1,332 abstracts considered were eligible: 4 retrospective series, 1 prospective study, 1 randomized controlled trial, and 1 population study. Globally in the observed studies there was not a significant increase in the recurrence rate, measured by the relative risk, in the EC survivors using HRT compared with the controls in tumour stages I and II. The bias was that HRT was prescribed only to low-risk patients,

who were young and had a low stage of disease. **Conclusion:** This systematic review shows that HRT use had no negative effect on prognosis in EC survivors in tumour stages I and II.

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Introduction

Endometrial cancer (EC) is the most common gynaecological cancer in developed countries. Only in 2018 was there a count of approximately 382,069 new cases and 89,929 deaths related to the disease [1]. More than 90% of cases of EC occur in women >50 years of age, with a median age at diagnosis of 63 years and 4% of women with EC are younger than 40 years [2]. The majority of EC are diagnosed early (80% in stage I), with 5-year survival rates of over 95%. However, 5-year survival rates are much lower if there is regional spread or distant disease (68 and 17%, respectively) [3]. The most common treatment for EC is hysterectomy with bilateral salpingo-oophorectomy with or without adjuvant (chemotherapy and/or radiotherapy) treatment depending on risk factors with all

Fig. 1. Flowchart of article selection process.

women entering a surgical menopause after treatment. Historically, EC has been classified, according to Bokhman's model, into two subtypes based on clinico-pathological and molecular features. Type I is the most common EC (60–70% of cases): it includes grade 1 and 2 tumours with a high expression of oestrogen receptors and progesterone receptors. It is characterised by increased oestrogen levels and endometrial hyperplasia, and it is usually associated with a good prognosis (median 5-year survival rates of 85.6%). Type II tumour represents about 30–40% of all ECs, it is oestrogen independent, and is associated with endometrial atrophy and a lack of hormone receptors [4]. Hormonal therapy (HT) is used frequently in EC treatment, particularly in patients with low-grade or oestrogen receptor- and/or progesterone receptor-positive disease [5, 6]. Commonly used agents include progestins, aromatase inhibitors, and selective oestrogen receptor modulators.

Overall 85% of EC survivors are cured and could be benefit from hormone replacement therapy (HRT); in particular 25% of the women with EC are premenopausal and 5% are under 40 years of age at primary surgery, leading to premature menopause [7]. Menopausal symptoms, particularly in reproductive women undergoing surgical treatment for EC, are common [8]. HRT has proven to be highly effective in alleviating menopausal symptoms such as hot flashes, night sweats, dyspareunia, sexual disorders, and insomnia and in preventing osteoporosis, but although no scientific data demonstrate the detrimental effect of HRT in EC survivors, many clinicians remain reluctant to prescribe it because of the concern over oes-

trogen use as an important aetiological factor for EC [9]. The aim of this systematic review is to evaluate the safety and the impact on prognosis of HRT in EC survivors.

Material and Methods

The research was conducted using the following electronic databases, MEDLINE (PubMed), Web of Science, ClinicalTrial.gov, and Cochrane Library, with the use of a combination of the following text words: “endometrial cancer,” “hormone replacement therapy,” and “menopausal status.” From the 1,332 studies initially identified we selected 68 reports and among these we considered 7 studies published from January 1986 to January 2019 (Fig. 1).

We used the following inclusion criteria: randomized controlled trials (RCTs) and non-randomized studies, observational prospective and retrospective cohort studies with a control group; patients who received surgical treatment for EC; postoperative HRT with no restriction on dose and method of administration (vaginal, oral, or both and transdermal patch); the outcome measures including recurrence rate, disease-free survival (DFS) or disease-free interval, overall survival (OS) or mortality rate measured by relative risks, odds ratios (ORs) or hazard ratios estimated with the 95% confidence interval (CI); English language; abstract available.

Results

Symptoms caused by iatrogenic menopause are usually more pronounced in comparison to those following a naturally occurring menopause and have a negative impact on the quality of life of the patients. It is, therefore, important to establish whether EC survivors can benefit

from HRT [10–12]. Few studies have been conducted in the literature and most of them are retrospective.

The present systematic review includes 7 studies: 4 retrospective series, 1 prospective study, 1 RCT, and 1 population study (Table 1).

Creasman et al. [13], in their retrospective study, evaluated 221 patients with endometrial adenocarcinoma stage IA and IB who had completed their cancer therapy. Forty-seven patients received conjugated oestrogen (oral or vaginal or both, 0.625 or 1.25 mg/day) after their therapy. Seven women received oral therapy, 34 vaginal therapy, and 6 both therapies. The mean interval before HRT was 15 months (0–81 months) and the mean follow-up after HRT was 32 months (range 6–84 months). A total of 174 patients treated in the same time period were used as a control group and compared with these patients. There was only 1 recurrence in the group of patients treated with HRT (2.1%) and 26 recurrences (14.9%) in the control group. Significantly longer DFS and OS were seen in the oestrogen-treated group.

In their retrospective case-control study Lee et al. [14] analysed 44 EC stage I treated with oral conjugated oestrogen 0.625 or 1.25 mg/day with or without combined progestin. They compared the oncologic outcomes of these patients with 99 stage I patients who did not receive HRT. The median age of the HRT group was 56.3 years and that of the control group was 61.5 years. The tumour stage was lower in the HRT group than in the control group (IA, IB vs. IA, IB, IC) and in the HRT group they selected patients with low-risk disease (grade 1 or 2 cancer, less than half myometrial invasion, and no metastases to lymph nodes or other organs). The mean interval before starting HRT from the time of surgery was <12 months and the mean follow-up was 64 months. They found no recurrence in the HRT group and 8 recurrences in the control group. The bias of this study was that 31 patients in the control group had high-risk disease. If only the low-risk patients were compared, there was no difference in the development of recurrences.

Chapman et al. [15], in their retrospective case-control study, analysed EC patients with tumour stage I or II. Sixty-two women received conjugated oestrogen (oral or oral/vaginal, or transdermal patch, mean 0.64 mg/day) with or without progesterone (oral, 2.5 mg/day), and 61 patients did not receive HRT. Fifty-seven patients received oral therapy, only 1 patient vaginal therapy, and 4 both therapies. The women started HRT after 8 months on average from the EC treatment. Only 2 women of the HRT group versus 8 of the control group had recurrences. The selection bias of this study was that the oestrogen replace-

ment therapy group had earlier-stage disease ($p = 0.04$) and less severe depth of invasion ($p = 0.003$); however, no significant differences in the recurrence rate or in OS were observed between the two groups.

Another retrospective matched cohort study was conducted by Suriano et al. [16]. They analysed 75 women in the HRT group and 75 women in the control group with similar characteristics. The overall population had tumour stage I, II, and III. The HRT group received conjugated equine oestrogen (oral, 0.625 mg/day) with or without medroxyprogesterone acetate (oral, 2.5 mg/day). In the HRT group a lower recurrence rate (1%) was observed (14% in the control group); moreover, HRT users had a significantly longer DFS ($p = 0.006$).

Ayhan et al. [17] conducted the first prospective study with 50 women in the HRT group and 52 in the control group. The overall population was uniform with similar clinical characteristics. The tumour stage was I and II in both groups. The HRT group received conjugated equine oestrogen (oral, 0.625 mg/day) plus medroxyprogesterone acetate (oral, 2.5 mg/day) after only 8 months from the EC treatment. No recurrence was observed in the HRT group. In the control group, 1 patient had a recurrence. This study showed that the immediate postoperative use of HRT did not increase the recurrence or death rates in EC survivors.

The only RCT was conducted by Barakat et al. [18]. It involved 1,236 women treated for EC randomized to oestrogens alone or to placebo only <5 months after the cancer therapy. The median age was 57 years and the tumour stage was IA, IB, IC and IIA, IIB in the overall population. The mean follow-up after HRT was 35.7 months. No significant difference in the recurrence rate was observed, being very low in both groups (2.1% in the 618 HRT users vs. 1.9% in the placebo group).

In 2014 Shim et al. [19] included all these studies in a meta-analysis. There were overall 896 EC survivors who used HRT, and 1,079 were non-users. The meta-analysis base indicates no significant increase in the risk of recurrence in EC survivors using HRT relative to the control group (OR: 0.53; 95% CI: 0.30–0.96, $I^2 = 49.0$). This pattern was also observed in the subgroup analysis for the stage and type of HRT.

In 2019 Cho et al. [20], using the Korean Health Insurance Review and Assessment Service (HIRA) database, conducted the first population study. The study included 5,667 women with a new diagnosis of EC who underwent surgical staging (hysterectomy + ovariectomy +/- pelvic/para-aortic lymphadenectomy). Of these patients 847 were treated with HRT (tibolone 32%, pro-

Table 1. Main characteristics of the 7 included studies: risk of EC recurrence and HRT

Authors	Year	Lo- cation	Study	Population HRT and age	Population no HRT and age	Tumor stage in population HRT	Tumor stage in population no HRT	Histological type	Myometrial invasion HRT, n (%)	Myometrial invasion no HRT	HRT type and route	Mean duration of HRT, months	Mean interval before HRT, months	Mean follow-up after HRT, months	Outcome recurrence rate HRT vs. control group
Creasman et al. (1986) [13]	1975– 1980 (6 years)	US	Retro- spective case-control study	47 (median age: 56.3)	174 (median age: 61.5)	IA: 30 IB: 17	IA: 115 IB: 57	Endometrial adenocarcinoma	–	–	Conjugated oestrogen (oral or vaginal or both, 0.625 or 1.25 mg/day) Oral: 7; vaginal: 34 and both: 6	26	15	32	1 vs. 26 The oestrogen group experienced significant longer DFS and OS
Lee et al. (1990) [14]	1975– 1985 (11 years)	US	Retro- spective case-control study	44 (median age: 56.3)	99 (median age: 61.5)	IA: 24 IB: 20 IC: 31	IA: 24 IB: 43 IC: 31	Endometrial adenocarcinoma	Endometrium only: 21 (48%) Inner 1/2: 23 (52%)	Endometrium only: 24 (24%) Inner 1/2: 43 (44%) Outer 1/2: 31 (31%) Unknown: 1 (1%)	Conjugated oestrogen (oral, 0.625 or 1.25 mg/day) with or without progesterin Oral: 44	64	<12	64	0 vs. 8 They found the rate of recurrence and death were higher in the no HRT group, although this group included participants with high-grade cancer
Chapman et al. (1996) [15]	1984– 1994 (13 years)	US	Retro- spective case-control study	62	61	IA and IB: 54 IC: 6 II: 2	IA: B: 43 IC: 9 II: 9	Endometrial adenocarcinoma	–	–	Conjugated oestrogen (oral or oral/vaginal, or transdermal patch, mean 0.64 mg/day) with or without progesterone (oral, 2.5 mg/day) Oral: 57; vaginal: 1 or both: 4	39.5	8	39.5	2 vs. 8 The oestrogen replacement therapy group had earlier stage disease ($p = 0.04$) and less severe depth of invasion ($p = 0.003$); however, the total number of deaths in each group was not significantly different
Suriano et al. (2001) [16]	1984– 1998 (15 years)	US	Retro- spective matched cohort study	75 (median age: 59.7)	75 (median age: 61.1)	IA: 14 IB: 44 IC: 6 IIA: 5 IIB: 3 IIIA: 3 IIIC: 1	IA: 14 IB: 43 IC: 7 IIA: 5 IIB: 2 IIIA: 3 IIIC: 1	Adenocarcinoma (90%) Papillary serous (5%) Clear cell (5%)	Endometrium only: 16 (21%) Inner 1/2: 49 (65%) Outer 1/2: 10 (13%)	Endometrium only: 12 (16%) Inner 1/2: 47 (63%) Outer 1/2: 16 (21%)	Conjugated equine oestrogen (oral, 0.625 mg/day) with or without medroxyprogesterone acetate (oral, 2.5 mg/day) Oral: 75	nr	<6	nr	2 vs. 11 In the HRT group a lower recurrence rate (1%) was observed (14% in the control group); moreover, HRT users had a significantly longer DFS ($p = 0.006$); data are insufficient to address any protective effects conferred by progesterone administration with respect to disease-free interval and disease-free survival
Ayhan et al. (2006) [17]	1992– 2001 (9 years)	Turkey	Prospec- tive study	50 (median age: 51.2)	52 (median age: 54.3)	I: 44 II: 6	I: 46 II: 6	Endometrioid type	Endometrium only: 15 (30%) Inner 1/2: 26 (52%) Outer 1/2: 9 (18%)	Endometrium only: 9 (17%) Inner 1/2: 27 (52%) Outer 1/2: 16 (31%)	Conjugated equine oestrogen (oral, 0.625 mg/day) plus medroxyprogesterone acetate (oral, 2.5 mg/day) Oral: 50	49.1	1–2	49.1	0 vs. 1 In the control group, 1 patient had a recurrence and subsequently died of the disease This study showed that immediate postoperative use of HRT did not increase the recurrence or death rates in endometrial cancer survivors
Barakat et al. (2006) [18]	1997– 2003 (7 years)	US	RCT	618 (median age: 57)	618 (median age: 57)	IA: 232 IB: 305 IC: 48 II: 1 IIA: 22 IIB: 8 Stage missing in 3 patients	IA: 238 IB: 302 IC: 42 IIA: 17 IIB: 16 Stage missing in 3 patients	Adenocarcinoma unspecified (40%) Endometrioid (71%) Serous (1.3%) Squamous (0.2%) Other (4.5%)	Endometrium only: 243 (39.6%) Inner 1/2: 313 (51%) Outer 1/2: 58 (9.4%)	Endometrium only: 248 (40.5%) Inner 1/2: 311 (50.7%) Outer 1/2: 54 (8.8%)	Oestrogen (oral, dose not otherwise specified) Oral: 618	35.7	<5	35.7	14 vs. 12 The percentage of participants alive with no evidence of disease at the end of the 36-month follow-up period was 94, 3% in HRT group and 95.6% in placebo group
Cho et al. (2019) [20]	2010– 2013 (3 years)	Korea	Population study	847	4,820	I and II	I and II	Endometrial adenocarcinoma	–	–	Tibolone, progesterone only, oestrogen only, oestrogen plus progesterone	15	11	47.5	50 vs. 396 HT did not increase the recurrence rate of EC (HR = 0.81; 95% CI = 0.31–2.10)

Risk of endometrial cancer recurrence and HRT. nr, not recorded.

gesterone only 30%, oestrogen only 22%, and oestrogen plus progesterone 16%) a mean time of 11 months after the cancer therapy. Recurrence was observed in 446 patients (7.8%), including 50 patients (5.9%) who received HT and 396 patients (8.2%) who did not receive it. Univariate analysis revealed a reduced recurrence rate in patients who received HT (hazard ratio = 0.62; 95% CI = 0.46–0.83). The results of this study should be interpreted with caution because, due to the nature of the HIRA database, the disease stage, which is the most important factor for survival and recurrence analysis, was unknown. Thus, those with no adjuvant treatment or receiving radiation therapy were classified as non-high-risk EC, and those receiving chemotherapy were classified as high-risk EC.

There is still some concern about oestrogen therapy and uterine sarcomas, which thankfully are not common and only constitute about 3–5% of all uterine malignancies. Even though there are a number of histological subtypes, namely leiomyosarcoma, endometrial stromal sarcoma and undifferentiated endometrial sarcoma, and even carcinosarcoma, there is a significant paucity of literature on the subject because of the rarity of the malignancies. The data that are available allude to the sarcomas collectively. There is some evidence to support that oestrogen therapy is contraindicated in women with endometrial stromal sarcoma but not the other types of cancer, even though both leiomyosarcoma and endometrial stromal sarcoma express oestrogen and progesterone receptors to varying degrees [21–24]. In consideration of these data, derived mainly from retrospective studies, we can understand why the guidelines are in conflict about the use of HRT in the EC survivors. In 2000, the Committee of Gynaecologic Practice of the American Congress of Obstetricians and Gynaecologists issued a vague statement that use of oestrogen for women with a previous history of EC should be determined on an individual basis in light of its benefits and risks [25]. In 2011, French guidelines specified that HRT can be administered to patients under the age 50 to treat symptoms due to iatrogenic menopause and that HRT should be administered to healthy women age 50 and over in accordance with its indications and contraindications [26]. Japanese guidelines for the treatment of EC [27], published in 2013, approved HRT after the treatment of EC. In contrast, the National Comprehensive Cancer Network (NCCN) Panel [28] states that oestrogen-only HRT is a reasonable option for patients who are at low risk of tumour recurrence, but that the exact therapy should be individualised and discussed in detail with the patient.

Discussion

Globally in the studies analysed no significant increase in recurrence rate measured by the relative risk in the EC survivors employing HRT compared with the controls was observed.

According to published data, HRT use had no negative effect on recurrence and OS after EC treatment. In the studies analysed a selection bias was present since HRT was prescribed only to low-risk patients that were younger and had a lower stage of disease. Moreover, most studies are retrospective and the individual sample size was not large enough to sufficiently explain the effect of HRT on EC recurrence.

The available studies (both the single RCT and non-randomised evidence) do not show significant problems with the use of HRT after surgical treatment for early-stage EC, but there is no information about the HRT use in the higher-stage EC (FIGO stage II and above), because most of studies targeted patients with early-stage EC for HRT use [13–15, 17, 18], and only one study included stage III EC patients [16], with 4 (5.3%) patients receiving HRT. Therefore, the evidence provides no support for the argument that HRT can be safely given to patients with advanced EC. Moreover, residual malignant cells after a suboptimal surgical effort for advanced EC may be re-stimulated by HRT, provoking a recurrence.

Among the published data, the duration of HRT ranged from 2 to 132 months. However, the mean duration of HRT in all studies was longer than 36 months except for Creasman et al. [13] (26 months), which was well beyond the interval for most recurrences.

Although most of the studies used the standard oral dose of oestrogen (0.625 mg of conjugated oestrogen daily), the dosage went up to 1.25 mg of conjugated oestrogen daily in three studies [13–15]. The administration route was generally oral except for two studies in which 34 (72.3%) and 1 (1.6%) received vaginal HRT [13, 15]. This suggests that, because topical oestrogens can significantly increase the level of systemic oestradiol [29], topical vaginal oestrogen was considered to represent systemic use, as in oral administration [15]. The RCT reported by Barakat et al. [18] overcomes many of the shortcomings reported by non-randomized studies and provides the best available data on the effect of HRT in EC survivors.

Conclusion

The results suggest that HRT use does not increase the risk of recurrence in women with stage I and/or II EC, although they are based mainly on retrospective, case, or cohort-controlled studies subject to a variety of biases. In the meantime, EC survivors interested in HRT should be informed of available data and the clinicians should apply the results in an individualized manner, taking into account accurate anamnesis, age, and other possible risk factors, in order to prescribe the best therapeutic option between a hormonal and a new non-hormonal regimen [30].

There is no statistically significant difference in the risk of EC recurrence and cancer-induced death if patients used HT (progesterone plus oestrogen or oestrogen alone) in the postoperative phase within 6 months from the time of endometrial surgery or did not have early-stage EC. These studies provide the most current and reliable data to assist patients in making informed decisions regarding HRT. The established long-term health benefits of oestrogen replacement, as well as the positive impact on the quality of life, seem to outweigh the unfounded suggestion of an increased risk of disease recurrence.

Other multicentric randomized studies are needed to deepen this topic and to better outline the potential risks and benefits of using HRT in cancer survivors.

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Statement of Ethics

The authors declare that all data were collected meeting ethical guidelines.

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Author Contributions

Conception, design, and coordination of the project: V. Di Donato and Innocenza Palaia.

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