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Ovarian cancer patients and hormone replacement therapy: a systematic review

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Abstract

Objective. Although the majority of patients with ovarian cancer are menopausal, approximately one-third are premenopausal at the time of diagnosis. Little information is available concerning the impact of hormone replacement therapy (HRT) on the clinical outcomes of patients previously treated for ovarian cancer. The objective of this review is to determine whether there is any adverse impact on survival among women with ovarian cancer on HRT.

Methods. A protocol was developed in advance of commencement of this systematic review. It detailed the plan for the search strategy, selection criteria for studies, and methods for data collection and analysis. No limitation of study design was made, and the details of the search strategy are described in the text of the review. Two reviewers independently evaluated the eligibility of all studies and abstracted the data.

Results. One randomized trial and two observational studies are included. Due to methodological heterogeneity of the included studies, results have not been pooled in a meta-analysis. The randomized trial presented differences between the intervention and control groups on median overall survival (44 months vs. 34 months/HRT vs. No-HRT) and disease-free survival (34 months vs. 27 months/HRT vs. No-HRT) that were not significant. Similarly, there were nonsignificant differences in survival and recurrence rates in the two included cohort studies.

Conclusions. This is a comprehensive systematic review of the evidence concerning HRT in ovarian cancer patients. Until more evidence becomes available, it appears that HRT is acceptable for patients with ovarian cancer as part of supportive and symptomatic therapy.

Keywords: Cancer; Meta-analysis; HRT

Introduction

On average, North American women can expect to live up to one-third of their lives in the menopausal state. Hormone replacement therapy (HRT) and issues surrounding its safety continue to challenge clinicians and patients. Hormone replacement therapy offers well-established clinical benefit for menopausal symptoms such as vasomotor instability, urogenital atrophy, atrophic vaginitis, poor concentration, and accelerated osteoporosis. A reduction in overall mortality has been shown in long-term users of HRT [1].

Protocols for the administration of HRT are now being intensely investigated and scrutinized both for their beneficial and harmful effects [2]. Many physicians are reluctant to prescribe HRT to ovarian cancer patients, fearing it may increase the risk of ovarian cancer recurrence and decrease overall survival by promoting tumor progression or stimulating angiogenesis [3]. Limited studies of HRT in ovarian cancer survivors to date cannot exclude the possibility that HRT might stimulate growth of disease in a subset of patients whose tumor expresses estrogen receptors. Given the widespread use of HRT, if there was an adverse impact of its use on survival, this would have important public health implications.

The objective of this review is to determine whether HRT compared to No-HRT has any adverse impact on survival among women with ovarian cancer.

Materials and methods

A protocol was developed in advance of conducting this review. It was submitted to a third party methodologist

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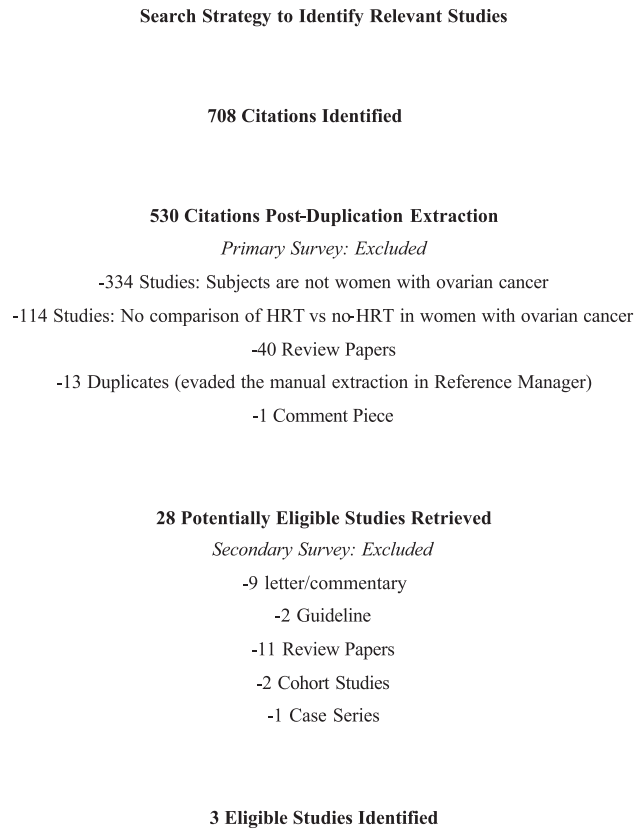

Fig. 1. Flowchart of methodological steps in the systematic review.

(DM) for assessment and critical appraisal. All participating reviewers participated in the development of the protocol. The QUORUM statement was reviewed as the protocol was developing to ensure optimal quality of reporting of this systematic review and the planned meta-analysis [4]. Fig. 1 outlines the methodological steps for this systematic review.

Data sources

A high level of sensitivity was desired in this search strategy, given that this is a narrow research area within gynecologic oncology. No methodological filter, limitation of design, or language of publication was applied. The search strategy was developed by the lead author and was then submitted to two independent information specialists (RS and AM) to ensure high recall. Using the Ovid interface, six electronic bibliographic databases were searched including Medline (1966–2003), Cancerlit (1975–2002), Embase (1980–2003), Cinahl (1982–2002), and HealthStar (1975–1986), HealthStar/Ovid HealthStar (1987–2002). The Cochrane Library (Issue 4, 2002) and Cochrane Controlled Trials Register were searched for additional randomized trials. Complete descriptions of the database search strategies are available from the authors. The search was extended to include gray literature in an attempt to discover results of studies with negative results that could introduce publication bias. This search strategy will be repeated on an annual basis by the primary author (LH) to identify any emerging evidence that can be used to update this review in the future.

Study selection and eligibility criteria

All randomized clinical trials (RCTs) or quasi-randomized trials of women with ovarian cancer who have received surgical treatment for their disease (including complete surgical staging) where the intention to allocate women to HRT versus No-HRT were included. Because it was anticipated that there would be insufficient evidence from published clinical trials to answer the question of whether HRT impacts survival, observational studies comparing utilization of HRT versus No-HRT (cohort studies with matched comparison group) in women with ovarian cancer were also included. Review articles, case series, opinion/consensus/comment pieces, guidelines, and letters were excluded.

The types of participants were women with epithelial ovarian cancer (all stages) who were treated with surgery for their disease. Women may have received or be receiving combination chemotherapy or radiation therapy as part of primary treatment for their disease. Studies were included that evaluated the use of HRT (any regimen or route of administration). The main outcome variable of interest was overall survival. Studies examining recurrence rates/time to recurrence, progress-free interval/disease-free interval, and/or quality of life outcomes (menopausal symptom relief) were included.

Screening process and data extraction

All references identified through the search strategy were assembled in Reference Manager. Duplicate references were deleted manually. There were two levels of screening of the citations, reflected in Fig. 1. There was no masking of the citations as there is conflicting evidence that this impacts the results of meta-analysis [5,6]. Two reviewers (LH and MF) independently evaluated the title and abstract of each citation to identify all studies including any possibility of a comparison of HRT versus No-HRT in women with ovarian cancer. All citations identified as being potentially eligible were retrieved for complete assessment. Reasons for exclusion were recorded on a citation assessment form. Where there was any discrepancy between reviewers, the entire citation was requested. Two content experts (LH and TL) then independently assessed each article for inclusion in the review based on the inclusion and exclusion criteria. A standardized record form was utilized. An assessment of method-

ological quality was made according to the method described by Jadad et al. [6]. The adequacy of concealment was also assessed. Any disagreements at this level were discussed until a consensus was reached. Although plans were made to have disagreements reviewed by a third content expert (MF), this was not required. No statistical assessment of inter-rater agreement was done. A standard "Table 1" to present descriptive data from each trial was derived.

In addition to the main outcome measures listed previously, information on the setting of the study (country, type of population, socioeconomic status), a detailed description of the hormone regimen used (drug, dose, frequency, and timing in relation to diagnosis of ovarian cancer), and definitions of outcome variables were collected. Individual participant data (stage at diagnosis, treatment received at time of study commencement, compliance with and duration of therapy) were also collected to allow difference and similarities of the results found indifferent settings to be inspected thoroughly.

A meta-analysis was planned if at least two or more acceptably controlled randomized trials could be identified. Summary relative risks were to be calculated and forest plots were to be displayed. Heterogeneity across studies was to be assessed by visual inspection of the forest plots and subsequently, in the framework of sensitivity analysis. In the absence of RCTs, the observational data was to be summarized in terms of direction of association.

Results

Three studies were identified that met the eligibility criteria for this systematic review. For a detailed description of included studies, see Table 1 (7–9): "Characteristics of included studies". For a description of the reasons for exclusion of studies, see Table 2 (10–31) : "Characteristics of excluded studies". Table 3 displays a matrix of included studies according to defined outcomes. Following the secondary survey, only three studies were eligible for inclusion in the review. Only one study was an RCT, the other two were retrospective cohort studies. Due to the methodological and clinical heterogeneity of the included studies, results have not been pooled. There were no retrievals from the attempts to uncover unpublished data. Canadian content experts (all academic centers polled with a 92% response rate) and Wyeth Pharmaceuticals were unaware of any unpublished or ongoing trials.

The methodological quality of the RCT by Gudozzi and Daponte [8] is good, and the results are valid for the study population. The quality of the reporting was moderate, limited by the absence of double blinding. The method of allocation concealment was adequate. This is reassuring given the increasing evidence that reports of RCTs with inadequate allocation concealment tend to overestimate the intervention effect by up to 30% [32,33]. Study groups were similar with respect to important prognostic indicators including age, stage, histology, and optimization of surgical

Table 1
Characteristics of included studies

Study ID	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Eeles, 1991	Retrospective Cohort Study	women with epithelial ovarian cancer (all stages) post-surgery, and chemo. *N* = 373; 78 hormone group, 295 no-hormone group. No age data provided	estrogen (0.625 mg po od) + estrogen and norgestrel (0.625 mg po od + 0.5 mg po od)–median start time 135 days post-diagnosis versus no hormones. Median duration of HRT: 28 months (1–200 months). No assessment of compliance	survival and recurrence rate. Median F/U entire group 42 mo.	London, England, 1972–1988 English language	not applicable
Guidozzi, 1999	Randomized Controlled Trial	women with epithelial ovarian cancer (all stages) post-surgery and chemotherapy. *N* = 130: 62 in hormone arm, 68 in no-hormone arm. No age data provided	estrogen (0.625 mg po od) started within 6–8 weeks post-op versus no hormones. Duration of ERT expressed as compliance: 95% at 1 year, 84.7% at 4 years	survival, recurrence rate, median disease-free interval. Median F/U 48 months—all participants	overall quality scale (Jadad) = 3 South Africa, 1987–1994. English language. Patients took oral chlorambucil for 1 year post-completion of primary therapy	adequate
Ursic-Vrscaj, 2001	Retrospective Cohort Study	women with epithelial ovarian cancer (stages I–III). *N* = 78, 24 in hormone group/mean age 41, 54 in no-hormone group/mean age 43	estrogen (2 mg estradiol + 1 mg estriol po od) or estrogen and progesterone (as above + norethisterone 1 mg) started at a mean of 21 months post-diagnosis. Duration of HRT: mean 24 months (1–70 months)	survival, recurrence rate, quality of life (modified Kupperman index)	Slovenia, 1987–1999. English language	not applicable

debulking. Ascertainment of outcome bias was minimal since the primary outcome variable was survival and the secondary outcome was disease recurrence. Follow-up was sufficiently long (48 months minimum) and complete with only three patients lost in the intervention group and two patients lost in the control group. A sample size calculation (power 0.8, alpha 0.05, MCID 0.2) was done, and the authors met their accrual goals. Differences between groups on median overall survival (44 months vs. 34 months/HRT vs. No-HRT) and disease-free survival (34 months vs. 27 months/HRT vs. No-HRT) were not significant. Although not provided in the paper, a relative risk of 0.873 (95% CI 0.647–1.179) was calculated from the available raw data. This would suggest a protective effect of HRT on recurrence, but the magnitude of the effect is weak and the confidence interval crosses unity. Unfortunately, data on the actual number of patients who died was unavailable and attempts to contact the authors by mail to obtain this data have not been successful.

The particular strength of the retrospective cohort study by Ursic-Vrscaj et al. [9] was its attempt to assess the effects of menopause on quality of life through the Kupperman index. All patients showed improved symptomatology within three months of starting HRT; however, the Kupperman index is quite limited. It was originally developed in the 1950s and uses a combination of self-report and physician ratings [34]. Modern psychometrics have since led to the publication of more reliable and valid scales for menopausal research that should have been used preferentially [35]. An odds ratio of 0.90 (95% CI 0.24–5.08) was reported for the estimated risk of dying for ovarian cancer patients who received HRT. Using the crude data provided, an OR of 0.58 (95% CI 0.18 – 1.86) was calculated as the estimated risk of recurrence in the group of patients receiving HRT. Differences between groups were not significant.

The second retrospective study by Eeles et al [7] is weakened by the fact that prognostic factors were not well-balanced between the study groups. In this study, the group receiving HRT comprised a slightly higher percentage of younger patients, those with early stage disease, and those with well-differentiated tumors. An attempt was made to adjust for this discrepancy using statistical analysis; however, this does not ensure that the groups compared are similar in other respects. This is the major vulnerability of the results of this work. The adjusted RR of death and recurrence in the HRT group versus the No-HRT group was 0.73 (95% CI 0.44–1.20) and 0.90 (95% CI 0.52–1.54), respectively. Again, differences between groups were not significant. Although information regarding thromboembolic complications in patients was not a component of the methodology for this review, this was the only paper among the included studies that provided this information. One patient in the study (not receiving HRT) died of a cerebrovascular accident.

Table 2
Characteristics of excluded studies

Study ID	Case series	Letter/ comment/ opinion	Review	Guideline	Other
Bebar, 2000	yes				
Belaisch, 2000		yes			
Beral, 1991		yes			
Breckwoldt, 1993			yes		
Burger, 1999			yes		
Collis, 1999		yes			
Darai, 2000			yes		
Delaloye, 1995		yes			
DiSaia, 1996			yes		
Drew, 2001		yes			
Genazzani, 1999			yes		
Genazzani, 2001			yes		
HRT, 1990— no author		yes			
HRT, 2002— no author		yes			
Kerbrat, 2001				yes	
Kerbrat P., 2001			yes		
Killackey, 2002			yes		
Kurabayashi, 1998					participants unclear
Newsbytes, 2002		yes			
Sommer, 1993	yes				
Stahle, 2002			yes		
Tserkezoglou, 1996			yes		
Wallace, 1993			yes		
Wren, 1996			yes		
Yasuda, 1994					participants unclear

Table 3
Matrix of included studies according to outcome

	Overall survival	Recurrence rate	Progress/ disease-free interval	Quality of life
Eeles, 1999	yes	yes	no	no
Guidozzi, 1999	yes	yes	yes	no
Ursic-Vrscaj, 2001	yes	yes	no	yes

Discussion

Hormone replacement therapy has been widely used for decades. On the basis of new data from the Womens' Health Initiative, the use of estrogen replacement therapy is being critically reviewed. The central, undisputed claim of HRT is that it remains the treatment of choice for psycho-vegetative hormone deficiency symptoms. These include insomnia (caused by hot flushes followed by freezing attacks) and fatigue that can result in severe disruptions to daily routine and ultimately lead to a depressive attitude.

No systematic review has been published on the use of HRT in ovarian cancer survivors. The number of review papers written on this subject outnumbers the actual experimental and analytic evidence by a ratio of almost 20:1. The strength of this systematic review is the comprehensiveness

of the literature search (included non-English language trials) and the attempt to find gray literature [36]. A very broad search was undertaken to identify all potential studies for inclusion. The search strategy is rigorous, transparently reported, and available for review. Review procedures were conducted in duplicate. Because agreement between reviewers was nearly perfect, no formal statistical method was used to quantify agreement. This is a potential limitation of this work. Nevertheless, no formal study of ''inter-observer reliability'' has shown that its quantitative assessment and/or variations in agreement impact the results of systematic reviews. It has been suggested that agreement of dichotomous decisions should be quantified with a kappa statistic [37], acknowledging that there is no absolute level of kappa below which the results of a systematic review become invalid [38]. Summary characteristics about the general features of the included studies have been provided. This is a strength of this review, allowing the reader to judge the pattern of characteristics of the included trials and to apply the results to their respective population of patients [38].

The major limitation of this review is the fact that there is only one RCT and two cohort studies for inclusion. Consequently, no meta-analysis is possible and additionally, there is substantial clinical heterogeneity. The data from the Gudozzi trial offers strong evidence that HRT is not detrimental to survival in ovarian cancer patients. Conversely, there is no compelling evidence of any beneficial effect. The interpretation of the data provided by the cohort studies is severely limited. It is amazing that there has been so much energy invested in the development of review papers and guidelines with such a dearth of evidence. Comments on the results of this review in light of the totality of evidence are limited for obvious reasons. The bulk of information available for clinicians is in the form of review papers (53 in total identified for this review) and guidelines/comment pieces. The overall consensus from assessment of the evidence is that HRT can and should be considered in ovarian cancer patients who exhibit troublesome menopausal symptomatology.

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