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Menopausal hormone therapy and risk of ovarian cancer: systematic review and meta-analysis

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Knowledge about the impact of menopausal hormone therapy (MHT) on the risk of ovarian cancer (OvC) is insufficient, and studies are inconsistent. Mortality from OvC ranks highest among cancer sites in female reproductive organs. We performed meta-analyses to assess the impact of specified types of MHT on the risk of OvC in cohort studies (CS), case-control studies (CCS), randomized controlled trials (RCT) and cancer registry studies (CRS). We used data published 1966–2006 on estrogen therapy (ET), estrogen/progestin therapy (EPT) or MHT (unspecified regimen) identified by a structured, computerized and manual literature search. We identified 42 studies (30CCS, 7CS, 1 RCT and 4 CRS) with 12 238 cases. The risk of OvC (ever-use, annual risk) is increased 1.28-fold by ET [confidence interval (CI) 1.18–1.40] and 1.11-fold by EPT (CI 1.02–1.21) with a suggestion of greater risks with ET. There appears to be no differential impact of any therapy on histological subtypes. Risks were greater in European than North American studies for both ET and EPT. In conclusion, ET as well as EPT, are risk factors for OvC. Given the widespread use of MHT, known benefits should be weighed against the increased risk of OvC, and more studies are warranted, particularly on factors with the greatest apparent risks.

Keywords: ovarian cancer/risk factor/estrogen (progestin) therapy/menopausal hormone therapy/hormone replacement therapy

Introduction

A multitude of studies has been conducted to elucidate the association between menopausal hormone therapy (MHT) and breast respective endometrial cancer. Information regarding the impact of hormone therapy (HT) on risk of ovarian cancer (OvC) is relatively restricted. Age-standardized cancer rates show that this cancer is the ninth most common cancer in women among 24 cancer sites considered (Kamangar *et al.*, 2006). However, given the higher mortality of OvC compared to other cancer sites of female reproductive organs, knowledge about associations between use of HT and OvC risk is important. There is good evidence to suggest that use of combined hormonal contraceptives decreases the risk of OvC (IARC, 2006). However, knowledge regarding HT is less unequivocal and results of previous meta-analyses varied. There was either no suggestion of or a weak if any association between use of HT an OvC (Whittemore *et al.*, 1992; Beral *et al.*, 1999; Coughlin *et al.*, 2000; Fernandez *et al.*, 2003; Farquhar *et al.*, 2005; Kurian *et al.*, 2005) and results were mainly restricted to findings of case-control studies (CCS). However, one meta-analysis found an increased risk of epithelial carcinoma in ever-users of HT (Garg *et al.*, 1998). Several prospective cohort studies (CS) were published recently, providing evidence for an increased risk of OvC in HT user (Rodriguez *et al.*, 2001; Lacey *et al.*, 2002a, b; Folsom *et al.*, 2004), and a suggestion of an increased risk by one specified estrogen/progestin regimen in one large randomized clinical trial (Andersen *et al.*, 2003).

Our hypothesis was that MHT, not restrict to ET, increases risk of OvC. Therefore we conducted a systematic search of the literature and performed meta-analyses of available evidence provided by CS, CCS, randomized controlled trials (RCT) and cancer registry studies (CRS) to analyse the impact of various menopausal hormone therapies [unopposed estrogen therapy (ET); estrogen/progestin therapy (EPT) and MHT (unspecified regimen)] on OvC risks. We explored associations between ever-use of these types of therapy and risks, analysed annual changes of risk, potentially different impact of therapies on histological subtypes and risk by geographical location of studies.

Materials and Methods

Identification of studies

We conducted topic-specific searches of several databases, using Medline (1 January, 1966–31 April 2006), CANCERLIT, EMBASE, Scopus, the Cochrane Library and the Cochrane Controlled Trials Register. We used the Medical Subject Headings and/or text words 'hormone replacement therapy', 'hormone

therapy', '(post) MHT', '(o)estrogen (replacement) therapy', 'estradiol (replacement) therapy', 'estrogen and progest* (replacement) therapy', 'HRT', 'ERT', 'HT', 'post(-)menopausal estrogens (hormones)', 'reproductive hormones', 'non-contraceptive hormones (estrogens)', OvC or 'carcinoma' or 'neoplasm' or 'tumo(u)r', 'case(-)control study', 'cohort study', 'cancer registry' and any of the terms 'randomised, randomized, controlled and clinical' in conjunction with 'trial' or 'study' in multiple combinations where applicable. All studies not conducted in women were a priori excluded. We used snowballing (review of references of identified studies), scrutinized systematic reviews addressing various aspects of HT, checked references of a previous systematic search regarding a related cancer topic (Greiser *et al.*, 2005) and of health technology assessment reports to potentially identify further studies (National Heart, Lung, and Blood Institute, 2002; Nelson *et al.*, 2002; IARC, 2006; U.S. Preventive Service Task Force, 2005). Search of editorials, supplements, proceedings, books, abstract books and proceedings of major menopause and OvC meetings, respectively, was restricted to the preceding five years (2002–April 2006). The titles and abstracts of all potentially relevant publications were examined to determine the relevance of the information; full articles were scrutinized if any potentially relevant information was found in a retrieved abstract. Searches were conducted independently by two reviewers (M.D. and C.M.G.). We did not impose language restrictions.

Inclusion criteria

We included CS, CCS, RCTs and CRS, if these publications contained information upon ever-use of any type of HT, risk by duration of use or increase of risk within a given time interval, respectively, of ET, or EPT or MHT (the combination of all regimens of MHT as reported including often unspecified/unknown preparations) in women of all ethnic groups (C.M.G., M.D. and E.M.G.). Studies were eligible if confidence intervals (CI) or standard errors of risk estimates and dates on conduct of the study were provided. In studies with multiple publications from the same population, we included only data from the most recent publication. In the case of double publication, we included only the data sets of the first publication or the one providing the most extractable data.

Data extraction, statistical methods and assessment of homogeneity

Data were abstracted and statistical analyses performed independently by two authors (C.M.G. and E.M.G.). Any differences in data extraction were resolved by discussion to reach consensus. Major a-priori objectives were to analyse the association between (i) specified groups of hormone regimens (ET, EPT and MHT) and risk of OvC, (ii) the magnitude of ever-use (estimate of a total) and annual risk in pre-specified hormone regimen groups (ET, EPT and MHT), (iii) the potential impact of specified hormone regimens on histological subtypes and (iv) the role of geographical study region for risk associations.

Statistical analyses were performed independently by two authors (C.M.G. and E.M.G.) using two different approaches. First, to summarize effects of HT on risk of OvC irrespective of duration or dosage, point estimates and CI were used in a fixed-effects model applying the general variance-based method (Petitti, 2000, see web appendix). Second, slopes for both individual studies and summary slopes were calculated using inverse variance-weighted least squares estimates in order to estimate summary slopes for calculation of increase of risk per year of use (Berlin *et al.*, 1993).

We examined heterogeneity across studies by applying the general variance-based method (Petitti, 2000), providing for Cochran's Q for individual substrata and for various totals of substrata. However, the reliability of Q to detect heterogeneity is deemed to be rather weak. To further analyse heterogeneity, we calculated the proportion of variance in pooled estimates due to heterogeneity in calculating I^2 (Higgins and Thompson, 2002; Higgins *et al.*, 2003). This group (Higgins *et al.*, 2003) discussed thresholds for various amounts of this measure; an I^2 value of 0 would indicate lack of heterogeneity (Supplementary data 1).

All analyses were stratified by type of HT, which included the three major groups ET, EPT and MHT. In a few instances analyses of a fourth group progestin-only therapy was feasible. MHT included combinations of all regimens and often either unspecified or unknown preparations. Where possible, analyses were further stratified by histological subtypes. When pooling was done in studies, which provided risk estimates for several mutually exclusive histological entities and other characteristics (grading as borderline or invasive; hysterectomized women versus women with intact uterus), we regarded these risk estimates as being derived from independent datasets, analogous to different independent studies. Subsequently, we are referring to 'datasets' instead of 'studies'. Models to analyse annual risk increases in the major groups were combined with a stratification for geographical study location (North America, Europe and other regions). Sensitivity analyses were performed to analyse the potential impact of type of controls in CCS. To determine potential publication bias we prepared funnel plots, using logarithms to the power of 10 of risk parameters (odds ratio (OR)/relative risk (RR) and the respective study weight, calculated as inverse of the variance (Petitti, 2000). We used SAS version 8.2 (SAS Institute, Cary, NC, USA) for all analyses.

Assessment of study quality

All authors contributed to this assessment. We based our assessment on criteria developed by the U.S. Preventive Services Task Force (Harris *et al.*, 2001). In case of different opinions consensus was sought after discussion of reasons that may lead to inclusion or exclusion of an individual study. All studies of all study types that were regarded not to have serious shortcomings were included.

Results

Study characteristics

We retrieved 255 citations including letters with contents potentially relevant to our study by computerized searches. These citations included individual studies, editorials, reviews, meta-analyses, pooled analyses of CCS and information of one book chapter providing extractable data otherwise not published previously. Manual searches retrieved two more articles. After screening all abstracts and consecutively full texts when the abstract appeared relevant, publications with a total of 42

studies were included for analyses. We retrieved 30 CCS (9938 cases and 25 505 controls), 7 CS, 1 RCT (CS + RCT: 425 704 women with 1882 incident cases of OvC) and 4 cancer registry based studies with computer-based searches. The registries provided standardized incidence ratio data (SIR), based on 150 654 women with 327 incident cancer cases, and standardized mortality ratio data (SMR), based on 27 123 women and 91 deaths due to OvC. We report upon 12 238 cases. Major characteristics of included studies (CS and RCT) are listed in Tables 1 and 2, CRS in Table 3, and excluded studies in supplementary files ($n = 49$; Supplementary Table 1 and Supplementary data 2). Most common reasons for exclusion were as follows: 14 publications used HT as confounder variable only, 12 publications overlapped with publications included, 9 provided insufficient or no statistical parameters for meta-analysis, 4 reported on effects of diethylstilbestrol (DES) and the remaining 10 studies were excluded for a variety of different, further reasons (Supplementary Fig. 1). Few studies provided extractable data for borderline, none for *in situ* carcinoma. Regarding time period of case ascertainment, the range of CCS covered the years 1935–2003, CS and RCTs the time period 1968–2002 and CRS included calendar years 1977–1999. One included international cooperative study (Kotsopoulos *et al.*, 2006) did not provide any information on the time period covered.

Summary estimates of risk are shown: for different HT groups (ever-use) in Table 4, with corresponding annual risk estimates in Table 5; for HT groups stratified by histological subtypes in Supplementary Table 2, with corresponding annual risk estimates in Supplementary Table 3; annual risk estimates stratified by study region in Table 6.

We found a wide range of HT regimens, and a large variation in reporting types of HT among studies, including a lack of specification of the type of MHT used. Acknowledging the changes of treatment with menopausal hormones within the last decades, we suspect that studies published many years ago are more likely to predominantly include ET, more recent studies to include ET and EPT and to report more specifically types and regimens of any hormonal therapy used. Funnel plots did not suggest publication bias except for EPT. There is a suggestion of underpublication of small-scale EPT studies showing increased cancer risks for ever-use (Supplementary Fig. 2; further plots not shown for ever-use of ET and MHT; for annual risks of ET, EPT and MHT).

Analyses of ever-use and annual risk of hormone therapies

Ever-use of hormone therapies was associated with an increase of risk in the ET group (OR/RR of 1.28) and in the EPT group (OR/RR 1.11; Table 4) with either no indication for heterogeneity (ET) or a low amount of heterogeneity (EPT), using quantifications as described (Higgins *et al.*, 2003). The increased risk is higher in the ET than the EPT group, however, the CI overlap. The analyses of annual increases also suggest a larger increase in the ET group (1.067, 18 datasets) than in the EPT group (OR/RR 1.040, 22 datasets (Table 5). However, the CI also overlap. We did not find heterogeneity within EPT datasets, and heterogeneity is low (21%) after ET. The large group of datasets ($n = 60$) of MHT showed an annual increase of 3.6%, but also a moderate amount of heterogeneity (43%).

Analyses of histological subtypes

Analyses of ever-use of HTs, stratified by histological type where available are shown in supplementary Table 2. There were small increases in risk in various defined histological groups of ET, EPT and MHT groups, respectively. We found no increases in EPT users, but in most of the histological subgroups significant increases in ET users (endothelial, epithelial, serous carcinomas as well as in the heterogenous group 'other'). When we analysed annual risk increases (Supplementary Table 3), we found significant increases for several histological subgroups (endothelial, epithelial and serous carcinoma) in EPT as well as in ET users. Overlapping CI indicate that increases after use of ET or EPT are not different among regimens. Further, scrutiny revealed that results were based on smaller number of data sets, as fewer studies provided extractable information. In the MHT group, we found major heterogeneity.

Risk and geographical region

There was evidence that effects of therapies differ according to region. Analyses of EPT data sets showed no heterogeneity when the regions Europe and North America were compared, but a major contrast in effects. North American studies did not suggest any increase of risk, whereas a significant annual increase of 5.9% was evident in European studies. In the ET group, we found an annual increase of 5.6% for North American studies compared to an estimate of 9.2% for European studies in the ET group (Table 6). Analyses showed a lack of heterogeneity for North American and a very low amount for European studies (10%) and almost no overlap of CI. Paucity of data did not allow other regional comparisons.

Population-based versus hospital-based control subjects (sensitivity analyses)

Risks of ever-use were significantly increased in population-based studies in the ET group, compared with hospital-based studies not indicating any change of risk. However, heterogeneity was high. All data sets for EPT except one included population-based controls, excluding a comparison. We could not perform meaningful analyses regarding associations between annual risk, study region and type of HT due to the dominance of population-based studies in the ET group, all data sets except one used population-based controls (data not shown).

Discussion

Our main finding, based upon 42 studies with 12 238 cases, is that both unopposed and estrogen/ progestin therapies are risk factors for OvC. We showed increased risks for both regimens for analyses of ever-use and use per year, respectively, for both types of HT. There was a (non-significant) suggestion that effects (ever-use) of ETs may exceed those of EPTs. ET, less evident combination therapy, increased risks for several defined histological subgroups. Studies conducted in European populations suggest larger effect sizes in increase compared to North American studies. Our main result is consistent with data of recently published CS reporting increased risks for both ET and EPT

Table 1: Included studies—CCS[a]

Authors	Study region	Begin month	Begin year	End month	End year	No. of cases	No. of controls	Age (years), study type	Type of HT	Histology	Further histological details
Kotsopoulos *et al.* (2006)	USA, Canada, Israel and European countries					162	375	48–86 PMP	MHT	ALL	Invasive ovarian, fallopian tube, or peritoneal cancer as well as cancer of the omentum
Annegers *et al.* (1979)	USA	1	1935	12	1974	116	464	50–79 PMP POP	ET	EPI	
Beard *et al.* (2000)	USA	1	1975	12	1991	103	103	POP	EPT ET PRO	EPI	
Weiss *et al.* (1982)	USA		1975		1979	205	611	50–74 POP	ET	EPI END MUC SER OTH	Plus one case each of 'adenocarcinoma with squamous metaplasia' and 'adenosquamous' cancer: Other epithelial tumors, primarily labeled as papillary, adenocarcinoma, or carcinoma without further specification
Kaufman *et al.* (1989)	USA, Israel and Canada	9	1976	10	1985	377	2030	18–69 HOS	ET EPT MHT	EPI MUC SER OTH OTH	 Mucinous adenocarcinoma Papillary serous (cyst)adenocarcinoma, endometrioid, clear cell adenocarcinoma, Malignant mixed mesodermal tumors undifferentiated carcinoma
Hildreth *et al.* (1981)	USA	7	1977	3	1979	62	1068	45–74 HOS	MHT	EPI	
Cramer *et al.* (1983)	USA		1978		1981	173	173	Analysis restricted to ≥40 POP	MHT	EPI	
Hartge *et al.* (1988)	USA	8	1978	6	1981	203	244	20–79 HOS	ET MHT	EPI END MUC OTH SER	
Booth *et al.* (1989)	UK	10	1978	2	1983	156	293	<65 PMP HOS	MHT	EPI	
La Vecchia *et al.* (1982)	Italy	5	1979	2	1980	135	437	40–69 HOS	MHT	END OTH OTH	 Clear cell, Serous, mucinous, undifferentiated
Smith *et al.* (1984)	USA	11	1980	7	1982	58	612	20–54 POP	MHT	ALL	
Lee *et al.* (1986)	USA	12	1980	4	1983	160	1223	20–54 PMP POP	ET	ALL	
Negri *et al.* (1999)[b]	Greece		1980		1981	112	188	HOS	MHT	EPI	

Hempling *et al.* (1997)	USA	10	1982	10	1995	470	705	HOS	MHT	EPI	
										END	
										SER	Serous cystadenocarcinoma
										OTH	Clear cell carcinoma
										OTH	Undifferentiated adenocarcinoma
Parazzini *et al.* (1994)	Italy	1	1983	12	1992	953	2503	23–74 HOS	MHT	ALL	
Polychronopoulou *et al.* (1993)	Greece	6	1989	3	1991	152	129	<79 PMP HOS	MHT	EPI	
Risch *et al.* (1996)	Canada	11	1989	10	1992	450	564	35–79 POP	MHT	EPI	
										MUC	
										SER	
										OTH	
Risch (1996)[c]	Canada		1989		1992	367	564	35–79 POP	EPT ET MHT	END MUC SER	
										OTH	All nonmucinous
Purdie *et al.* (1999)	Australia	8	1990	12	1993	793	855	18–79 POP	ET EPT	EPI MUC	
										SER	
									MHT	OTH	Endometrioid, clear cell
									PRO	OTH	Mixed epithelial, mesodermal
										OTH	undifferentiated
Chiaffarino *et al.* (2001)	Italy	1	1992	9	1999	1031	2411	<80 HOS	MHT	EPI	
Pike *et al.* (2004a)	USA	10	1992	10	1998	477	660	18–74 PMP POP	ET EPT	ALL	
Riman *et al.* (2001)	Sweden	10	1993	12	1995	193	3899	50–74 POP	ET EPT MHT	EPI MUC SER	
Royar *et al.* (2001)	Germany	1	1993	12	1996	282	533	21–75 POP	MHT	ALL	
Tung *et al.* (2003)	USA		1993		1999	558	607	>17 POP	MHT	EPI	
										END	
										MUC	
										SER	All other
										OTH	Clear cell
										OTH	Nonmucinous
										OTH	
Riman *et al.* (2002a)	Sweden	10	1993	12	1995	655	3899[d]	50–74 POP	MHT	EPI	
										END	
										MUC	
										SER	
										OTH	Clear cell
Riman *et al.* (2002b)[e]	Sweden	10	1993	12	1995	655	3899[d]	50–74 POP	ET EPT	EPI END	
										MUC	
										SER	

Continued

Table 1: *Continued*

Authors	Study region	Begin month	Begin year	End month	End year	No. of cases	No. of controls	Age (years), study type	Type of HT	Histology	Further histological details
Mori *et al.* (1998)	Japan	10	1994	7	1996	55	180	30–85 PMP POP	MHT	EPI	
Modugno *et al.* (2001)	USA	5	1994	7	1998	767	1367	20–69 POP	MHT	EPI END MUC SER OTH	
Sit *et al.* (2002)[f]	USA	5	1994	7	1998	484	926	45–69 POP	ET EPT MHT PRO	EPI	
Salazar-Martinez *et al.* (1999)	Mexico		1995		1997	84	668	HOS	MHT	EPI	
Glud *et al.* (2004)	Denmark	1	1995	5	1999	376	1111	35–79 POP	MHT	EPI	
Moorman *et al.* (2005)	USA	1	1999	3	2003	364	370	<75 PMP POP	ET EPT MHT PRO	EPI MUC SER OTH OTH	Endometrioid, clear cell
Mills *et al.* (2004)	USA	1	2000	12	2001	256	1122	>17 POP	MHT	MUC SER END OTH	Endometrioid, clear cell Other epithelial
Mills *et al.* (2005)[g]	USA	1	2000	12	2001	256	1122	POP	MHT	EPI END MUC SER OTH OTH	Other epithelial Only clear cell
Total						9938	25 505[h]				

[a]Listing of studies according to year of start, ascending order; [b]only data set of one study (Tzonou *et al.*, 1984) included as extractable data set from a re-analysis (Negri *et al.*, 1999), the other three studies analysed in this re-analysis are included studies listed separately in Table 1 (see also supplementary Tables 1 web appendix/excluded studies); [c]study population (Risch, 1996) identical with (Risch *et al.*, 1996), selected data extracted for meta-analyses, excluded for calculation of totals of cases and controls, respectively; [d]same control group as Riman *et al.*, 2001; [e]study population (Riman *et al.*, 2002b) identical with (Riman *et al.*, 2002a), selected data extracted for meta-analyses, excluded for calculation of totals of cases and controls, respectively; [f]study population (Sit *et al.*, 2002) identical with (Modugno *et al.*, 2001), selected data extracted for meta-analyses, excluded for calculation of totals of cases and controls, respectively; [g]study population (Mills *et al.*, 2004) identical with (Mills *et al.*, 2005), selected data extracted for meta-analyses, excluded for calculation of totals of cases and controls, respectively; [h]Summation of controls (individual studies) includes only one set of controls/study. ALL, all histological classifications combined or histology not specified; END, endometrioid carcinoma; EPI, epithelial carcinoma; EPT, estrogen/progestin therapy, ET, unopposed ET; PRO, progestin therapy; HOS, hospital-based CCS; MHT, combination of all regimens of MHT, including unspecified/unknown preparations; MUC, mucinous carcinoma; OTH, other malignancies or unspecified other malignancies; PMP, postmenopausal women; POP, population-based CCS; SER, serous carcinoma.

(Lacey *et al.*, 2006; 214 incident cases) and ET (Danforth *et al.*, 2007; 389 incident cases).

Prior systematic reviews, largely based on CCS, yielded inconsistent findings. They suggested absence of or at best a non-significant trend between use of (largely unspecified) HT and OvC risk [Whittemore *et al.*, 1992 (pooled analysis of CCS conducted in the USA); Fernandez *et al.*, 2003 (re-analysis of Italian CCS; Farquhar *et al.*, 2005 (cochrane review restricted to one RCT); Kurian *et al.*, 2005 (pooled analysis of US CCS)]. Increases of risks were reported not until 1998 by meta-analyses, all of whom report on unspecified HT and did not report on pattern of risk change in histological subtypes. One meta-analysis of both cohort and CCS, not restricted to region or study types, reported increased risks of epithelial ovarian carcinoma (Garg *et al.*, 1998). The second reported increased risks in mostly CCS, accounting for hysterectomy, but lack of risk increase in a different set of mostly CCS if hysterectomy was not considered (Beral *et al.*, 1999). Yet a third meta-analysis of population-based CCS, did not suggest an overall change of risk; however there was a suggestion that duration of hormone use was relevant for increase of risk (Coughlin *et al.*, 2000). The updated analysis of a previous collaborative re-analysis of CCS, restricted to European populations, reported increased risks (Bosetti *et al.*, 2001).

The issue of risk modification by geographical location was addressed in one previous analysis (Coughlin *et al.*, 2000) suggesting lesser risks in North American studies. We also found that European women bear larger risks than North American women, irrespective of use of ET and EPT, a finding also described for the risk of breast cancer in conjunction with MHT (Steinberg *et al.*, 1991; Greiser *et al.*, 2005). Apparent geographic differences may reflect different treatment modalities across communities, and (changes of) trends in the use of both estrogens and progestins in all study regions considered, yet may furthermore be due to a variety of factors beyond the scope of our analyses. Since it was acknowledged in the 1970s that use of ET increases endometrial cancer risk, the use of EPT has increased (Hemminki *et al.*, 1988; Wysowski *et al.*, 1995; Brett and Madans, 1997), subsequently use of unopposed estrogen declined. This development may have restricted the ability of earlier studies to detect an association between HT and risk of OvC. In the last years, use of EPT and also ET decreased after publications of outcomes of the Women's Health Initiative trials both in the USA and other countries (Hing and Brett, 2006; Morabia and Constanza, 2006). Whether these trends will be depicted in studies analysing cancer risks is yet unknown.

The lifetime risk for 50-year-old women (data from the USA) of developing OvC (1.4%) is considerably lower than those for breast (12.7%) and endometrial including uterine cancers (2.5%), the lower risk is offset by the relatively poor survival of women diagnosed with OvC. Whereas the 5-year relative survival rate is 44.7% for OvC, rates for breast and endometrial/uterine cancers are 88.5% and 83.2%, respectively (Ries *et al.*, 2006). Thus, even a small increase in risk of OvC, such as the one associated with ever-use of HT, is of clinical concern. Data reported for increased mortality after long-term use of estrogens are consistent with this reasoning.

The mechanisms underlying an association between use of exogenous, non-contraceptive estrogens and OvC are not understood. Estrogen stimulation of ovarian tissue via various pathways is one mechanism suggested (Risch, 1998). We cannot provide a plausible explanation why risk is also increased by EPT. The progestins used differ from those of combined oral contraceptives containing synthetic estrogens and progestins and the effect of the estrogen compound may override the one of the progestin compound. The compositions of the latter medication, shown to be a protective factor for OvC, appear to be too different from EPT regimes in use today to exclude a role for EPT as risk factor for OvC. Data on depot medroxyprogesterone acetate (DMPA) suggest that in younger women using this contraceptive compound risk of OvC is decreased (The WHO Collaborative Study of Neoplasia and Steroid Contraception, 1991), which does not enhance the understanding why progestins administered after the menopause may increase risk. Limited evidence from our analyses suggest that progestin-only therapies, which we confidently assume not to include DMPA, may not be inert regarding risk of OvC, but few studies were available for analyses.

Strengths of our analyses are the large if not the largest number of included cases of OvC we are aware of for analyses, which included cancer registry data and one RCT. For our meta-analysis, we not only tested for heterogeneity the amount of effect variation between studies with Cochran's Q, but also calculated I^2. I^2 statistics allow the discrimination between significant Q-values where I^2 demonstrates 'little or no' heterogeneity, compared to significant Q-values where I^2 indicates 'moderate to considerable' heterogeneity. Use of I^2 allowed the inclusion of different types of outcome data from a complex set of studies derived from four study types. Hence with additional calculation of I^2 demonstration of absence of heterogeneity was possible more reliably.

However, there are a number of limitations. First, observational studies are susceptible to various biases. Second, the choice of control patients may distort results. Third, we have to acknowledge that it was not possible to control for the very different adjustments performed in individual studies for the large variety of confounding factors acknowledged today including reproductive history, socio-economic status, lifestyle factors and ethnicity; reporting was too diverse to perform meaningful (subgroup) analyses, and individual study participant data were not available for analyses. Fourth, reporting of histological details of cancer cases and reported use of varying classifications was most complex. The mode of reporting histopathological details and non-uniform use of pathological classification reference systems may have obscured existing associations between use of HT and impact on distinct types of OvC. Fifth, many studies in the relatively large MHT group provided data of unspecified HTs, which was likely to be a mix of different regimens, and, thus, did not allow more detailed analyses. Additionally, this mix of preparations most likely changed over time. In studies conducted in earlier years it is likely that predominantly ET was assessed, whereas in later years a varying mix of ET and EPT may be assumed or was increasingly more frequently reported, respectively. Finally, use of the analytic variable ever-use has shortcomings compared to a measure to capture duration of use, a proxy for total doses of hormones used. However, restricting analyses to those studies reporting data on risks by duration would have resulted in the exclusion of a considerable body of published information on the association between OvC and use of HT, in particular older publications initiating research to assess OvC risk.

Table 2: Included studies—CS and RCTs[a]

Authors	Study region	Begin month	Begin year	End month	End Year	No. of persons	Person-years	Follow-up years	No. of cases	Age (years), study type	Type of HT	Histology	Further histologic details
Pettiti *et al.* (1987)	USA	12	1968	12	1983	6093		13	12	18–54	ET	ALL	
Kiani *et al.* (2006)	USA		1974		1992	13 281			54	PMP	MHT	EPI	
Lacey *et al.* (2002a, b) (full paper and letter)	USA		1979		1998	44 241	589 213	13,4	329	36– 89 years at start	ET EPT MHT	EPI END SER OTH OTH	 Unclassified tumors Unavailable histology
Rodriguez *et al.* (2001)	Puerto Rico, USA		1982	12	1996	211 581	2 811 860	14	944	PMP	MHT	ALL	
Folsom *et al.* (2004)	USA	1	1986	12	2000	31 381	411 648	15	223	55–69 years in 1986 PMP	MHT	EPI	
Kumle *et al.* (2004)	Norway Sweden		1991	12	2000	103 551			214	30–49 years in 1991/1992	MHT	EPI	Epithelial ovarian neoplasias
Bakken *et al.* (2004)	Norway		1991			30 115			74	45–64	MHT ET EPT	ALL	
Anderson *et al.* (2003)	USA	9	1993	10	1998	16 608		5,6	32	50–79 PMP	EPT	ALL EPI OTH OTH	 Primary peritoneal and fallopian tube carcinoma Serous papillary; adenocarcinoma (not otherwise specified carcinoma); clear cell; endometrioid; embryonal; mixed mullerian tumors
Total						456 851			1882				

[a]Listing of studies according to year of start, ascending order: Pettiti (1987), Walnut Creek contraceptive drug study; Kiani (2006), The Adventist Health Study (AHS); Lacey (2002) Breast Cancer Detection Demonstration Project (BCDDP); Rodriguez (2001), The American Cancer Society's Cancer Prevention Study II (CPS-II); Folsom (2004), Iowa Women's Health Study Cohort; Kumle (2004), Norwegian-Swedish Women's Lifestyle and Health Cohort; Bakken (2004) NOWAC Norwegian Women and Cancer Study; Anderson (2003), Women's Health Initiative Randomized Trial.

Table 3: Cancer registry studies

Authors	Study region	Type of registry study	Begin (month)	Begin year	End (month)	End year	No. of Persons	Person-years	Follow-up years	No. of cases	Type of HT	Histology
Persson *et al.* (1996)[a]	Sweden	SIR	n.a	1977	12	1991	22 597	297 977	13,2	131	MHT	ALL
Hunt *et al.* (1987)[a]	UK	SIR	n.a.	1973	6	1983	4544		n.a.	6	MHT	ALL
Olsson *et al.* (2003)	Sweden	SIR	n.a	1990	12	1999	29 508	226 611	n.a.	63	MHT	ALL
Pukkala *et al.* (2001)	Finland	SIR	1	1994	12	1997	94 005	301 447	3,2	127	EPT	ALL
Subtotal							150 654			327		
Persson *et al.* (1996)[b]	Sweden	SMR	n.a.	1977	12	1991	22 597	n.a.	13,2	83	MHT	ALL
Hunt *et al.* (1987)[b]	UK	SMR	n.a.	1973	6	1983	4544	n.a.	n.a.	8	MHT	ALL
Subtotal							27 141			91		

[a]subset with data on SIR only; [b]same studies; n.a., not applicable; SIR, standardized incidence ratio; SMR, standardized mortality ratio.

Table 4: Summary estimates of risks in three HT groups (ever use)

HT	Data sets (*n*)	OR/RR (95% CI)	Cochrane *Q* value	*P*-value	I^2 (95% uncertainty interval)
EPT	31	1.110 (1.020–1.207)	35.4	0.227	15.4 (0.0–41.6)
ET	48	1.284 (1.178–1.399)	90.2	0.000	47.9 (32.5–58.6)
MHT	72	1.023 (0.978–1.070)	189.4	0.000	62.5 (55.9–67.7)
PRO	5	1.341 (0.842–2.136)	6.3	0.175	36.9 (0.0–67.4)

Table 5: Summary estimates of risk increases per year in three HT groups

HT	Data sets (*n*)	OR/RR (95% CI)	Cochrane *Q* value	*P*-value	I^2 (95% uncertainty interval)
EPT	22	1.040 (1.016–1.064)	19.24	0.570	0.0 (0.0–41.7)
ET	18	1.067 (1.055–1.080)	21.47	0.206	20.8 (0.0–49.5)
MHT	60	1.036 (1.028–1.043)	103.78	0.000	43.1 (27.2–54.4)

Within the last years, considerable information about a spectrum of effects of MHT became available, mainly due to results of the Women's Heath Initiative Randomized Controlled Trials (RCT) (The Womens' Health Initiative Scientific Resources Website). Opinions about risks and benefits of HT vary among scientific communities, and frameworks for assessing multiple effects of HT on multiple outcomes (Col, 2005; Ettinger *et al.*, 2006) try to meet challenges regarding generalizability of study findings and translating population-risks into recommendations which are useful for guidance of both scientists and women potentially concerned. At present, OvC does not appear to be a well recognized area of concern in conjunction with use of non-contraceptive estrogens and progestins, likely due to a paucity of good-quality studies (U.S. Preventive Service Task Force, 2005).

In conclusion, available evidence showed an increased risk of OvC in ever-users of estrogen as well as estrogen/progestin therapies. Our results are consistent with the suggestion that MHT is a yet further risk factor for this reproductive organ site. Risk increases appear to be evident in common histological subtypes and are relatively greater in European populations, findings which merit further scrutiny.

Table 6: Summary estimates of risk increase per year in three HT groups, stratified by region

HT	Region	Data sets (*n*)	OR/RR (95% CI)	Cochrane *Q* value	*P*-value	I^2 (95% uncertainty interval)
EPT	North America	7	1.001 (0.964–1.040)	2.40	0.879	0.0 (0.0–61.7)
EPT	Europe	14	1.059 (1.028–1.091)	10.14	0.682	0.0 (0.0–49.0)
EPT	Other	1	1.107 (0.999–1.227)	–	–	–
ET	North America	10	1.056 (1.040–1.072)	4.75	0.856	0.0 (0.0–54.9)
ET	Europe	7	1.092 (1.071–1.114)	6.66	0.353	9.9 (0.0–64.1)
ET	Other	1	1.000 (0.926–1.081)	–	–	–
MHT	North America	51	1.032 (1.023–1.040)	90.01	0.000	44.5 (27.6–56.0)
MHT	Europe	8	1.055 (1.035–1.075)	9.23	0.237	24.1 (0.0–57.8)
MHT	Other	1	1.038 (0.981–1.099)	–	–	–

Supplementary material

Supplementary data are available at http://humupd.oxfordjournals.org/.

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Author contributions

Conceptions and design: CMG, EMG, MD
Acquisition of data, assessment of study quality: CMG, MD, EMG
Data analyses and interpretation: CMG, EMG, MD
Drafting and editing of the manuscript: MD, EMG, CMG
All authors approved the final version of the manuscript.

Conflict of interest statement

M.D. participates in a phase III study of a drug tested for prevention of osteoporosis in postmenopausal women, sponsored by Pfizer, USA; M. D. is member of an advisory board for Women's health issues of the Federal Centre for Health Information (Germany;http://www.frauengesundheitsportal.de/?uid=08c61583f2c66abc96042e584af7b9fa&id=Seite1294).

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