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The influence of menopausal hormone therapy on tumour characteristics and survival in endometrial cancer patients

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ABSTRACT

Introduction: Menopausal hormone therapy (MHT) is a well-established factor in endometrial carcinogenesis, and therefore, could have prognostic implications. We investigated the effects of ever use of MHT on tumour grade and depth of myometrial invasion and 5-year relative survival in postmenopausal endometrial cancer patients.

Materials and methods: We used a nationwide, population-based case–case design, of 683 Swedish women aged 50–74 years diagnosed with endometrial cancer during 1994 to 1995, followed up to 5 years after diagnosis. We applied polytomous multiple logistic regression to investigate the associations between the use of MHT and tumour grade, and myometrial invasion and Poisson regression for modelling 5-year excess mortality.

Results: Compared to never use, ever use of any MHT entailed lower risks of having moderately and poorly differentiated tumours. The lowest odds ratios for poorly differentiated tumours were seen for ever users of cyclically combined oestrogen–progestin [OR = 0.23 (95% CI = 0.07 – 0.73)]. Ever users of any form of MHT; particularly, medium potency MHT users, had significantly lower risks for tumours with deep myometrial invasion. Adjusted estimated relative excess hazard ratios revealed significantly improved survival for ever users of any form of MHT [RER = 0.40 (95% CI = 0.16 – 0.97)]; in particular ever users of any form of oestrogens [RER = 0.38 (95% CI = 0.15 – 0.99)].

Conclusion: Endometrial cancer patients who were ever users of MHT had more favourable tumour characteristics and better survival compared to never users of MHT. These findings support the notion that MHT induces endometrial cancer with less aggressive characteristics.

1. Introduction

Exogenous hormones are well established factors in endometrial carcinogenesis. The use of menopausal hormone therapy (MHT) has been found to variably, increase risk – with variable doses of unopposed oestrogens,[1–5] cyclically combined oestrogens and progestins[6–9] or continuously combined oestrogens and progestins[3]; decrease risk – with the use of continuously combined regimes[6]; or findings of no increased risk – for users of continuous combined regimes,[6,8,10,11] or cyclically combined regimes.[10]

The influence of MHT on endometrial cancer histopathologic characteristics and survival is less well addressed in large sample populations, and the results are conflicting.[12–21] Two studies found improved survival among users of oestrogens,[14,21] one study found higher survival rates among oestrogen users before accounting for grade only[18] and two studies found an increased mortality in ever users of

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exogenous hormones[15] and among unopposed oestrogen users.[19] All previous studies investigating MHT, tumour characteristics and mortality have had limited power, with the exception of one study.[14]

The association of MHT with a better prognosis in many cancers has been hypothesised to be due to the development of less aggressive tumours among MHT users.[14] On the other hand, it has been reasoned that findings of improved survival among users of oestrogens could be attributed to earlier detection of tumours due to increased medical surveillance among hormone users,[14,18] or users being from higher socio-economic classes with better access to health care.[18] Using the unique equitable nature of the Swedish health care system, and a large population-based cohort, we addressed the effects of MHT use on the histopathological characteristics, and mortality in postmenopausal endometrial cancer patients.

2. Patients and methods

2.1. Study design

This study is an extension of a population-based case-control study of all Swedish women born in Sweden, aged 50–74 years between January 1, 1994 and December 31, 1995 and described in detail elsewhere.[5,9,22] To investigate the relationships between the use of MHT, tumour characteristics and endometrial cancer relative survival, we used a case–case design; in which we obtained odds ratios and estimated excess hazard ratios as measures of relative risk comparing endometrial cancer cases' ever and never use of MHT.

2.2. Parent study

During the study period, all endometrial cancer cases were identified through the six Regional Cancer Registries in Sweden, which provides complete information on incident cancers. The study was restricted to women who had not undergone hysterectomy or who had a previous diagnosis of breast or endometrial cancer. Eligible patients were those women with a histopathologically confirmed endometrial cancer as reported to the cancer registry. Of all eligible cases, 802 (76%) women participated in this initial questionnaire-based study. The primary reasons for non-participation were patient and physician refusal. Detailed information on the use of MHT, including the brand, dose and dates of use for each type of treatment was collected. Recall of MHT was facilitated by colour picture charts of all brands commercially available throughout Sweden during 1950 to 1995. Other relevant information collected covered data on medical, reproductive, lifestyle and anthropometric factors, including age at diagnosis, age at menarche, total parity, age at first and last births, age at natural menopause, body mass index and smoking. Findings from this study have been previously published.[5,9,22–26]

2.3. Present study – participants

For our current study, we performed additional linkage with the Swedish Cause of Death Register. In order to confirm previous endometrial cancers from the parent study, we linked the cohort of 802 cases to the national Swedish Cancer Register for confirmed endometrial cancers with an *International Classification of Diseases* (ICD) codes 172, 182 and C54 (*7th, 9th and 10th editions, respectively*). Of the original 802 cases, two had missing personal identification numbers, making record linkage impossible, whilst 19 cases did not have a primary diagnosis of endometrial cancer, and 10 cases were benign. After restricting our analyses to postmenopausal women, the final cohort comprised 683 endometrial cancer patients born and resident in Sweden. Out of 1055 eligible women in the parent study, the participation rate in the current study was 65%.

2.4. Protocol

The study was approved by the ethical review board at the Karolinska Institute. Prior to participation via a mailed questionnaire, written consent was obtained from all patients. The mean interval between diagnosis and data collection was 8.4 months (standard deviation 4.6 months).

2.5. Classification of MHT

MHT use was categorised as having ever used the therapy, or never. Ever use of any particular MHT was not mutually exclusive; meaning a woman could be considered an ever user of more than one type of hormone therapy. The classification of MHT was as follows:

1. Any form of medium potency MHT
2. Any form of medium potency conjugated or synthetic oestrogens (oestradiol or other synthetic oestrogens); with or without progestins
3. Combined medium potency conjugated or synthetic oestrogens and progestins (progesterone-like progestins, i.e. 17-hydroxy-progesterone derivatives; or testosterone-like progestins, i.e. 19-nor-testosterone derivatives):

a. In cyclic form (cyclic progestins added to oestrogens for less than 16 days per cycle, mostly for 10–14 days per cycle)

b. In continuous form (progestins added to oestrogens for 19 or more days per cycle, typically daily)

4. Low potency vaginal oestrogens (oestriol 0.5 mg, dienoestrol 0.5 mg, or oestradiol 0.25 μg) applied daily during the initial two to three weeks of treatment, and followed by bi-weekly applications
5. Low potency oral oestrogens consisting of one or two milligrams per day

All hormone exposures were censored after an index date; defined as six months before the date of diagnosis.

2.6. Histopathological classification

Information regarding tumour characteristics was retrieved from all 35 pathology departments in Sweden and reviewed and reclassified by the study pathologist, who was blinded

to hormone use and other exposures. The histological specimens of patients were reclassified as: endometrioid adenocarcinoma ($n = 624$% or 91%), or non-endometrioid adenocarcinoma comprising; seropapillary carcinoma ($n =$ 36% or 5%), clear-cell carcinoma ($n = 8$% or 1%), adenoacanthoma ($n = 3$% or 0.4%) or adenosquamous carcinoma ($n = 12$% or 2%). Endometrioid adenocarcinomas were further classified as Grade 1 (well differentiated, $n = 230$% or 37%), Grade 2 (moderately differentiated, $n = 281$% or 45%) or Grade 3 (poorly differentiated, $n = 113$% or 18%). All endometrioid adenocarcinomas were analysed separately to non-endometrioid adenocarcinomas. However, due to low power among the specific sub-types of non-endometrioid adenocarcinomas, we analysed these carcinomas as one entity. Hysterectomy specimens were obtainable for 525 women (77%). Among these women, the depth of myometrial invasion was classified as none or less than 50% ($n = 348$% or 51%), and 50% or more of myometrial thickness or penetration through the serosa ($n = 177$% or 26%).

2.7. Follow-up data on survival

The Swedish National Registration Number, a unique 12-digit number for each Swedish resident was used to link the cohort with the Swedish National Population Register, and the Swedish Cause of Death Register, to obtain data on emigrations, and the dates of death, respectively. The latter register covers all residents in Sweden. Patients were followed up to five years after the date of diagnosis of endometrial cancer. One woman was found to have emigrated during follow-up and was consequently censored at the date of emigration.

2.8. Statistical analyses

2.8.1. Tumour presentation

The significance of differences between tumour characteristics and the use of MHT was evaluated using frequencies with Chi-square tests of association. All probability values of $p < 0.05$ were considered significant. Odds ratios (OR) with 95% confidence intervals (CI) were calculated using polytomous multiple logistic regression[27] with tumour characteristics as the dependent variables; with the reference group being the category of tumour characteristic with the best prognosis, and the remaining categories as the outcome. Potential confounders were included in the models in a step-wise approach based on established biological knowledge of confounders particular to the associations of interest between MHT and prognostic tumour characteristics, rather than solely based on a 10% shift in the estimates.

2.8.2. Relative survival analyses

Relative survival ratios, defined as the observed survival among patients divided by the expected survival of a directly comparable group from the general Swedish population and assumed to be free of endometrial cancer, were used to estimate excess mortality. The calculation of relative survival ratios accounts for competing causes of death. Observed survival for the cohort was based on deaths from all causes. The expected survival proportion was estimated from the Swedish population's life tables stratified by age, sex and calendar time. Estimates of the expected survival proportions are based on tables of annual probabilities of all-cause mortality in the general Swedish population. We used the Ederer II method[28] for estimating expected survival, in which the matched individuals were considered to be at risk until the corresponding endometrial cancer patient died or was censored. Estimated relative excess hazard ratios (RERs), a measure of excess mortality, were modelled in the structure of generalised linear models using Poisson regression, and adjusted for age and calendar time of diagnosis, with never users of MHT as the reference group.

3. Results

Background characteristics of the study participants in relation to ever use of MHT are summarised in Table 1. Age at diagnosis was significantly associated with the use of all forms of MHT, with the exception of oestrogens. Ages at menarche, last birth and natural menopause were not associated with the use of any MHT. A low body mass index was also significantly associated with increased use of all MHT, except low potency vaginal oestrogens. Medium potency MHT was more commonly used by non-smokers than smokers.

3.1. Ever use of MHT and tumour characteristics

The association of ever use of MHT with tumour grade and depth of myometrial invasion are shown in Table 2. We found ever use of any form of MHT was significantly associated with tumour grade (p-value = 0.02). Specific sub-types of MHT showed no significant associations with tumour grade. The depth of myometrial invasion was significantly associated with ever use of any form of MHT (p-value = 0.001); oestrogens (p-value = 0.002); oestrogens and progestins (p-value = 0.001); and in particular oestrogens with cyclic progestins (p-value = 0.001).

Overall, ever use of any MHT entailed lower risk estimates of having tumours of moderate and poorly differentiated grade compared to never use (Table 3). After multivariate adjustment, we found ever users of cyclic oestrogens and progestins, and low potency oral oestrogens to have significantly lower risks of having the poorest differentiation of tumour grade [OR = 0.23 (95% CI = 0.07 – 0.73)]; and [OR = 0.44 (95% CI = 0.21 – 0.91)], respectively.

The protective effect of ever use of MHT against tumours with a potential poor prognosis was observed for the depth of myometrial invasiveness (Table 4). After multivariate adjustment, we found ever users of any form of MHT; in particular, users of any form of oestrogens, combined oestrogens and progestins, and cyclic use of oestrogens and progestins; to have significantly lower risks of having tumours with the deepest myometrial invasion.

3.2. MHT and relative survival

Overall, we observed 96 deaths during 3179 person-years at risk during five years of follow-up (Table 5). We found that all never users of any MHT had slightly lower relative survival ratios at five years. Analyses of the adjusted estimated

Table 1 – Distribution of background factors with ever use of menopausal hormone therapy for postmenopausal women diagnosed with endometrial cancer in Sweden between 1993 and 1995.

Background factors	MHT[a]									
	Any form of MHT		Oestrogens[b,c]		Oestrogens with progestins[c,d,e,f]		Low potency vaginal oestrogens[g]		Low potency oral oestrogens[h]	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
	n (%)		*n* (%)		*n* (%)		*n* (%)		*n* (%)	
All 683 cases[i]	486	196	499	182	556	110	584	98	546	135
Age at diagnosis										
50–59 years	94 (64)	53 (36)	101 (69)	45 (31)	102 (71)	42 (29)	136 (93)	11 (7)	134 (92)	12 (8)
60–69 years	247 (72)	94 (28)	253 (74)	88 (26)	285 (86)	48 (14)	283 (83)	58 (17)	269 (79)	72 (21)
⩾70 years	145 (75)	49 (25)	145 (75)	49 (25)	169 (89)	20 (11)	165 (85)	29 (15)	143 (74)	51 (26)
p-Value[j]	0.074		0.447		0.000		0.022		0.000	
Age at menarche										
<12 years	104 (74)	36 (26)	106 (76)	34 (24)	114 (83)	23 (17)	121 (86)	19 (14)	117 (84)	23 (16)
12–14 years	240 (68)	112 (32)	247 (70)	105 (30)	282 (83)	60 (18)	302 (86)	50 (14)	276 (78)	76 (22)
>14 years	94 (74)	33 (26)	96 (76)	30 (24)	109 (87)	16 (13)	105 (83)	22 (17)	104 (83)	22 (17)
p-Value[j]	0.269		0.280		0.467		0.635		0.342	
Parity										
Nulliparous	71 (72)	28 (28)	73 (74)	26 (26)	80 (82)	18 (18)	87 (88)	12 (12)	78 (79)	21 (21)
1–2 Children	284 (70)	123 (30)	290 (71)	116 (29)	324 (82)	72 (18)	350 (86)	57 (14)	320 (79)	86 (21)
⩾3 Children	131 (74)	45 (26)	136 (77)	40 (23)	152 (88)	20 (12)	147 (84)	29 (16)	148 (84)	28 (16)
p-Value[j]	0.519		0.341		0.134		0.581		0.318	
Age at last birth										
<25 years	67 (66)	34 (34)	67 (67)	33 (33)	81 (84)	16 (16)	89 (88)	12 (12)	84 (84)	16 (16)
25–34 years	275 (72)	105 (28)	284 (75)	96 (25)	305 (82)	66 (18)	321 (84)	59 (16)	307 (81)	73 (19)
>34 years	73 (72)	28 (28)	75 (74)	26 (26)	90 (91)	9 (9)	86 (85)	15 (15)	76 (75)	25 (25)
p-Value[j]	0.478		0.290		0.110		0.656		0.278	
Age at natural menopause										
<50 years	129 (72)	49 (27)	131 (74)	47 (26)	150 (86)	24 (14)	152 (85)	26 (15)	137 (77)	41 (23)
50–54 years	257 (70)	108 (30)	266 (73)	99 (27)	291 (82)	65 (18)	314 (86)	51 (14)	297 (81)	68 (19)
>54 years	94 (75)	32 (25)	96 (76)	30 (24)	104 (84)	20 (16)	109 (87)	17 (13)	103 (82)	23 (18)
p-Value[j]	0.646		0.767		0.425		0.961		0.432	
Body mass index[k]										
Underweight/normal	158 (61)	100 (39)	165 (64)	93 (36)	193 (76)	61 (24)	215 (83)	43 (17)	196 (76)	62 (24)
Overweight	163 (73)	61 (27)	168 (75)	56 (25)	191 (87)	29 (13)	188 (84)	36 (16)	176 (79)	48 (21)
Obese	165 (82)	35 (18)	166 (83)	33 (17)	172 (90)	20 (10)	181 (90)	19 (10)	174 (87)	25 (13)
p-Value[j]	0.000		0.000		0.000		0.064		0.007	
Smoking										
No	139 (61)	88 (39)	142 (63)	84 (37)	167 (76)	52 (24)	200 (88)	27 (12)	185 (82)	41 (18)
Yes	347 (76)	108 (24)	357 (78)	98 (21)	389 (87)	58 (13)	384 (84)	71 (16)	361 (79)	94 (21)
p-Value[j]	0.000		0.000		0.000		0.193		0.438	

a Menopausal hormone therapy. Ever use of MHT is not mutually exclusive; medium potency exogenous hormones unless otherwise stated.
b Ever use of oestrogens with or without progestins.
c Conjugated oestrogens; oestradiol; or other synthetic.
d Use of oestrogens and progestins, cyclic and/or continuous.
e Cyclic progestins: added to oestrogens for less than 16 days/cycle, mostly for 10–14 days; continuous progestins: added to oestrogens for 19 or more days per cycle, mostly daily.
f Progesterone-like progestins (17-hydroxy-progesterone derivatives); or testosterone-like progestins (19-nor-testosterone derivatives).
g Oestriol 0.5 mg; dienoestrol 0.5 mg; oestradiol 0.25 μg. Daily applications during initial 2–3 weeks of treatment, followed by applications twice per week.
h 1–2 mg daily.
i MHT users and non-users may not total to 683 cases due to missing values.
j *p*-Value: Pearson Chi-squared tests of association between groups.
k Body mass index categories of underweight and normal were combined as only 4 cases were underweight.

relative excess hazard ratios revealed significantly improved survival for ever users of any form of MHT [RER = 0.40 (95% CI = 0.16 – 0.97)]; in particular ever users of any form of oestrogens [RER = 0.38 (95% CI = 0.15 – 0.99)]. All estimates for specific forms of MHT were below unity. We additionally conducted analyses of the adjusted excess hazard ratio model

Table 2 – Distribution of ever use of menopausal hormone therapy with endometrial cancer tumour-defined characteristics in postmenopausal women.

Use of MHT[b]	Tumour characteristics							
	Grade[a] Frequency *n*(%)					Depth of myometrial invasion Frequency *n*(%)		
	1	2	3	Other carcinomas	*p*-Value[c,d]	None/<50% thick	⩾50% Thick/ through serosa	*p*-Value[c]
Any form of MHT[e]								
No	150 (31)	203 (42)	89 (18)	44 (9)	0.020	229 (62)	141 (38)	0.001
Yes	80 (41)	78 (40)	23 (12)	15 (8)		119 (77)	36 (23)	
Any form of oestrogens[e,f,g]								
No	157 (31)	208 (42)	89 (18)	45 (9)	0.090	238 (62)	144 (38)	0.002
Yes	72 (40)	73 (40)	23 (13)	14 (7)		109 (77)	33 (23)	
Oestrogens and progestins[e,g,h,i,j]								
No	182 (33)	228 (41)	96 (17)	50 (9)	0.256	272 (63)	157 (37)	0.001
Yes	43 (39)	48 (44)	13 (12)	6 (5)		68 (83)	14 (17)	
Oestrogens with cyclic progestins[e,g,i,j]								
No	186 (32)	240 (42)	101 (18)	50 (9)	0.080	284 (64)	161 (36)	0.001
Yes	36 (42)	36 (42)	8 (9)	5 (6)		54 (86)	9 (14)	
Oestrogens with continuous progestins[e,g,i,j]								
No	209 (34)	257 (41)	101 (16)	52 (8)	0.559	310 (65)	165 (35)	0.121
Yes	10 (27)	17 (46)	8 (22)	2 (5)		23 (79)	6 (21)	
Low potency vaginal oestrogens[k]								
No	198 (34)	242 (41)	94 (16)	50 (9)	0.837	290 (65)	157 (35)	0.102
Yes	32 (33)	39 (40)	18 (18)	9 (9)		58 (74)	20 (26)	
Low potency oral oestrogens[l]								
No	175 (32)	224 (41)	95 (17)	52 (10)	0.194	274 (65)	149 (35)	0.152
Yes	54 (40)	57 (42)	17 (13)	7 (5)		73 (72)	28 (28)	

a Endometrioid carcinoma grades1–3 correspond to histological differentiation: well, moderate and poor, respectively, other carcinomas include: seropapillary carcinoma, clear-cell carcinoma, adenoacanthoma and adenosquamous carcinoma.
b Ever use of menopausal hormone therapies is not mutually exclusive.
c *p*-Value: Pearson Chi-squared tests of association between groups.
d *p*-Value association does not include other carcinomas.
e Medium potency MHT.
f Ever use of oestrogens with or without progestins.
g Conjugated oestrogens; oestradiol; or other synthetic.
h Use of oestrogens and progestins, cyclic and/or continuous.
i Cyclic progestins: added to oestrogens for less than 16 days/cycle, mostly for 10–14 days; continuous progestins: added to oestrogens for 19 or more days per cycle, mostly daily.
j Progesterone-like progestins (17-hydroxy-progesterone derivatives); or testosterone-like progestins (19-nor-testosterone derivatives).
k Oestriol 0.5 mg; dienoestrol 0.5 mg; oestradiol 0.25 μg. Daily applications during initial 2–3 weeks of treatment, followed by applications twice per week.
l 1–2 mg daily.

excluding non-endometrioid Type II tumours, and the significance of results remained unchanged.

4. Discussion

In our study, ever use of any MHT seemed to induce less aggressive tumours – as measured by tumour grade and depth of myometrial invasion; with consequently better survival observed among ever users compared to never users. We found stronger associations of increased 5-year survival among medium potency MHT users than among low potency vaginal and oral oestrogens.

Our study's findings showing that MHT users have less aggressive tumours are in agreement with all previous studies investigating MHT and endometrial tumour characteristics, despite methodological differences,[13,14,16,17,20,21] with the exception of two studies.[12,20] One example of a study showing consistent results with our findings is the large study by Collins et al.[14] where oestrogen use was associated with earlier stage, lower grade of tumour and less frequent myometrial invasion. On the other hand, the most recent study, the Women's Health Initiative Randomised Trial,[12] found no ascertainable differences in the distribution of tumour histology, stage or grade of endometrial cancer between users and non-users of MHT.

Previous studies investigating MHT and endometrial cancer survival have been conflicting. Similar to our findings of significantly better survival among users of MHT are the majority of other studies.[13,14,18,21,29,30] Contrastingly, some studies found an increased mortality with MHT use.[15,19] The

Table 3 – The relation of ever use of menopausal hormone therapy to endometrial cancer tumour grade in postmenopausal women.

	Tumour grade[a]			
	Unadjusted OR (95% CI)[c]		Adjusted OR (95% CI)[c,d]	
Use of MHT[b]	2	3	2	3
Any form of MHT[e]				
No				
Yes	0.72 (0.49–1.05)	0.48 (0.28–0.82)	0.82 (0.47–1.45)	0.52 (0.23–1.20)
Any form of oestrogens[e,f,g]				
No				
Yes	0.76 (0.52–1.13)	0.56 (0.33–0.96)	0.74 (0.42–1.32)	0.59 (0.27–1.31)
Oestrogens and progestins[e,g,h,c,i,j]				
No				
Yes	0.89 (0.56–1.40)	0.57 (0.29–1.12)	0.89 (0.50–1.57)	0.55 (0.22–1.33)
Oestrogens with cyclic progestins[e,g,,c,i,j]				
No				
Yes	0.78 (0.47–1.28)	0.41 (0.18–0.91)	0.64 (0.34–1.18)	0.23 (0.07–0.73)
Low potency vaginal oestrogens[k]				
No				
Yes	1.00 (0.60–1.65)	1.18 (0.63–2.22)	0.91 (0.50–1.64)	1.00 (0.48–2.07)
Low potency oral oestrogens[l]				
No				
Yes	0.82 (0.54–1.26)	0.58 (0.32–1.05)	0.74 (0.45–1.20)	0.44 (0.21–0.91)

a Endometrioid carcinoma grades1–3 correspond to histological differentiation: well, moderate and poor, respectively.
b Ever use of menopausal hormone therapies is not mutually exclusive.
c OR: odds ratio; CI: confidence interval; reference group: grade 1 endometrioid carcinoma and never users of each type of MHT.
d All MHT exposure models adjusted for age at diagnosis, parity, age at natural menopause, body mass index, use of oral contraceptives, age at last birth and smoking; with additional adjustments for the following models: Any form of MHT – duration of use of oestrogens only, duration of use of progestins only and duration of use of low potency oral oestrogens. Any form of oestrogens – duration of use of oestrogens and progestins (cyclic and/or continuous), duration of use of progestins only and duration of use of low potency oral oestrogens. Oestrogens and Progestins (cyclic and continuous) – duration of use of oestrogens only, duration of use of progestins only, duration of use of low potency oral oestrogens; and for the analyses of cyclic addition of progestins also adjusted for duration of use of continuous use of progestins, and vice versa Low potency vaginal and oral oestrogens – duration of use of oestrogens only, duration of use of progestins only and duration of use of oestrogens and progestins (cyclic and/or continuous).
e Medium potency MHT.
f Ever use of oestrogens with or without progestins.
g Conjugated oestrogens; oestradiol; or other synthetic.
h Use of oestrogens and progestins, cyclic and/or continuous.
i Cyclic progestins: added to oestrogens for less than 16 days/cycle, mostly for 10–14 days; continuous progestins: added to oestrogens for 19 or more days per cycle, mostly daily.
j Progesterone-like progestins (17-hydroxy-progesterone derivatives); or testosterone-like progestins (19-nor-testosterone derivatives).
k Oestriol 0.5 mg; dienoestrol 0.5 mg; oestradiol 0.25 μg. Daily applications during initial 2–3 weeks of treatment, followed by applications twice per week.
l 1–2 mg daily.

study by Schairer et al.[19] found that mortality from endometrial cancer was not related to the prescription of weak oestrogens with or without progestins; however, mortality was reportedly 40% higher in women who were prescribed more potent unopposed oestrogens. In the recent study by Khan et al.[15] a significant increased risk of endometrial cancer mortality was found for ever users of sex hormones; however, this study was severely hampered by a small number of deaths.

Previously, it has been argued that the findings of improved survival among users of MHT could be attributable to earlier detection of tumours due to increased medical surveillance among ever users of hormone therapies,[14,18] or hormone therapy users being from more socio-economically advantaged classes with greater accessibility to health care.[18] In our study, we utilised data from Sweden with the unique equitable nature of the Swedish health care system, which would be less prone to inequalities in health and health care evident in other European countries.[31–34] In recent comparisons of 23 European countries using the EUROCARE study investigating cancer patient survival, Sweden had the second highest 5-year relative survival for breast, ovarian and endometrial cancers.[31,33,34] Similarly, in a recent study investigating the socio-economic inequalities in health in 22 European countries, Sweden is one of the few countries in Europe with the lowest average rate of death from any cause, and one of the lowest due to causes amenable to medical intervention.[32] Consequently, the improved survival observed in our study would be unlikely to be due to earlier detection of

Table 4 – The relation of ever use of menopausal hormone therapy to endometrial cancer depth of myometrial invasion in postmenopausal women.

	Depth of myometrial invasion	
	Unadjusted OR (95% CI)[b]	Adjusted OR (95% CI)[b,c]
Use of MHT[a]	⩾50% Thick/through serosa	⩾50% Thick/through serosa
Any form of MHT[d]		
No		
Yes	0.49 (0.32–0.75)	0.34 (0.17–0.71)
Any form of oestrogens[d,e,f]		
No		
Yes	0.50 (0.32–0.78)	0.46 (0.23–0.91)
Oestrogens and progestins[d,f,g,h,i]		
No		
Yes	0.36 (0.19–0.65)	0.34 (0.15–0.76)
Oestrogens with cyclic progestins[d,f,h,i]		
No		
Yes	0.29 (0.14–0.61)	0.27 (0.10–0.73)
Low potency vaginal oestrogens[j]		
No		
Yes	0.63 (0.37–1.10)	0.67 (0.36–1.23)
Low potency oral oestrogens[k]		
No		
Yes	0.70 (0.44–1.14)	0.60 (0.34–1.03)

a Ever use of menopausal hormone therapies is not mutually exclusive.
b OR: odds ratio; CI: confidence interval; reference group: myometrial invasion <50% thick or none, and never users of each type of MHT.
c All MHT exposure models adjusted for age at diagnosis, parity, age at natural menopause, body mass index, use of oral contraceptives, age at last birth and smoking; with additional adjustments for the following models: Any form of MHT – duration of use of oestrogens only, duration of use of progestins only and duration of use of low potency oral oestrogens. Any form of oestrogens – duration of use of oestrogens and progestins (cyclic and/or continuous), duration of use of progestins only and duration of use of low potency oral oestrogens Oestrogens and Progestins (cyclic and continuous) – duration of use of oestrogens only, duration of use of progestins only, duration of use of low potency oral oestrogens; and for the analyses of cyclic addition of progestins also adjusted for duration of use of continuous use of progestins, and vice versa. Low potency vaginal and oral oestrogens – duration of use of oestrogens only, duration of use of progestins only and duration of use of oestrogens and progestins (cyclic and/or continuous).
d Medium potency exogenous hormones.
e Ever use of oestrogens with or without progestins.
f Conjugated oestrogens; oestradiol; or other synthetic.
g Use of oestrogens and progestins, cyclic and/or continuous.
h Cyclic progestins: added to oestrogens for less than 16 days/cycle, mostly for 10–14 days; continuous progestins: added to oestrogens for 19 or more days per cycle, mostly daily
i Progesterone-like progestins (17-hydroxy-progesterone derivatives); or testosterone-like progestins (19-nor-testosterone derivatives).
j Oestriol 0.5 mg; dienoestrol 0.5 mg; oestradiol 0.25 μg. Daily applications during initial 2–3 weeks of treatment, followed by applications twice per week.
k 1–2 mg daily.

tumours as a result of increased medical surveillance among ever users of MHT.

In the present study, we have been able to show findings consistent with the interpretation of a better prognosis for both tumour characteristics and survival with ever use of MHT. Furthermore, when comparing the particular MHT compounds used in this study, for use of any type of medium potency ingested MHT, the estimates for survival are fairly similar and well below unity. In comparison, low potency oral and vaginal oestrogens are closer to unity, with low potency vaginal oestrogens showing almost no effect. This is biologically plausible given that expected effects would be weaker for lower potency preparations, and the weakest with topical vaginal applications. This additionally provides further evidence of our findings not being due to detection and surveillance bias.

Cancers associated with prior MHT use may result in less aggressive tumours, thereby resulting in potentially improved survival.[14] This hypothesis is supported by the bulk of recent evidence for both breast[35–38] and ovarian[39] cancers, but contrasted by a few studies.[40,41] Despite the extent of evidence reporting favourable tumour characteristics and survival among users of MHT for endometrial, breast and ovarian cancers, this does not imply that MHT use is safe, simply because of an illusive improvement in survival.[14]

5. Strengths and limitations

Our study is one of the largest population-based studies of endometrial cancer cases, with detailed information on MHT exposures and confounding factors. The histopathological classification of tumours was consistent, and undiffer-

Table 5 – Observed and relative survival ratios using the Ederer II method, and adjusted estimated relative excess hazard ratios (RER) from the relative survival model using Poisson regression for postmenopausal women diagnosed with endometrial cancer in Sweden during 1993–1995 with 5-year follow-up; in relation to menopausal hormone therapy use.

Use of MHT[a]	5 Years		5-Year follow-up	
	Observed survival	Relative survival ratio (95% CI)	Observed number of deaths	RER (95% CI)[b]
All 683 cases with 3179 person-years at risk for 5-year follow-up	–	–	96	–
Any form of MHT[c]				
No	0.84	0.90 (0.87–0.94)	75	1.00 (reference)
Yes	0.89	0.95 (0.90–0.99)	21	0.40 (0.16–0.97)
Any form of oestrogens[c,d,e]				
No	0.85	0.91 (0.87–0.94)	76	1.00 (reference)
Yes	0.89	0.95 (0.89–0.99)	20	0.38 (0.15–0.99)
Oestrogens and progestins[c,e,f,g,h]				
No	0.85	0.91 (0.87–0.94)	84	1.00 (reference)
Yes	0.93	0.98 (0.91–1.02)	8	0.17 (0.01–1.96)
Oestrogens with cyclic progestins[c,e,g,h]				
No	0.85	0.91 (0.88–0.94)	86	1.00 (reference)
Yes	0.94	0.99 (0.92–1.04)	5	0.23 (0.04–1.47)
Low potency vaginal oestrogens[i]				
No	0.86	0.92 (0.88–0.94)	83	1.00 (reference)
Yes	0.87	0.93 (0.84–0.99)	13	0.95 (0.39–2.29)
Low potency oral oestrogens[j]				
No	0.86	0.91 (0.88–0.94)	78	1.00 (reference)
Yes	0.87	0.94 (0.86–0.99)	18	0.76 (0.34–1.71)

a Ever use of menopausal hormone therapies is not mutually exclusive.
b Adjusted for age and year of diagnosis.
c Medium potency MHT.
d Ever use of oestrogens with or without progestins.
e Conjugated oestrogens; oestradiol; or other synthetic.
f Use of oestrogens and progestins, cyclic and/or continuous.
g Cyclic progestins: added to oestrogens for less than 16 days/cycle, mostly for 10–14 days; continuous progestins: added to oestrogens for 19 or more days per cycle, mostly daily.
h Progesterone-like progestins (17-hydroxy-progesterone derivatives); or testosterone-like progestins (19-nor-testosterone derivatives).
i Oestriol 0.5 mg; dienoestrol 0.5 mg; oestradiol 0.25 μg. Daily applications during initial 2–3 weeks of treatment, followed by applications twice per week.
j 1–2 mg daily.

entiated in relation to the use of MHT. We censored exposures at an index date of 6 months prior to diagnosis, thereby reducing the possibility of detection bias. However, some limitations of the study included limited power to analyse in detail the use of continuous combined oestrogens and progestins therapy, as well as exclusive use of the hormone regimes, in addition to evaluating the effects of differing doses, duration and recency of use of hormonal treatments. We cannot exclude the possibility that women receiving menopausal hormone therapies could have a greater likelihood of more intense surveillance; as oestrogens are established in the causation of endometrial cancer. However, the nature of the Swedish health care system would be less prone to such differences with equitable access to all citizens, and would ensure that primary symptoms result in an immediate endometrial biopsy, regardless of hormonal exposures. Our findings of a better prognosis among users of MHT may partly be explained by a selection process in which women who were healthier and had fewer risk factors for endometrial cancer, may have been more likely to be prescribed MHT, as opposed to non-users. Finally, selection bias in the parent study may account for our findings of a better prognosis. It is conceivable that patients with advanced stages of disease may have been less willing to participate. However, all comparisons in our study were made between women who participated and could therefore be considered internally valid.

6. Conclusion

The findings of our study show that ever users of MHT have favourable tumour characteristics and improved survival compared to never users of MHT with endometrial cancer. Notwithstanding the bulk of evidence whereby users of MHT have been shown to have improved tumour characteristics and survival for endometrial, breast and ovarian cancers, evidence to the contrary from large studies has been reported and continues to be cause for concern. Caution is imperative in the decision to prescribe MHT to women seeking relief for

climacteric symptoms, and should be based on a thorough workup of female cancer risk factors, as well as the overall health of patients seeking MHT treatments.

Conflict of interest statement

None declared.

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