Society for Endocrinology

Endocrine Oncology (2025) **5** e240066
https://doi.org/10.1530/EO-24-0066

Received 8 October 2024
Accepted 5 March 2025
Available online 5 March 2025
Version of Record published 18 March 2025

RESEARCH

Prospective cohort of pre-diagnosis hormone exposure and post-diagnosis sex hormone levels with survival outcomes: Alberta Endometrial Cancer Cohort Study

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Abstract

Purpose: To examine the associations between pre-diagnosis exogenous hormone exposure and endogenous sex hormone levels shortly after diagnosis with survival outcomes in endometrial cancer survivors.

Methods: In this population-based cohort, females with endometrial cancer were followed from diagnosis to death or January 27, 2022. History of hormone exposure pre-diagnosis and sex-hormone levels shortly after diagnosis were obtained. The associations between hormone exposure and sex-hormone levels with disease-free survival (DFS) and overall survival (OS) were estimated using Cox proportional hazards regression by multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: During a median 16.9 years of follow-up (IQR = 15.5–18.1 years), 152 of the 540 participants had a recurrence and/or died. There were no statistically significant associations between exposure to hormonal contraception or menopausal hormone therapy before diagnosis and DFS or OS. Higher estrone levels post-diagnosis were associated with lower DFS (HR 1.56, 95% CI 1.04–2.34) and lower OS (HR 1.76, 95% CI 1.15–2.72). Lower DFS was also observed with higher estradiol levels (HR 1.56, 95% CI 1.02–2.41).

Conclusion: There were no associations between pre-diagnosis hormonal contraception or menopausal hormone therapy use and endometrial cancer survival in our study. Endometrial cancer survivors with higher estrogen levels shortly after diagnosis had lower DFS and OS. Further research is needed to confirm these findings.

Keywords: endometrial cancer; survival; mortality; hormone; hormonal contraception; postmenopausal hormone replacement therapy

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Introduction

Endometrial cancer is the most common cancer affecting female reproductive organs (Sheikh *et al.* 2014). Endometrial cancer incidence has been increasing over the past 30 years, with further increases predicted over the next decade (Yang *et al.* 2023). In Canada, there were an estimated 8,100 incident cases of endometrial cancer and 1,500 deaths in 2022 (Brenner *et al.* 2022), and the 5-year survival is estimated at 82% (Canadian Cancer Society 2023). With a rise in incidence of endometrial cancer, there has also been an increase in survivorship leading to a growing need to identify risk factors for recurrence and mortality in this population (Felix & Brinton 2018).

Endometrial cancer recurrence and mortality associated with exogenous hormone use before cancer diagnosis or sex steroid hormone levels shortly after the time of diagnosis are not well-understood. Published studies have reported conflicting findings regarding the relationship between endometrial cancer survival and pre-diagnosis use of exogenous hormones in the form of menopausal hormone therapy (Robboy & Bradley 1979, Collins *et al.* 1980, Persson *et al.* 1996, Orgeas *et al.* 2009, Felix *et al.* 2015). Similarly, the reported associations between endogenous sex steroid hormones and endometrial cancer survival reported by two recently published studies (Forsse *et al.* 2020, Merritt *et al.* 2021) have been mixed.

Therefore, our primary aim was to examine the associations between exogenous hormone use up until endometrial cancer diagnosis and survival outcomes including disease-free survival (DFS) and overall survival (OS). Our secondary aim was to examine the associations between sex hormone levels shortly after diagnosis and endometrial cancer survival outcomes.

Materials and methods

Setting and participants

The Alberta Endometrial Cancer Cohort Study is a population-based cohort of incident cases of histologically confirmed endometrial cancer identified through the Alberta Cancer Registry between 2002 and 2006. Details of the study have been published previously (Friedenreich *et al.* 2010). An overview of the study timeline is provided in Fig. 1. All participants provided informed consent. Ethics approval was provided and annually renewed through the University of Calgary, University of Alberta, and former Alberta Cancer Board.

Data collection

Interviews were conducted by trained interviewers using cognitive interviewing methods shortly after diagnosis (median 4.4 months after diagnosis) in the participants' homes (Willis 1994). Details were collected on exposures and behaviors that occurred pre-diagnosis including demographic information, medical history, family history of cancer, medical comorbidities, physical activity and exposure to smoking and alcohol. Clinical details including cancer stage, histology and primary and adjuvant treatment(s) were abstracted by trained health record technicians from the Alberta Cancer Registry. Cancer grade was assessed by the study's pathologist using the International Federation of Gynecology and Obstetrics guidelines, as previously described (Amankwah *et al.* 2013). Cancer stage was determined as defined by the American Joint Committee on Cancer (1997). Direct standardized anthropometric measurements for height, weight, waist and hip circumference were captured (Csizmadi *et al.* 2007), and fasting blood samples after a minimum of 8 hours of fasting were collected at participating laboratories across Alberta.

Exogenous hormone exposure

Reproductive and fertility histories were collected. Participants were asked questions regarding menarche, menstrual periods, menopause any pregnancies and lactation. They were also asked about a history of uterine fibroids, endometriosis, oophorectomy or infertility. A detailed history was taken regarding exposure to exogenous hormones before endometrial

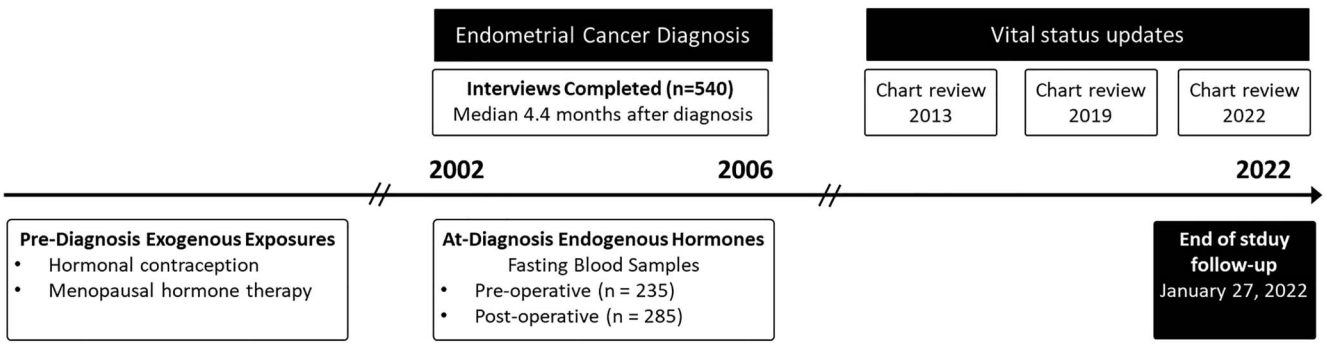

Figure 1

Study timeline.

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https://doi.org/10.1530/EO-24-0066

cancer diagnosis including hormonal contraception, menopausal hormone therapy and fertility drugs.

For hormonal contraception exposure, participants were asked whether they had used hormonal contraception in the form of a pill, injection or implant in their lifetimes. If participants had used hormonal contraception at any time, details on the number of episodes of hormonal contraception use and start and end dates for each episode of hormonal exposure were collected. Participants were also asked if they had used menopausal hormone therapy. If they reported taking this therapy at any time, participants were asked further details about menopausal hormone use including the type(s), form(s), number of episodes of hormone use and the start and end dates for each episode of use.

Endogenous hormones

Fasting blood samples were collected from participants before surgery (n = 235) or within 6 weeks of surgery (n = 285) when blood sample collection was not possible before surgery. Blood samples were not available for 20 participants. Within 24 h of collection, blood samples were processed into blood fractions (i.e., plasma, serum, red blood cells and buffy coat) and frozen. All blood samples were stored at −86°C in a biorepository at the Tom Baker Cancer Centre in Calgary, Alberta, Canada. In brief, androstenedione, estradiol, estrone, sex hormone-binding globulin (SHBG) and total testosterone were analyzed by a technician in the laboratory of Dr David C W Lau at the University of Calgary using a 96-well enzyme-linked immunosorbent assays (Alpco Diagnostics, USA). Precision criteria were met as previously described (Friedenreich *et al.* 2020), evidenced by intra- and inter-batch coefficients of variation as follows: 2.2 and 3.6% for androstenedione, 2.2 and 2.1% for estradiol, 2.1 and 4.5% for estrone, 3.0 and 4.0% for SHBG and 3.9 and 4.7% for total testosterone.

Ascertainment of outcomes

DFS was defined as time to first recurrence or death from any cause, and OS was defined as death from any cause. Participants were followed from the date of diagnosis to death or January 27, 2022, whichever occurred first. Vital status was obtained through record linkages with Vital Statistics Alberta done through Cancer Surveillance and Reporting, Cancer Care Alberta, Alberta Health Services.

Statistical analysis

The total durations of hormonal contraception and menopausal hormone therapy use were calculated based on the number of episodes of hormone use and the start and end dates for each episode. We used Cox proportional hazard models to estimate multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for DFS and OS with hormone use and sex hormone levels. Survival time was measured from the time of endometrial cancer diagnosis. The proportional hazards assumption was assessed via visual and statistical assessments of Schoenfeld residuals. Based on biological plausibility, all models were minimally adjusted for age at diagnosis (years), cancer stage (I, II, III/IV), cancer grade (I/II, III, unknown/non-applicable) and primary treatment (hysterectomy, chemotherapy, radiation, multiple treatments or not received). The following covariates for multivariable models were also considered: body mass index (BMI), parity, timing of blood collection (i.e., pre- vs post-surgical), menopausal status at the time of diagnosis, smoking status, education level, family history of uterine or colorectal cancer and personal history of infertility, uterine fibroids, endometriosis and metabolic syndrome. Following backward elimination, the final models for the exogenous hormones were adjusted for parity and BMI in addition to the variables selected based on biological plausibility above, and the final models for the endogenous hormones were adjusted for parity, age at diagnosis, cancer stage, cancer grade and primary treatment. A stratified analysis was conducted for timing of blood collection (i.e., pre- vs post-surgical) to determine if this timing changed the associations between sex hormone levels and survival outcomes as hysterectomy can impact ovarian function (Huang *et al.* 2023). In addition, a stratified analysis was conducted to assess the impact of limiting the sample to post-menopausal women on the associations between sex hormone levels and survival outcomes. All analyses were two-sided and performed with the STATA version 17 (StataCorp LLC, USA). A P-value of <0.05 was considered statistically significant.

Results

Participant characteristics

The Alberta Endometrial Cancer Cohort has been described previously (Friedenreich *et al.* 2010). Participant characteristics for the 540 women included in this study are presented in Table 1 and Supplementary Tables 4 and 5 (see section on Supplementary materials given at the end of the article). In brief, in the follow-up period, 152 participants had a recurrence and/or died and there were 134 deaths overall. The median age at diagnosis was 59 years (interquartile range (IQR) 53–65 years) and the median BMI was 31.1 kg/m^2 (IQR 26.5–37.0 kg/m^2). Most participants (79%) were stage I, FIGO grade I/II (79%) and underwent surgical treatment with hysterectomy (98%). The majority (69%) were married, of European ethnic ancestry (95%) and post-menopausal (77%).

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Table 1 Characteristics of the Alberta Endometrial Cancer Cohort participants and exogenous hormone use before diagnosis by vital status, 2002–2022.

Characteristic	All participants median (IQR)/*n* (%) *n* = 540	Alive median (IQR)/*n* (%) *n* = 406	DFS events* Median (IQR)/*n* (%) *n* = 152	Overall deaths median (IQR)/*n* (%) *n* = 134
Age at diagnosis (years)	59 (53–65)	57 (52–63)	64 (57.5–72)	64 (59–72)
BMI (kg/m^2)	31.1 (26.5–37.0)	31.0 (26.1–37.1)	31.2 (27.3–36.7)	31.2 (27.4–36.6)
Highest education level achieved				
High school diploma	177 (33)	123 (30)	60 (40)	54 (40)
Non-university certificate	249 (46)	189 (47)	68 (45)	60 (45)
University degree	114 (21)	94 (23)	24 (15)	20 (15)
Married or common-law	372 (69)	287 (71)	96 (63)	85 (63)
European ethnic ancestry	513 (95)	383 (94)	144 (95)	130 (97)
Overall AJCC stage†				
I	428 (79)	344 (85)	95 (63)	84 (62)
II	69 (13)	44 (11)	28 (18)	25 (19)
III/IV	43 (8)	18 (4)	29 (19)	25 (19)
FIGO grade				
I/II	413 (76)	330 (81)	93 (61)	83 (62)
III	73 (14)	41 (10)	36 (24)	32 (24)
Other	54 (10)	35 (9)	23 (15)	19 (14)
Primary treatment‡				
Surgery	527 (98)	399 (98)	140 (92)	128 (96)
Chemotherapy	45 (8)	26 (6)	20 (13)	19 (14)
Hormone therapy	6 (1)	6 (2)	2 (1)	6 (5)
Radiation therapy	168 (31)	118 (29)	57 (38)	50 (38)
Menopausal status				
Pre- and peri-menopausal	125 (23)	115 (28)	17 (12)	10 (7)
Post-menopausal	415 (77)	291 (72)	135 (88)	124 (93)
Ever used HC	328 (61)	266 (66)	71 (47)	62 (46)
MHT use in post-menopausal participants				
Never or <6 months	241 (58)	155 (53)	93 (69)	86 (69)
Estrogen + progesterone only	83 (20)	68 (24)	18 (14)	16 (12)
Other hormone therapy regimen	91 (22)	67 (23)	23 (17)	17 (18) 14n

BMI, body mass index; AJCC, American Joint Committee on Cancer; FIGO, International Federation of Gynecology and Obstetrics; HC, hormonal contraception; MHT, menopausal hormone therapy; SHBG, sex hormone-binding globulin; DFS, disease-free survival.
*Participants who experienced endometrial cancer recurrence and/or death from any cause. †Participants with incomplete TNM staging (*n* = 8) were classified as stage I based on available lymph node and metastasis information. ‡Participants could have received multiple treatments.

Hormonal contraception and menopausal hormone therapy use pre-diagnosis

Among all participants in the cohort, 328 (61%) had used hormonal contraception, with 142 (26%) using hormonal contraception for 60 or more months in total over their lifetimes. We did not observe any statistically significant associations between exposure to hormonal contraception pre-diagnosis and DFS or OS (Table 2) or by the duration of hormonal contraception use.

Among the 415 participants in this cohort who were post-menopausal at the time of endometrial cancer diagnosis, most (58%) participants reported that they had never used menopausal hormone therapy or had used menopausal hormone therapy for less than six months pre-diagnosis. There were 83 (20%) participants that had used combined estrogen and progesterone for menopausal hormone therapy, while 91 (22%) had used other hormone therapy regimens pre-diagnosis. There were no statistically significant associations between exposure to menopausal hormone therapy of any type before endometrial cancer diagnosis and DFS or OS (Table 3). When stratified by type of menopausal hormone therapy (i.e., estrogen and progesterone or other hormone therapy regimen), we did not observe any statistically significant associations between menopausal hormone therapy type and DFS or OS or by the duration of exposure to estrogen and progesterone therapy.

Endogenous hormone levels at diagnosis

Among all participants, there were no statistically significant associations between androstenedione, SHBG or total testosterone at the time of diagnosis with either DFS or OS (Table 4). Participants with estrone levels in the highest tertile (>123.86 pg/mL) had lower DFS (HR 1.56, 95% CI 1.04–2.34) and lower OS (HR 1.76, 95% CI 1.15–2.72) than those in the lowest tertile (<48.61 pg/mL).

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Table 2 DFS and OS outcomes for exposure to hormonal contraception pre-diagnosis in the Alberta Endometrial Cancer Cohort.

	DFS			OS		
	Events/cases	Minimally adjusted* HR (95%CI)	Fully adjusted† HR (95%CI)	Events/cases	Minimally adjusted* HR (95%CI)	Fully adjusted† HR (95%CI)
Hormonal contraception use						
Never or <6 months	81/212	1.00	1.00	72/212	1.00	1.00
Ever	71/328	0.68 (0.49, 0.96)	0.74 (0.52, 1.04)	62/328	0.68 (0.47, 0.97)	0.73 (0.51, 1.06)
Duration of hormonal contraception use						
Never or <6 months	81/212	1.00	1.00	72/212	1.00	1.00
6–35 months	29/128	0.70 (0.45, 1.08)	0.71 (0.46, 1.11)	23/128	0.59 (0.37, 0.96)	0.62 (0.38, 1.02)
36–59 months	13/58	0.80 (0.44, 1.46)	0.90 (0.49, 1.66)	12/58	0.77 (0.40, 1.46)	0.85 (0.44, 1.64)
60+ months	29/142	0.63 (0.41, 0.98)	0.71 (0.45, 1.10)	27/142	0.73 (0.46, 1.16)	0.81 (0.51, 1.30)

DFS, disease-free survival; OS, overall survival.
*Adjusted for grade, stage, treatment and age. †Adjusted for grade, stage, treatment, age, parity and BMI.

Similarly, participants in the highest tertile of estradiol levels (>12.41 pg/mL) at the time of diagnosis had lower DFS (HR 1.56, 95% CI 1.02–2.41) than those within the lowest tertile (<3.37 pg/mL). When limited to individuals who were post-menopause, participants with the highest levels of estrone (>128.86 pg/mL) at diagnosis had lower OS (HR 1.69, 95% CI 1.08–2.64) compared with the lowest tertile (<48.61 pg/mL), but the associations between estrogen (i.e., estradiol and estrone) and DFS were no longer statistically significant (Supplementary Table 1). Stratified analyses for the timing of blood collection (pre- vs post-operatively) for the endogenous hormones showed that there were no meaningful differences between groups for the associations between endogenous hormone levels and DFS (Supplementary Table 2) or OS (Supplementary Table 3).

Discussion

Among endometrial cancer survivors in this cohort, we did not find any statistically significant associations between the use of exogenous hormones in the form of hormonal contraception or menopausal hormone therapy before endometrial cancer diagnosis and either DFS or OS. We found that higher estrogen levels (i.e., estradiol and estrone) shortly after diagnosis were associated with lower DFS and OS, while there was no association observed with androstenedione, SHBG or total testosterone for DFS or OS.

There is consistent evidence for hormonal contraceptive use reducing the risk of endometrial cancer; however, evidence on survival post-endometrial cancer diagnosis is less clear. A meta-analysis of 36 studies found that longer duration of oral contraceptive use was associated with greater reductions in endometrial cancer risk, which can last for several decades after oral contraceptive discontinuation (Collaborative Group on Epidemiological Studies on Endometrial Cancer 2015, Karlsson *et al.* 2021). Oral contraceptive use has not been associated with mortality from endometrial cancer (Charlton *et al.* 2014). In this study, we found no association between hormonal contraception use of any duration before endometrial diagnosis with DFS or OS.

Table 3 DFS and OS outcomes for exposure to menopausal hormone therapy pre-diagnosis in the Alberta Endometrial Cancer Cohort among post-menopausal women.

	DFS			OS		
	Events/cases	Minimally adjusted* HR (95%CI)	Fully adjusted† HR (95%CI)	Events/cases	Minimally adjusted* HR (95%CI)	Fully adjusted† HR (95%CI)
Menopausal hormone therapy use						
Never or <6 months	93/241	1.00	1.00	86/241	1.00	1.00
Ever	42/174	0.43 (0.17, 1.06)	0.78 (0.52, 1.16)	38/174	0.65 (0.44, 0.97)	0.70 (0.46, 1.07)
Menopausal hormone therapy use						
Never	93/241	1.00	1.00	86/241	1.00	1.00
Estrogen and progesterone only	18/83	0.61 (0.36, 1.02)	0.75 (0.44, 1.29)	15/83	0.57 (0.33, 0.99)	0.63 (0.36, 1.13)
Other hormone therapy regimen	24/91	0.70 (0.44, 1.13)	0.80 (0.49, 1.29)	23/91	0.72 (0.44, 1.17)	0.76 (0.46, 1.24)
Duration of menopausal hormone therapy use for estrogen and progesterone use only						
Never or <6 months	93/241	1.00	1.00	86/241	1.00	1.00
6–59 months	8/33	0.90 (0.43, 1.87)	0.97 (0.46, 2.04)	6/33	0.72 (0.31, 1.66)	0.73 (0.31, 1.68)
60+ months	10/50	0.49 (0.25, 0.95)	0.59 (0.30, 1.19)	9/50	0.51 (0.26, 1.03)	0.54 (0.26, 1.11)

DFS, disease-free survival; OS, overall survival.
*Adjusted for grade, stage, treatment and age. †Adjusted for grade, stage, treatment, age, parity and BMI.

Table 4 DFS and OS outcomes by sex hormone level at time of endometrial cancer diagnosis in the Alberta Endometrial Cancer Cohort among all participants.

	DFS			OS		
	Events/cases	Minimally adjusted* HR (95%CI)	Fully adjusted† HR (95%CI)	Events/cases	Minimally adjusted* HR (95%CI)	Fully adjusted† HR (95%CI)
Androstenedione						
<1.16 ng/mL	59/174	1.00	1.00	53/174	1.00	1.00
1.16–1.59 ng/mL	45/173	0.93 (0.62, 1.38)	0.92 (0.62, 1.37)	39/173	0.91 (0.59, 1.40)	0.90 (0.59, 1.38)
>1.59 ng/mL	40/173	0.90 (0.60, 1.36)	0.90 (0.60, 1.36)	36/173	0.99 (0.64, 1.53)	0.98 (0.63, 1.52)
Per 1 ng/mL	152/520	1.05 (0.74, 1.50)	1.16 (0.74, 1.50)	134/520	1.03 (0.71, 1.49)	1.02 (0.71, 1.48)
Estradiol						
<3.37 pg/mL	45/174	1.00	1.00	43/174	1.00	1.00
3.37–12.41 pg/mL	48/173	1.37 (0.90, 2.08)	1.38 (0.91, 2.10)	40/173	1.13 (0.72, 1.75)	1.12 (0.73, 1.75)
>12.41 pg/mL	51/173	1.71 (1.12, 2.61)	1.72 (1.12, 2.62)	45/173	1.56 (0.99, 2.43)	1.56 (0.99, 2.43)
Per 1 pg/mL	152/520	1.00 (0.99, 1.01)	1.01 (0.99, 1.01)	134/520	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
Estrone						
<48.61 pg/mL	41/174	1.00	1.00	36/174	1.00	1.00
48.61–123.86 pg/mL	47/173	1.36 (0.89, 2.10)	1.36 (0.88, 2.09)	40/173	1.19 (0.75, 1.88)	1.19 (0.75, 1.90)
>123.86 pg/mL	56/173	1.52 (1.01, 2.28)	1.52 (1.01, 2.87)	52/73	1.65 (1.07, 2.54)	1.66 (1.08, 2.55)
Per 1 pg/mL	152/520	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	134/520	1.00 (0.99, 1.00)	1.00 (1.00, 1.00)
SHBG						
<34.30 nmol/L	47/174	1.00	1.00	41/174	1.00	1.00
34.30–77.42 nmol/L	48/173	0.86 (0.57, 1.30)	0.85 (0.57, 1.29)	47/173	1.05 (0.68, 1.60)	1.04 (0.67, 1.59)
>77.42 nmol/L	49/173	0.84 (0.56, 1.27)	0.84 (0.56, 1.27)	40/173	0.75 (0.48, 1.17)	0.75 (0.48, 1.18)
Per 1 nmol/L	152/520	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	134/520	0.99 (0.99, 1.00)	0.99 (0.99, 1.00)
Total testosterone						
<1.54 ng/mL	60/174	1.00	1.00	55/174	1.00	1.00
1.54–2.35 ng/mL	40/173	0.92 (0.61, 1.38)	0.92 (0.61, 1.39)	34/173	0.85 (0.55, 1.32)	0.86 (0.55, 1.33)
>2.35 ng/mL	44/173	1.05 (0.71, 1.57)	1.05 (0.70, 1.57)	39/173	1.04 (0.68, 1.60)	1.07 (0.68, 1.59)
Per 1 ng/mL	152/520	0.99 (0.91, 1.07)	0.99 (0.91, 1.07)	134/520	0.99 (0.90, 1.07)	0.99 (0.90, 1.07)

SHBG, sex hormone-binding globulin; DFS, disease-free survival; OS, overall survival.
*Adjusted for grade, stage, treatment and age. †Adjusted for grade, stage, treatment, age and parity.

While menopausal hormone therapy in the form of estrogen (without cyclic or continuous progestins) has been associated with increased risk of developing endometrial cancer, the use of combined estrogen–progestin menopausal hormone therapy has not (Brinton & Felix 2014). Given this evidence, clinical practice guidelines recommend that menopausal hormone therapy be prescribed as combined estrogen–progestin therapy for individuals with a uterus (National Institute for Health & Care Excellence 2019). A meta-analysis of 1801 endometrial cancer survivors found that use of menopausal hormone therapy prescribed to treat menopausal symptoms after endometrial cancer diagnosis was not associated with the overall disease recurrence or survival, although there may be associations for different racial groups (Londero *et al.* 2021).

In our cohort, the majority of which were on combined estrogen–progestin menopausal hormone therapy, we did not find an association between menopausal hormone therapy use before diagnosis and DFS or OS. This null finding has been demonstrated in some endometrial cancer cohorts (Robboy & Bradley 1979, Persson *et al.* 1996), while others have demonstrated better survival among individuals treated with menopausal hormone therapy before diagnosis (Collins *et al.* 1980, Orgeas *et al.* 2009, Felix *et al.* 2015). Menopausal hormone therapy has been associated with more favorable tumor characteristics including lower grade and less myometrial invasion (Orgeas *et al.* 2009). Adjustment for tumor grade and stage in some (Robboy & Bradley 1979, Collins *et al.* 1980), but not all, studies explains the variability in findings with different therapy regimens. Furthermore, many studies examining the relationship between menopausal hormone therapy and endometrial cancer survival outcomes include participants who were diagnosed several decades ago (Robboy & Bradley 1979, Collins *et al.* 1980, Persson *et al.* 1996), and recommendations regarding menopausal hormone therapy have since changed (Cho *et al.* 2023).

Higher levels of circulating sex steroid hormones at the time of diagnosis including estradiol, estrone, testosterone, androstenedione and SHBG have been associated with an increased risk of endometrial cancer incidence (Lukanova *et al.* 2004, Allen *et al.* 2008, Audet-Walsh *et al.* 2011, Forsse *et al.* 2020, Friedenreich *et al.* 2020, Merritt *et al.* 2021). However, findings on post-diagnosis sex steroid hormone levels and survival outcomes are less clear. Consistent with previous

studies (Forsse *et al.* 2020, Merritt *et al.* 2021), we did not find an association between DFS or OS with SHBG, testosterone or androstenedione measured at the time of endometrial cancer diagnosis.

We found that study participants with higher estradiol levels at the time of diagnosis, regardless of menopause status, had lower DFS compared with those with lower estradiol levels. Similarly, Merritt *et al.* (2021) studied 816 participants with stage II-IV endometrial cancer and found that participants who were post-menopausal and not using menopausal hormone therapy, there was a higher risk of recurrence for those classified in the highest tertile of estradiol at the time of diagnosis compared with the lowest (HR 1.55, 95% CI 1.02–2.36) when adjusted for age at diagnosis, cancer stage and grade. Conversely, a smaller cohort study of 100 endometrial cancer survivors, who were post-menopausal, did not find an association between estradiol levels and endometrial cancer survival (Forsse *et al.* 2020). Endogenous estrogens may contribute to DNA damage, cellular proliferation and decreased apoptosis, and may differentially affect tumor type and grade, with estradiol more strongly associated with type 1 and low-grade tumors in post-menopausal women (Brown & Hankinson 2015, Brinton *et al.* 2016).

With respect to estrone levels, our study found an association between estrone levels and lower DFS and OS, regardless of menopause status. This finding is inconsistent with published results from other cohorts (Forsse *et al.* 2020, Merritt *et al.* 2021). Forsse *et al.* found no association between estrone levels and endometrial cancer survival (Forsse *et al.* 2020), while Merritt *et al.* reported higher recurrence rates among women in the second tertile of circulating estrone compared with the lowest tertile but not in the highest tertile (Merritt *et al.* 2021). The variable findings from these cohorts may be complicated by variability in hormone levels across the menstrual cycle, in peri-menopause and analytical chemistry techniques used for measuring the sex steroid levels (Faupel-Badger *et al.* 2010).

Our study has several strengths including being a population-based cohort of incident endometrial cancer cases from across the province of Alberta, Canada. In addition, data collection using cognitive interviewing methods (Willis 1994), a method that improves recall, allowed for a comprehensive assessment of pre-diagnosis exposure to exogenous hormones including hormonal contraception and menopausal hormone therapy and assessment of covariates. Furthermore, comprehensive long-term follow-up for all survival outcomes and treatments was conducted by the Alberta Cancer Registry (ACR) health record technicians ensuring rigorous ascertainment of outcomes. The laboratory assays were conducted by one technician using tightly controlled methods with high reproducibility. Important limitations include that some of the analyses may have been underpowered due to small sample sizes for some exposure groups, and multiple comparisons were made, which could have led to findings occurring by chance.

Conclusion

We found no associations between pre-diagnosis hormonal contraception or menopausal hormone therapy use and endometrial cancer survival in our study. Overall, the inconsistent findings with respect to endogenous sex hormone levels shortly after endometrial cancer diagnosis and DFS and OS suggest that more research is needed to establish this relationship, with repeated measures of sex steroid hormones post-diagnosis. These associations merit further consideration to guide clinical practice and allow informed discussions between patients and their providers.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EO-24-0066.

Declaration of interest

The authors have no relevant financial or non-financial interests to disclose. The funders had no role in study design and conduct of the study, data collection and analysis, data interpretation or manuscript preparation and decision to submit the manuscript for publication.

Funding

This work was supported by the National Cancer Institute of Canada through the Canadian Cancer Society (NCIC No. 12018, NCIC No. 13010, NCIC Grants No. 17323) and by the former Alberta Cancer Board (ACB Grant 22190). CM Friedenreich received career awards from the Canadian Institutes of Health Research and the Alberta Heritage Foundation for Medical Research/Alberta Innovates (AHFMR/Alberta Innovates). LS Cook and KS Courneya held Canada Research Chairs and LS Cook also received career award funding from AHFMR. LS Cook receives support from the US National Cancer Institute (NCI P30CA118100).

Author contribution statement

KSC, LSC, CMF helped in funding acquisition, investigation and methodology. KSC and LSC helped in project administration. CMF helped in data curation; resources and supervision. Formal analysis was done by JLB. Writing of the original draft, conceptualization writing review and editing was done by JLB, RLKP, JM, KSC, LSC and CMF.

Acknowledgements

We would like to thank the participants and staff of the Endometrial Disease and Physical Activity Study and Alberta Endometrial Cancer Cohort Study for their contributions to the original case–control and follow-up cohort study. We would also like to acknowledge Dr David Lau and Angela Krawetz for their contributions to the endogenous hormone analysis.

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