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ORIGINAL PAPER

Prospective cohort of pre- and post-diagnosis alcohol consumption and cigarette smoking on survival outcomes: an Alberta Endometrial Cancer Cohort Study

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Abstract

Purpose To examine the independent and joint relationships between cigarette smoking and alcohol consumption with survival outcomes after endometrial cancer diagnosis.

Methods Pre- and post-diagnosis smoking and drinking histories were obtained from endometrial cancer survivors diagnosed between 2002 and 2006 during in-person interviews at-diagnosis and at ~3 years post-diagnosis. Participants were followed until death or January 2022. Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated with Cox proportional hazards regression for associations with disease-free survival (DFS) and overall survival (OS).

Results During a median 16.9 years of follow-up (IQR = 15.5–18.1 years), 152 of the 540 participants had a DFS event (recurrence: n = 73; deaths: n = 79) and 134 died overall. Most participants in this cohort were current drinkers (pre = 61.3%; post = 64.7%) while few were current cigarette smokers (pre = 12.8%; post = 11.5%). Pre-diagnosis alcohol consumption was not associated with survival, yet post-diagnosis alcohol intake ≥ 2 drinks/week was associated with worse OS compared with lifetime abstention (HR = 2.36, 95%CI = 1.00-5.54) as well as light intake (HR = 3.87, 95% CI = 1.67–8.96). Increased/consistently high alcohol intake patterns were associated with worse OS (HR = 2.91, 95% CI = 1.15–7.37) compared with patterns of decreased/ceased intake patterns after diagnosis. A harmful dose-response relationship per each additional pre-diagnosis smoking pack-year with OS was noted among ever smokers. In this cohort, smoking and alcohol individually were not associated with DFS and combined pre-diagnosis smoking and alcohol intakes were not associated with either outcome.

Conclusion Endometrial cancer survivors with higher alcohol intakes after diagnosis had poorer OS compared with women who had limited exposure. Larger studies powered to investigate the individual and joint impacts of cigarette smoking and alcohol use patterns are warranted to provide additional clarity on these modifiable prognostic factors.

Keywords Endometrial cancer · Survival · Mortality · Smoking · Alcohol

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Introduction

Over the past 30 years, increasing endometrial cancer incidence coupled with a relatively favorable five-year cancer survival rate of 82% have led to a growing global population of endometrial cancer survivors [1, 2]. Given that most women with endometrial cancer initially survive their cancer, the risk of recurrence and mortality from other causes are a major concern during survivorship [3]. Therefore, understanding the prognostic role of modifiable factors at and after endometrial cancer diagnosis is becoming increasingly important to improve long-term health and survival outcomes in this population [4].

Alcohol consumption is a modifiable risk factor with increasing prevalence among women [5, 6]. Additionally, health risks associated with alcohol consumption have been shown to increase more steeply for women than men with intakes above two drinks per week [7]. Several mechanisms have been proposed to explain the sex-related disparity in alcohol-related harm including body size, organ function and metabolism [7]. While the health effects associated with light drinking have long been debated, recent studies have illustrated that several cancers among women can be attributed to alcohol intake at any quantity including low levels of drinking [8]. Current recommendations from recent reviews and the World Cancer Research Fund have stated that there is no safe limit for the relationship between alcohol consumption and the diagnosis of and death from cancer [9–11].

Cigarette smoking is another modifiable behaviour that is associated with an increased risk of several cancers and other non-communicable diseases [12]. However, few studies have examined the prognostic role of pre- and post-diagnosis smoking among endometrial cancer survivors. Prior studies have reported a ~ 1.5-fold increase in all-cause mortality yet inconsistent associations with recurrence for current compared to never smokers at endometrial cancer diagnosis [13–15]. Likewise, post-diagnosis smokers experience an approximate 2.6-fold increase in endometrial cancer-specific-, cardiovascular disease-, and all-cause mortality [16].

Several knowledge gaps exist regarding the impact of alcohol and smoking across the cancer continuum [11]. Despite previous research that has shown consistent relationships between smoking and alcohol consumption patterns [17], the evidence regarding the synergistic effects of smoking and alcohol consumption for cancer types beyond upper aero-digestive tract cancers remains limited [11, 18, 19]. Of note, no study to date has examined the joint effects of these two exposures among endometrial cancer survivors. Moreover, several questions remain regarding the potential confounding and modifying effects of other related factors, such as physical activity and obesity, on these associations [11].

The aim of the present study was to examine the independent and joint prognostic relationships between cigarette smoking and alcohol consumption with survival outcomes after endometrial cancer diagnosis. Specifically, the primary objective was to assess the associations between pre-diagnosis and post-diagnosis cigarette smoking and alcohol consumption with disease-free survival (DFS) and overall survival (OS) outcomes. Our secondary objective was to assess associations between cigarette smoking and alcohol consumption lifetime changes from pre- to post-diagnosis with OS. Lastly, we explored whether or not these relationships were modified by obesity or physical activity.

Methods

Setting and participants

Full details of the Alberta Endometrial Cancer Cohort Study have been previously described [20, 21]. Briefly, survivors of primary histologically confirmed endometrial cancer who were originally identified between 2002 and 2006 through the Alberta Cancer Registry (ACR) were included [20]. Of the 540 participants, 425 participants also completed a follow-up assessment between 2006 and 2011. Twenty-nine survivors refused further participation, 35 were lost to follow-up and 51 died before follow-up [21, 22]. All participants provided informed, written consent. This work was completed in alignment with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Guidelines [23]. The University of Calgary, University of Alberta, and former Alberta Cancer Board provided ethical approval for this study and follow-up assessments.

Data collection

Pre- and post-diagnosis interviews were conducted by trained interviewers using cognitive interviewing methods at diagnosis (median = 4.4, interquartile range (IQR) = 3.4–5.7 months) and follow-up (median = 3.4, IQR = 3.2–3.8 years). At both time points, participants were asked questions regarding their cigarette smoking status, duration and quantity of smoking, age at first exposure, and years since quitting. Participants' alcohol consumption patterns across their lifetimes were assessed for beer, wine, and liquor by determining the start and end ages for each drinking pattern that included the type and quantity of alcohol consumed. Demographic information, reproductive and medical histories, hormone use, major comorbidities, family history of cancer and direct standardized anthropometric measurements

were captured at both interviews [24]. Physical activity from childhood to diagnosis was ascertained with the Lifetime Total Physical Activity Questionnaire (LTPAQ) [25]. At follow-up, a modified LTPAQ and the Charlson Comorbidity Index assessed post-diagnosis physical activity and comorbidities, respectively [25, 26]. Trained health record technicians abstracted clinical histories including cancer stage (American Joint Committee on Cancer [27]), histology, and primary and adjuvant treatment(s) from the ACR. Cancer grade (International Federation of Gynecology and Obstetrics Guidelines [28]) was assessed by the study's pathologist.

Alcohol and cigarette smoking exposures

Participants who reported never having consumed ≥ 6 alcoholic drinks in any given year were defined as lifetime abstainers and participants who had stopped drinking > 1 year before diagnosis were considered former drinkers. Non-, former- and current drinker groups were used to categorize post-diagnosis alcohol consumption status so that non-drinkers included participants who had not consumed ≥ 6 drinks in a given year after diagnosis, former drinkers had stopped drinking > 1 year before follow-up interviews and current drinkers were active consumers. Alcohol consumption was measured in Canadian Standard Drinks (CSD; 13.45 g alcohol/drink) from beer (12 oz /341 ml), wine (5 oz/140 ml), or liquor (1.5 oz/45 ml) [29] and assessed as the average number of CSD/week during a participant's active drinking years. Alcohol consumption quantity was assessed using the risk groups defined by the 2022 Updated Canada Low-Risk Alcohol Drinking Guidelines (low: 1–2 CSD/week; moderate 3–6 CSD/week; high > 6 CSD/week) [7]. Due to the limited number of participants within the *high-risk* group of the guidelines, the moderate and high alcohol intake levels were combined resulting in a final dichotomy of low (< 2 CSD/week) and high drinking levels (≥ 2 CSD/week) in this cohort. Patterns of alcohol consumption across pre- and post-diagnosis time frames were defined by alcohol status groups including never drinkers, former drinkers (before or after diagnosis), renewed drinkers ((re)started after diagnosis), always drinkers as well as by consumption quantity (never drinker, stop or decreased intake, consistently low levels, increased or consistently high).

Smoking exposures were assessed for participants who reported ever smoking ≥ 100 cigarettes in their lifetime (ever smokers). Pre-diagnosis smoking status was self-reported by participants as never, former, or current at the time of cancer diagnosis. Participants' post-diagnosis smoking status was categorized as non-smokers (participants who had not smoked ≥ 100 cigarettes after diagnosis), former smokers (participants who reported quitting after diagnosis, or had been current smokers at diagnosis and non-smokers at follow-up) and current smokers. Cigarette smoking quantity was summarized by pack-years and categorized by median threshold of ever smokers' exposure levels. Lifetime smoking patterns were defined as never smokers, former smokers (before or after diagnosis) and re-started/always smokers.

Combined smoking and alcohol consumption groups were based on ever/never smoking status and alcohol consumption status (abstainer, former, current) and level (CSD/week).

Ascertainment of outcomes

A trained health record technician with the ACR abstracted the medical charts to identify any cancer recurrences as well as all treatment and follow-up care data. Endometrial cancer recurrence was defined as endometrial cancer that returned after a disease-free period of ≥ 6 months, with no residual tumour noted at the time of surgery. Vital status was ascertained through record linkages with Vital Statistics Alberta to January 27, 2022. DFS and OS were defined as the time to the first recurrence/death, and death from any cause, respectively.

Statistical analysis

Participants' characteristics were described with median (IQR) and counts (%) while comparisons were conducted via t-test and test of proportions for continuous and categorical variables, respectively. Cox proportional hazards models estimated multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CI) for alcohol consumption, cigarette smoking, and joint exposures with DFS and OS. Additionally, sensitivity analyses excluding lifetime abstainers and non-smokers were conducted due to the potential for social desirability to lead to under-reporting and create misclassification of these groups [30–32]. Survival time was measured from cancer diagnosis and follow-up interviews in baseline and follow-up analyses, respectively. Only OS was assessed in post-diagnosis analysis since most recurrences are expected to occur within 3 years of diagnosis [33]. The proportional hazards assumption was assessed via visual and statistical assessments of Schoenfeld residuals. Results from analyses with < 5 events/group were not reported. All analyses were two-sided and performed with STATA version 17 (StataCorp LLC. College Station, TX).

Age at diagnosis (years), cancer stage (I, II, III/IV), grade (I/II, III, unknown/non-applicable), primary treatment(s) (hysterectomy, chemotherapy, radiation, any adjuvant, missing), were selected as covariates for multivariable models *a priori* based on biological plausibility. Following

augmented backwards elimination, models were additionally adjusted for waist circumference, major comorbidities, family history of colorectal or uterine cancer, education level, parity, and lifetime total physical activity (metabolic equivalent task [MET]-hours/week/year). Smoking models were adjusted for continuous alcohol intake and vice versa. When relevant, follow-up analyses used lifetime variables assessed at follow-up rather than diagnosis (i.e., post-diagnosis Charlson Comorbidity Index). There was insufficient evidence that non-linear age, marital, menopausal or, hormone therapy status confounded the associations of interest.

Lastly, potential effect modification of the cigarette smoking and alcohol consumption survival associations by obesity (<30, ≥ 30 kg/m^2), and physical activity (median threshold: 102 METS-hours/week/year) were explored using Wald tests.

Results

Participant characteristics

The median participant follow-up time was 16.9 years (IQR = 15.5–18.1 years), during which 152 participants had a recurrence and/or died, with 134 deaths overall. At diagnosis, participants had a median age of 59.0 years (IQR = 53.0–65.0), were primarily of European ancestry (95.0%), diagnosed with early stage (I: 79.3%) and grade cancers (I/II: 76.5%), and had a hysterectomy as part of their primary treatment (97.6%; Table 1). Participant characteristics were not notably different between those who did and did not complete follow-up assessments (data not shown).

At diagnosis, 61.3% of participants were current drinkers, 20.4% were lifetime abstainers, and 18.3% were former drinkers (Table 1). Most participants consumed low levels (<2 CSD/week) of alcohol at pre-diagnosis (76.5%) and at post-diagnosis (89.6%). Nearly half (49.8%) of the participants were never smokers at diagnosis, while 12.8% were current smokers at diagnosis and 11.5% reported being current smokers at follow-up. Compared with participants who were never smokers at diagnosis, ever smokers were less likely to be lifetime alcohol abstainers (9.2% vs. 31.6%), and more likely to be current drinkers (51.3% vs. 71.2%), to consume either moderate levels of alcohol (8.6% vs. 20.7%) or consume high levels of alcohol (1.2% vs. 7.0%; Supplementary Table S1). At baseline, 45.5% of participants were both smokers and alcohol consumers and 15.7% had never had either exposure.

Pre-diagnosis, post-diagnosis and, change in alcohol consumption and smoking

Pre-diagnosis alcohol consumption and cigarette smoking measures were not associated with DFS or OS when compared to lifetime abstainers and never smokers, respectively (Tables 2 and 3). Likewise, combined pre-diagnosis smoking and alcohol measures were not associated with survival outcomes (Table 4). At follow-up, compared with non-drinkers, high levels of post-diagnosis alcohol consumption were associated with worse OS (HR = 2.36, 95% CI = 1.00-5.54), although a dose-response relationship was not observed. Compared with those who remained lifetime abstainers of alcohol both pre- and post-diagnosis, the various patterns of changes in alcohol consumption status or quantity were not associated with OS (Table 5). Post-diagnosis smoking as well as pre- to post-diagnosis smoking patterns were not associated with OS (Tables 3 and 5).

Smoker and alcohol consumer only sensitivity analysis

In the analysis excluding lifetime alcohol abstainers, pre-diagnosis alcohol consumption was not associated with survival outcomes (Table 2). However, high post-diagnosis levels of alcohol consumption were associated with nearly four-fold worse OS compared to low levels of alcohol intake (HR = 3.87, 95% CI = 1.67–8.96). Moreover, compared with participants who stopped or decreased their alcohol intake levels after cancer diagnosis, increased alcohol intake or consistently higher levels of consumption were associated with worse OS (HR = 2.91, 95% CI = 1.15–7.37, Table 5). Among participants who reported ever smoking before diagnosis, each additional smoking pack-year was associated with a 2% decrease in OS (HR = 1.02, 95% CI = 1.00-1.03, Table 3). No associations between post-diagnosis or changes in smoking patterns with OS were observed in this cohort.

Effect modification

Obesity status [body mass index (BMI): $<30, \geq 30$ kg/m^2] significantly modified the dose-response relationships between smoking pack-years and survival outcomes among those with a smoking history (DFS: $p < 0.01$; OS: $p = 0.04$). Specifically, for those with a cigarette smoking history in the <30 kg/m^2 BMI group, each additional pre-diagnosis smoking pack-year was associated with 4% (95% CI = 1.01–1.06) worse DFS and 3% (95% CI = 1.01–1.06) worse OS, while null associations were observed in the ≥ 30 kg/m^2 group. Modification by physical activity status was not observed in this cohort (DFS: $p > 0.05$; OS: $p > 0.05$, data not shown).

Table 1 Characteristics of the Alberta Endometrial Cancer Cohort participants and pre-diagnosis (n = 540) and post-diagnosis (n = 425) smoking and alcohol use by vital status, 2002–2022

Characteristic	All Median (IQR)/N (%)	Alive Median (IQR)/N (%)	Disease-free survival (Median (IQR)/N (%)	Overall deaths Median (IQR)/N (%)
Participants	540	406	152	134
Age at diagnosis (year)	59.00 (53.00–65.00)	57.00 (52.00–63.00)	64.00 (57.50–72.00)	64.00 (59.00–72.00)
Highest education				
High school diploma	177 (32.78)	123 (30.30)	60 (39.47)	54 (40.30)
Non-university certificate	249 (46.11)	189 (46.55)	68 (44.74)	60 (44.78)
University degree	114 (21.11)	94 (23.15)	24 (15.79)	20 (14.93)
Married or common-law	372 (68.89)	287 (70.69)	96 (63.16)	85 (63.43)
European ethnic ancestry	513 (95.00)	383 (94.33)	144 (94.74)	130 (97.01)
Overall AJCC stage[b]				
I	428 (79.26)	344 (84.73)	95 (62.50)	84 (62.69)
II	69 (12.78)	44 (10.84)	28 (18.42)	25 (18.66)
III/IV	43(7.96)	18 (4.43)	29 (19.08)	25 (18.66)
FIGO grade				
I/II	413 (76.48)	330 (81.28)	93 (61.18)	83 (61.94)
III	73 (13.52)	41 (10.10)	36 (23.68)	32 (23.88)
Unknown/Non-applicable	54 (10.00)	35 (8.62)	23 (15.13)	19 (14.18)
Primary treatment[c]				
Surgery	527 (97.59)	399 (98.28)	140 (92.11)	128 (95.52)
Chemotherapy	45 (8.33)	26 (6.40)	20 (13.16)	19 (14.18)
Hormone therapy	6 (1.11)	6 (1.48)	2 (1.32)	0 (-)
Radiation therapy	168 (31.11)	118 (29.06)	57 (37.50)	50 (37.31)
BMI (kg/m^2)	31.12 (26.49–36.96)	30.99 (26.13–37.05)	31.24 (27.33–36.72)	31.23 (27.43–36.60)
Physical activity (METS-hours/week/year)	102.13 (80.05-127.56)	101.11 (79.95-125.54)	107.59 (80.35-135.19)	108.33 (80.15-136.01)
Pre-diagnosis smoking[d]				
Never smoker	269 (49.81)	199 (49.01)	81 (53.29)	70 (52.24)
Former smoker	202 (37.41)	158 (38.92)	49 (32.24)	44 (32.84)
Current smoker	69 (12.78)	49 (12.07)	22 (14.47)	20 (14.93)
Pack-years[e]	15.75 (5.15–31.2)	13.71 (4.90–30.00)	20.70 (6.30-38.74)	20.40 (6.30-38.74)
Post-diagnosis smoking				
Non-smoker	358 (84.24)	293 (84.44)		65 (83.33)
Former smoker	18 (4.24)	14 (4.03)		4 (5.13)
Current smoker	49 (11.53)	40 (11.53)		9 (11.54)
Pack-years[e]	1.72 (1.03–2.99)	1.85 (1.06-3.00)		1.31 (0.43–2.25)
Pre-diagnosis alcohol status				
Lifetime abstainer	110 (20.37)	74 (18.23)	38 (25.00)	36 (26.87)
Former drinker	99 (18.33)	74 (18.23)	28 (18.42)	25 (18.66)
Current drinker	331 (61.30)	258 (63.55)	86 (56.58)	73 (54.48)
Pre-diagnosis alcohol level[f]				
Low	329 (76.51)	252 (75.90)	90 (78.95)	77 (78.57)
Moderate	79 (18.37)	65 (19.58)	17 (14.91)	14 (14.29)
High	22 (5.12)	15 (4.52)	7 (6.14)	7 (7.14)
Post-diagnosis alcohol status				
Non-drinkers	122 (28.71)	91 (26.22)		31 (39.74)
Former drinker	28 (6.59)	22 (6.34)		6 (7.69)
Current drinker	275 (64.71)	234 (67.44)		41 (52.56)
Post-diagnosis alcohol level				
Low	251 (89.64)	215 (91.10)		36 (81.82)

Table 1 (continued)

Characteristic	All Median (IQR)/N (%)	Alive Median (IQR)/N (%)	Disease-free survival (Median (IQR)/N (%)	Overall deaths Median (IQR)/N (%)
Moderate	23 (8.21)	16 (6.78)		7 (15.91)
High	6 (2.14)	5 (2.12)		1 (2.27)

[a]AJCC = American Joint Committee on Cancer; BMI = body mass index; FIGO = International Federation of Gynecology and Obstetrics

[b]Participants with incomplete TNM stage (n = 8) were classified based on available lymph node inclusion and metastatic information as stage I

[c]The frequencies for treatment are not mutually exclusive since participants could have multiple treatments

[d]Former smokers included ex-occasional (n = 31; usually less than one cigarette per day and has quit) and ex-daily smokers (n = 171; smoke cigarettes daily and have quit); Current smoker include active occasional (n = 3) and daily smoker

[e]Pack-years were computed for current and ex-smokers only and could not be assessed for occasional, ex-occasional, or never smokers; Post-diagnosis pack-year measures were only available for n = 54 survivors (n = 43 alive, n = 11 dead)

[f]Canadian standard drink contains 13.45 g of pure alcohol; Low levels:<2 drinks/week, Moderate levels: 2–6 drinks/week, High levels: >6 drinks/week

Discussion

Among endometrial cancer survivors in this cohort, elevated post-diagnosis alcohol intake and long-term high alcohol intake patterns were associated with worse survival outcomes. Specifically, post-diagnosis alcohol levels of ≥ 2 CSD per week were associated with approximately threefold decreases in OS. Moreover, an increase to or continuation of these levels of alcohol intake were related to poor OS compared with reduced or ceased intakes after cancer diagnosis. A harmful dose-response relationship was noted in this cohort for each additional pre-diagnosis smoking pack-year with OS among ever smokers. Conversely, when compared with participants without any cigarette smoking history, no pre- or post-diagnosis smoking measures were associated with survival outcomes.

To the best of our knowledge, this study is the first to investigate the effects of alcohol consumption on survival outcomes in endometrial cancer survivors. A prior systematic review noted that for each 12.5 g increase in daily ethanol intake (~ 0.93 CSD), women in the general population experienced a 3.9% increase in cancer mortality when compared with non-/occasional drinkers, with evidence of a J-shaped relationship which favored light drinking [34]. Inconsistent although primarily null and J-shaped survival relationships with alcohol intake and prognostic outcomes have also been seen in breast and colorectal cancer survivors, respectively [35, 36]. Although a J-shaped relationship between alcohol consumption and mortality outcomes is plausible, the protective effects of light drinking are often attributable to a possible misclassification of former and occasional drinkers and misrepresentation of heavy drinking episodes in average estimates [37–40]. Such mechanisms were highlighted by Ko et al. [37], who reported relationships between levels of alcohol consumption with cancer mortality beginning with low intake when compared with lifetime abstainers. However, this relationship followed a J-shape when former drinkers were not separated from abstainers [37]. In the current study, participants at follow-up who had consumed an average of ≥ 2 CSD/week after their diagnosis had reduced survival compared with non-drinkers as well as light drinkers. Moreover, our results illustrated harmful OS associations for pre- to post-diagnosis increased/consistently elevated drinking patterns compared with decreased/ceased alcohol patterns. While these results provide early evidence that reducing alcohol intake improves survival outcomes for endometrial cancer survivors and supports behavior change interventions at cancer diagnosis, future studies with larger samples are needed to confirm these findings.

Prior studies have reported that current smokers at endometrial cancer diagnosis experience between 1.3- and 1.7-fold reductions in OS compared to never smokers [13–15]. Of the two studies that have examined the smoking status and endometrial cancer recurrence association, only one observed a harmful DFS association for current smokers (HR = 1.38, 95% CI = 1.09–1.75) [14, 15]. For endometrial cancer survivors in the National Health Interview Survey, active smoking after diagnosis and greater number of cigarettes/day were associated with worse cancer-specific and OS [16]. Although the current study did not observe an association between smoking status and survival when compared with never smokers, we did observe dose-response survival relationships whereby greater cigarette smoking (in pack-years) among ever smokers was associated with poorer survival. Decreased efficacy of cancer treatment and adverse treatment outcomes seen with active tobacco use by cancer patients may partially explain these results [41]. Moreover, there was evidence that obesity status modified this association such that harmful associations with DFS and OS for each additional pack-year were observed for survivors with a BMI < 30 kg/m^2 only. Prior research has also noted complexities in the relationships between cigarette

Table 2 Disease free survival and overall survival outcomes for pre-diagnosis (n = 540) and post-diagnosis (n = 425) alcohol drinking status and alcohol intake level in the Alberta Endometrial Cancer Cohort Study, 2002–2022

	Disease-free Survival			Overall Survival		
	Events/ Cases	HR (95% CI)	Restricted HR (95% CI)[a]	Events/ Cases	HR (95% CI)	Restricted HR (95% CI)[a]
Pre-diagnosis[b]						
Drinking status						
Lifetime abstainer	38/110	1.00		36/110	1.00	
Former	28/99	1.34 (0.79–2.25)		25/99	0.94 (0.55–1.64)	
Current	86/331	1.15 (0.76–1.74)		73/331	0.84 (0.55–1.29)	
Alcohol level						
Lifetime abstainer	38/110	1.00		36/110	1.00	
Low	90/329	1.19 (0.79–1.79)	1.00	77/329	0.87 (0.57–1.32)	1.00
High	24/101	1.20 (0.68–2.11)	1.07 (0.66–1.73)	21/101	0.85 (0.47–1.52)	0.98 (0.58–1.64)
Per 1 drink/week	152/540	1.02 (0.96–1.08)	1.01 (0.95–1.08)	134/540	1.02 (0.96–1.09)	1.03 (0.96–1.10)
Post-diagnosis[c]						
Drinking status						
Non-drinker				31/122	1.00	
Former				6/28	0.87 (0.35–2.15)	
Current				41/275	0.76 (0.46–1.27)	
Alcohol level						
Non-drinker				31/122	1.00	
Low				26/251	0.73 (0.44–1.23)	1.00
High				8/29	2.36 (1.00-5.54)	3.87 (1.67–8.96)
Per 1 drink/week				78/425	1.07 (0.90–1.27)	1.07 (0.92–1.26)

[a]Restricted HR (95% CI) excluding pre-diagnosis lifetime abstention of alcohol and post-diagnosis non-drinkers

[b]Pre-diagnosis models adjusted for: age at diagnosis, stage, grade, treatment, at diagnosis waist circumference, pre-diagnosis comorbidities (number of major comorbidities), family history of uterine or colorectal cancer, parity, education level, pre-diagnosis lifetime physical activity, pre-diagnosis smoking pack-years

[c]Post-diagnosis models adjusted for: age at diagnosis, stage, grade, treatment, post-diagnosis waist circumference, post-diagnosis comorbidities (Charlson Comorbidity Index), family history of uterine or colorectal cancer, parity, education level, post-diagnosis physical activity, post-diagnosis smoking pack-years

[d]Low: <2 drinks/week; High: ≥2 drinks/week; Canadian standard drink contains 13.45 g of pure alcohol

smoking, obesity, and mortality [42]. These studies have reported that compared with normal-weight smokers, overweight and obese ex-smokers had reduced all-cancer and caner-specific mortality [42].

Despite the widespread intake of both smoking and alcohol, limited literature is available regarding the combined impact of these risk factors on mortality outcomes [11, 43]. Prior studies of combined smoking and alcohol exposure frequently report positive associations with mortality, although these estimates are primarily derived from male-only analyses [44–46]. Given the sex- and gender-specific associations with drinking and smoking behaviours, there

Table 3 Disease free survival and overall survival outcomes for pre-diagnosis (n = 540) and post-diagnosis (n = 425) smoking in the Alberta Endometrial Cancer Cohort, 2002-2022

	Disease-free Survival			Overall Survival		
	Events/ Cases	HR (95% CI)	Restricted HR (95% CI)[a]	Events/ Cases	HR (95% CI)	Restricted HR (95% CI)[a]
Pre-diagnosis[b]						
Smoking status						
Never	81/269	1.00		70/269	1.00	
Former	49/202	0.75 (0.52–1.09)		44/202	0.77 (0.52–1.14)	
Current	22/69	0.84 (0.50–1.40)		20/69	0.92 (0.53–1.60)	
Smoking pack-years						
Never	81/269	1.00		70/269	1.00	
< 15.8 pack-year	25/125	0.65 (0.41–1.04)	1.00	22/125	0.64 (0.39–1.04)	1.00
≥ 15.8 pack-year	41/124	0.86 (0.57–1.29)	1.40 (0.81–2.42)	37/124	0.93 (0.60–1.45)	1.63 (0.91–2.91)
Per 1 pack-year	147/518	1.00 (0.99–1.01)	1.01 (0.99–1.03)	129/518	1.00 (0.99–1.02)	1.02 (1.00-1.03)
Smoking duration						
Non-smoker	81/269	1.00		70/269	1.00	
< 23 years	28/141	0.68 (0.43–1.05)	1.00	25/141	0.68 (0.42–1.08)	1.00
> 23 years	40/123	0.85 (0.56–1.29)	1.34 (0.79–2.26)	36/123	0.91 (0.58–1.42)	1.47 (0.84–2.56)
Per 1 year	149/533	1.00 (0.99–1.01)	1.01 (0.99–1.03)	131/533	1.00 (0.99–1.01)	1.01 (0.99–1.04)
Smoking cessation						
< 20 years	26/104		1.00	21/104		1.00
≥ 20 years	23/98		0.70 (0.38–1.30)	98/202		0.96 (0.50–1.87)
Per 1 year	49/202		0.99 (0.97–1.01)	44/202		1.00 (0.97–1.02)
Post-diagnosis[c,d]						
Smoking status						
Non-smoker				65/358	1.00	
Former				4/18		
Current				9/49	0.82 (0.39–1.72)	
Smoking pack-years						
Non-smoker				65/358	1.00	
< 1.7 pack-year				7/27	1.09 (0.47–2.49)	
≥ 1.7 pack-year				4/27		
Per 1 pack-year				76/412	0.80 (0.57–1.11)	0.54 (0.25–1.15)

[a]Restricted models excluded pre-diagnosis never smokers (n = 269) and post-diagnosis non-smokers (n = 54)

[b]Pre-diagnosis models adjusted for: age at diagnosis, stage, grade, treatment, at diagnosis waist circumference, pre-diagnosis comorbidities (number of major comorbidities), family history of uterine or colorectal cancer, parity, education level, pre-diagnosis lifetime physical activity, pre-diagnosis alcohol intake

[c]Post-diagnosis models adjusted for: age at diagnosis, stage, grade, treatment, post-diagnosis waist circumference, post-diagnosis comorbidities (Charlson Comorbidity Index), family history of uterine or colorectal cancer, parity, education level, post-diagnosis physical activity, post-diagnosis alcohol intake

[d]Some estimates are not shown in the post-diagnosis analysis due to insufficient events (n < 5)

Table 4 Disease free survival and overall survival outcomes for combined pre-diagnosis smoking and alcohol measures groups in the Alberta Endometrial Cancer Cohort Study, 2002–2022

	Disease-free Survival		Overall Survival	
	Event/cases	HR (95% CI)	Event/cases	HR (95% CI)
Smoking Status & Drinking Status				
Non-smoker/ Never Drinker	28/85	1.00	26/85	1.00
Non-smoker/ Former Drinker	13/46	1.58 (0.79–3.13)	12/46	1.53 (0.76–3.10)
Non-smoker/ Current Drinker	40/138	1.36 (0.81–2.27)	32/138	1.06 (0.61–1.84)
Smoker/ Never Drinker	10/25	0.90 (0.42–1.94)	10/25	1.38 (0.64–2.95)
Smoker/ Former Drinker	15/53	1.14 (0.59–2.19)	13/53	0.85 (0.42–1.71)
Smoker/ Current Drinker	46/193	0.97 (0.59–1.60)	41/193	0.88 (0.53–1.47)
Smoking Status & Alcohol Level				
Non-smoker/ Lifetime abstainer	28/85	1.00	26/85	1.00
Non-smoker/ Low Alcohol	50/158	1.53 (0.94–2.48)	42/158	1.28 (0.77–2.13)
Non-smoker/ High Alcohol	3/26		2/26	
Smoker/ Lifetime abstainer	10/25	0.92 (0.43–1.99)	10/25	1.41 (0.66–3.03)
Smoker/ Low Alcohol	40/171	0.88 (0.53–1.46)	35/171	0.75 (0.44–1.27)
Smoker/ High Alcohol	21/75	1.36 (0.75–2.48)	19/75	1.21 (0.65–2.25)

[a]Pre-diagnosis models adjusted for: age at diagnosis, stage, grade, treatment, at diagnosis waist circumference, pre-diagnosis comorbidities (number of major comorbidities), family history of uterine or colorectal cancer, parity, education level, pre-diagnosis lifetime physical activity

[b]Estimates are not shown in the non-smoker/high alcohol group due to insufficient events ($n < 5$)

Table 5 Overall survival for pre-diagnosis and post-diagnosis lifetime change patterns in smoking status, alcohol drinker status and alcohol level in the Alberta Endometrial Cancer Cohort Study, 2002–2022

	Events/Cases	HR (95% CI)	Restricted HR (95% CI)
Smoking Status Patterns			
Never smoker	40/207	1.00	
Decreased	27/165	0.70 (0.42–1.16)	1.00
Increased or always smoker	11/53	0.83 (0.41–1.69)	1.66 (0.75–3.67)
Alcohol Drinker Status Patterns			
Never drinkers	22/68	1.00	
Former drinker	15/81	0.67 (0.33–1.33)	1.00
Renewed drinkers	6/40	0.71 (0.28–1.83)	1.06 (0.38–2.99)
Always drinker	35/236	0.64 (0.36–1.14)	1.06 (0.53–2.11)
Alcohol Level Patterns			
Never drinkers	22/68	1.00	
Stop or decreased	12/93	0.50 (0.23–1.06)	1.00
Consistently low	31/194	0.68 (0.38–1.22)	1.41 (0.69–2.89)
Increased or consistently high	10/47	1.32 (0.58–3.02)	2.91 (1.15–7.37)

[a]Restricted HR (95% CI) excluding lifetime abstaining of alcohol or never smokers

[b]Lifetime change pattern models adjusted for: age at diagnosis, stage, grade, treatment, post-diagnosis waist circumference, post-diagnosis comorbidities (Charlson Comorbidity Index), family history of uterine or colorectal cancer, parity, education level, post-diagnosis physical activity

[c]Smoking models were additionally adjusted for alcohol intake; alcohol models were additionally adjusted for smoking pack-years

is limited generalizability of results from male-only studies to an endometrial cancer survivor population [39, 47]. Previously, the EPIC study reported that compared with women who were never smokers/light drinkers (< 2.55 CSD/week), never smokers/never drinkers, never smokers/heavy drinkers (≥ 15.6 CSD/week) and current smokers with any level of alcohol consumption had between a 1.3- and 2.1-fold decrease in OS [48]. Similarly, women in China who had smoked > 100 lifetime cigarettes and drank alcohol ≥ 1/month were reported to experience greater

premature mortality compared with non-smokers/non-drinkers (OR = 4.95, 95% CI = 2.00-12.27) [49]. In this cohort, null relationships between cigarette smoking and alcohol groups with survival were observed when compared with never smokers/lifetime alcohol abstainers. These null results may be partially explained by the low tobacco and alcohol intakes observed in our cohort, resulting in limited differences between those with and without these exposures.

Contrary to early notions, some recent reports have shown that women who smoke may have higher concentrations of circulating estrogen than non-smokers [50, 51]. Alcohol consumption has also been associated with increased estrogen levels and dehydroepiandrosterone-sulphate, an estrogen precursor [50, 52]. The unopposed estrogen hypothesis is a primary mechanism of endometrial cancer development and progression, in which estrogen without sufficient progesterone stimulates cell proliferation and inhibition of cell apoptosis [53]. Furthermore, ethanol, a primary carcinogen in alcoholic beverages, and tobacco smoke have pro-inflammatory properties including increases in tumour necrosis factor-alpha, nuclear factor-kB, and several interleukins that act on a key inflammatory pathway to cancer progression [52–55]. Of note, a reduction in these inflammatory markers has been reported following smoking cessation [56]. Furthermore, alcohol consumption has been hypothesized to lead to ethanol-induced promotion of tobacco smoke carcinogenic agents [52].

This study has several strengths including the ascertainment of both pre- and post-diagnosis cigarette smoking and alcohol consumption histories. We had a comprehensive assessment of potential confounding factors obtained by our interviewers trained in cognitive interviewing methods that improve participant recall [57]. Additionally, medical chart abstractions conducted by qualified health record technicians and on-going record linkages for vital status ensured high quality outcome and treatment data during follow-up. However, the overall sample size and subsequent exposure groups resulted in some analyses being underpowered to observe an association. Insufficient group sizes also limited our capacity to explore some individual and joint exposures, and effect modification after diagnosis. Additionally, social stigmas related to the exposures of interest may have contributed to an under-reporting of smoking and alcohol intakes. Finally, exposure to secondhand smoke and heavy or binge drinking episodes could not be accounted for in participants' level of exposure.

Conclusion

Given the growing number of women living with endometrial cancer globally, identifying and understanding prognostic factors within this population is becoming increasingly important. Although endometrial cancer is not considered an alcohol- or smoking-linked cancer, these modifiable lifestyle behaviours have been previously associated with several known endometrial cancer-related comorbidities and OS. This study provides early evidence that endometrial cancer survivors with higher alcohol intakes after diagnosis may have worse prognosis during survivorship compared to women with no or low levels of alcohol intake. Therefore, efforts to promote drinking cessation are warranted for this population. Moreover, for survivors with a history of cigarette smoking, trends were observed between more extensive pre-diagnosis smoking levels and reduced survivorship. Highlighting the need for larger studies powered to investigate the individual and joint impact of these behaviours will provide additional clarity on these potential prognostic factors.

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Data Availability The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate This study was performed in line with the principles of the Declaration of Helsinki. The Ethics Committee of the University of Calgary, University of Alberta, and former Alberta Cancer Board provided ethical approval for this study and follow-up assessments.

Consent to participate Informed written consent was obtained from all individual participants included in the study.

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