

# Endometrial Cancer Associated Symptoms: A Case-Control Study

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## Abstract

**Background:** The majority of women with endometrial cancer (EC) present at an early stage with an associated 5-year survival rate of >90%. High rates of early detection are attributed to warning symptoms; however, the prevalence of such symptoms has not been well defined.

**Methods:** A case-control study was conducted assessing the prevalence of symptoms in EC patients at a large cancer center compared with healthy controls. Controls included patients seen for an annual gynecologic care visit (AV) or for a gynecological problem-based visit (PV). A self-administered questionnaire was given to all participants addressing EC-associated symptoms, at the time of initial clinic visit. Odds ratios (ORs) were used to compare prevalence of symptoms between EC cases and controls. Logistic regression was used to determine the impact of menopausal status and obesity on symptom prevalence.

**Results:** The cases ( $n=75$ ) were significantly older than the AV ( $n=203$ ) and PV ( $n=151$ ) controls (59.7 vs. 49.8 vs. 51.0 years,  $p<0.01$ ), had a higher body mass index (35.5 vs. 29.4 vs. 30.9 kg/m<sup>2</sup>,  $p<0.01$ ), and were more likely to be postmenopausal (76% vs. 53.7% vs. 52.0%,  $p<0.01$ ). The cases were more likely to report postmenopausal bleeding (OR=32.99 and 5.83,  $p<0.01$ ) and abnormal vaginal discharge (OR=8.8 and 3.3,  $p<0.01$ ) compared with the AV and PV groups. Overall, 55.4% of cases reported abnormal vaginal discharge.

**Conclusions:** Symptoms of both postmenopausal bleeding and abnormal vaginal discharge were significantly higher in EC compared with controls. The presence of such symptoms should raise concern for malignant disease and prompt immediate gynecological evaluation.

**Keywords:** endometrial cancer, cancer symptoms, postmenopausal bleeding

## Introduction

ENDOMETRIAL CANCER (EC) is the most common gynecological malignancy estimated to affect over 54,000 new women in 2015.<sup>1</sup> Despite the high incidence of EC, 70% of these malignancies are diagnosed at an early stage with localized disease confined to the uterus, and have a favorable 5-year overall survival approaching 95%.<sup>1</sup> This early detection is often attributed to the presence of disease-associated symptoms, such as abnormal uterine bleeding or vaginal discharge, which occur early in the disease process prompting evaluation. Although this observation is frequently referenced, there is little data in the literature documenting the prevalence of such symptoms in EC patients compared with the healthy population.

In patients who present with postmenopausal bleeding, several studies have shown the rates of EC to be 4%–8% in those women.<sup>2–4</sup> Additionally, recurrent episodes of postmenopausal bleeding, without prior evaluation, is even more predictive of underlying malignancy.<sup>2</sup> With regard to symptom prevalence, studies have investigated the rates of overall potential gynecological cancer symptoms.<sup>5,6</sup> These studies have shown high rates of gynecological cancer symptoms, in the general population, with 44%–80% of women experiencing at least one cancer-related symptom, and many women reporting multiple symptoms. Postmenopausal bleeding, specifically, has been shown to occur in 1%–10% of women overall<sup>5–7</sup> and incidence decreases with time from menopause.<sup>7</sup> These studies, however, have not compared the rates of these symptoms to rates in those patients diagnosed with a gynecological cancer.

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EC is also strongly associated with obesity that is proportionally related to increasing body mass index (BMI).<sup>8</sup> Previous studies of gynecological cancer symptoms have not evaluated the relationship between obesity and such symptoms. Obese patients with EC may have a different symptom profile and prevalence that could raise concern for the presence of disease, and could be targeted by public health initiatives.

The aim of this study was to determine the prevalence of potential EC-associated symptoms in EC cases compared with healthy controls.

**Materials and Methods**

After institutional review board approval was obtained from both M.D. Anderson Cancer Center and Kelsey-Seybold Clinic (KSC), a case-control study was conducted to assess the prevalence of symptoms in EC compared with control patients. Cases were recruited from The University of Texas, M.D. Anderson Cancer Center (MDACC) Gynecologic Oncology Clinic. Patients included were those with a new diagnosis of EC of any histology type, and were within 12 weeks of their initial diagnosis. Patients were excluded from the cases if they were unwilling to participate or had undergone prior definitive treatment for EC. Controls, without a diagnosis of EC, were recruited from primary care and gynecology clinics of the KSC, a large community-based practice located throughout Houston, TX. The controls included two groups<sup>1</sup>: patients seen for an annual gynecologic care visit (AV) and<sup>2</sup> patients seen for a gynecological problem-based visit (PV). Those in the AV group included women seeking care for annual check-up, well woman exams, or family planning. Those in the PV group included women stating that their primary reason for the visit was irregular bleeding, vaginal discharge, or pain. Patients were excluded from participation in the control group if they had a previous or current diagnosis of a gynecological malignancy (including cervical, endometrial, ovarian, vulvar, or vaginal cancer), were undergoing active treatment for any malignancy other than

nonmelanoma skin cancer, or were pregnant. Patients from any of the groups were also excluded if they were unable to speak or comprehend English. Patients in the control groups underwent additional work-up, such as endometrial biopsy, based on reported symptoms at the discretion of their provider. Medical records of the control groups were later reviewed to identify any patients subsequently diagnosed with EC. None of these patients was found to have EC.

A self-administered study questionnaire in English was given at the time of enrollment. Before initiation of the study, the questionnaire was piloted on research nurses for readability and length of time to complete. The first page of the questionnaire included a consent statement, and consent was implied if the questionnaire was completed. All participants completed the same questionnaire addressing basic demographic factors, medical history, reproductive and menstrual history, and contraception and hormone use. Participants were also asked about the presence or absence of 12 potential EC-related symptoms. Half of these related to the presence of menstrual symptoms, including irregular menses, intermenstrual bleeding, heavy menses, prolonged menses, bleeding after sex, and bleeding after menopause. The other six nonmenstrual symptoms surveyed included: presence of pelvic pain, pelvic pressure, urinary frequency or urgency, change in bowel habit patterns, abnormal vaginal discharge, and fatigue (Table 1). A complete version of the survey is also available upon direct request to the corresponding author. Enrollment of 75 cases and 300 total controls (150 AV and 150 PV) was used for an estimated power of 86% to detect a 20% difference in symptom prevalence when 90% of the cases present with a particular symptom.

Based on questionnaire responses, the prevalence of EC-associated symptoms were compared between cancer cases and control groups using logistic regression and odds ratios (ORs). Two-sided testing was conducted on 12 symptoms of primary interest with a significance level of 0.008 to adjust for multiple testing for a familywise statistical significance of 10%. Comparison of other data was done using Fisher's test, *t*-test, or Wilcoxon rank sum test based on data distribution. All

TABLE 1. SAMPLE OF SURVEY QUESTIONS

	<i>Have you ever had the following problem?</i>	<i>Are you currently (in the last 6 months) experiencing the problem?</i>	<i>How long did you have the problem?</i>	<i>Did you seek care from a doctor or healthcare provider for the problem?</i>
9. Irregular or unpredictable menstrual periods	<input type="checkbox"/> Yes <input type="checkbox"/> No (If "No," skip to the next row)	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Never <input type="checkbox"/> Less than 6 months <input type="checkbox"/> 6–12 months <input type="checkbox"/> More than 1 year <input type="checkbox"/> Always	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Never had irregular periods
10. Bleeding in between menstrual periods	<input type="checkbox"/> Yes <input type="checkbox"/> No (If "No," skip to the next row)	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Never <input type="checkbox"/> Less than 6 months <input type="checkbox"/> 6–12 months <input type="checkbox"/> More than 1 year <input type="checkbox"/> Always	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Never had bleeding in between periods
11. Heavy menstrual periods	<input type="checkbox"/> Yes <input type="checkbox"/> No (If "No," skip to the next row)	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Never <input type="checkbox"/> Less than 6 months <input type="checkbox"/> 6–12 months <input type="checkbox"/> More than 1 year <input type="checkbox"/> Always	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Never had heavy periods

secondary analyses were tested at a 0.05 significance level. To test whether menopausal status or obesity affected the prevalence of EC symptoms logistic regression models were constructed. Obesity was defined as a BMI greater or equal to 30 kg/m<sup>2</sup>. In these models, occurrence of the symptom was the dependent variable, and study group, menopausal status, and obesity served as the independent variables. Stata v12.0 (College Station, TX) was used for statistical analysis.

**Results**

From October 2010 to November 2011, 429 women were enrolled in the study. Of these, 75 were recruited from MDACC with a new diagnosis of EC and comprised the cases. The remaining 354 patients were recruited from the KSC system with 203 included in the AV control group and 151 in the PV control group. Demographic data for the three groups are shown in Table 2. Specifically, patients in the cases were significantly older (59.7 vs. 49.8 vs. 51.0 years, *p*<0.01), had a higher BMI (35.5 vs. 29.4 vs. 30.9 kg/m<sup>2</sup>, *p*<0.01), and were more likely to be postmenopausal (76.0% vs. 53.7% vs. 52.0%, *p*<0.01) than either the AV or PV controls, respectively. Cases had a lower percentage of black patients than both the AV and PV controls (10.7% vs. 37.8% vs. 50.3%, *p*<0.01), and were less likely to have used birth control than the AV controls (73.3% vs. 84.8%, *p*=0.04). There was no significant difference, however, in age at menopause, menstrual patterns, or use of hormone replacement therapy.

We first compared reported symptoms between cases and the AV controls. Of the 12 symptoms examined, six were

found to be significantly associated with the cases compared with the AV controls (Table 3). Most notably, the symptom of postmenopausal bleeding was more likely to be reported in cases with an OR of 32.99 (95% confidence interval [CI]: 13.61–79.97; *p*<0.008). The symptoms of abnormal vaginal discharge (OR=8.80, 95% CI: 4.73–16.37; *p*<0.008), pelvic pain (OR=4.31, 95% CI: 2.46–7.55; *p*<0.008), pelvic pressure (OR=6.38, 95% CI: 3.32–12.23; *p*<0.008), urinary frequency (OR=3.03, 95% CI: 1.74–5.25; *p*<0.008), and fatigue (OR=2.49, 95% CI: 1.45–4.28) were also significantly associated with EC. There was no difference in reported symptoms of irregular menses, intermenstrual bleeding, heavy menses, or bleeding after sex.

Reported symptoms in cases versus PV controls was then compared, and postmenopausal bleeding (OR=5.83, 95% CI: 2.54–13.40; *p*<0.008) and abnormal vaginal discharge (OR=3.30, 95% CI: 1.85–5.91; *p*<0.008) continued to be significantly associated with cases (Table 3). However, the odds of pelvic pain (OR=1.75, 95% CI: 0.99–3.10; *p*=0.05), pelvic pressure (OR=1.58, 95% CI: 0.89–2.81; *p*=0.12), urinary frequency (OR=1.43, 95% CI: 0.82–2.50; *p*=0.20), or fatigue (OR=1.38, 95% CI: 0.79–2.43; *p*=0.26) were not increased in the cases compared with PV controls, as seen in the AV control comparison.

Overall, 55.4% of cases reported the symptom of abnormal vaginal discharge compared with just 12.4% in the AV controls (*p*<0.008) and 27.3% in the PV controls (*p*<0.008). There was no significant difference seen in the histology of cases that reported discharge (*p*=0.75). Of those who reported abnormal vaginal discharge, there was no significant difference in

TABLE 2. DEMOGRAPHICS OF STUDY PARTICIPANTS

Characteristic	Endometrial cancer cases (n=75)	Annual visit controls (n=203)		Problem visit controls (n=151)	
				p	p
Mean age (year)	59.7	49.8	<0.01	51.0	<0.01
Mean BMI (kg/m <sup>2</sup> )	35.5	29.4	<0.01	30.9	<0.01
Race, n (%)			<0.01		<0.01
White	56 (74.7)	107 (53.2)		47 (32.0)	
Black	8 (10.7)	76 (37.8)		74 (50.3)	
Asian	0 (0)	6 (3)		10 (6.8)	
Other	11 (14.6)	12 (6)		16 (10.9)	
Mean age at menarche (year)	12.7	12.8	0.48	12.2	0.03
Mean age at menopause (year)	51.6	50.3	0.06	51.2	0.64
Menstrual status, n (%)			<0.01		<0.01
Regular menses	4 (5.3)	63 (31.3)		37 (24.7)	
Irregular	14 (18.7)	30 (14.9)		35 (23.3)	
Postmenopausal	57 (76.0)	108 (53.7)		78 (52.0)	
Pattern of menstrual cycle, n (%)			0.08		0.61
Regular	57 (76.0)	173 (85.2)		120 (79.5)	
Irregular	18 (24.0)	30 (14.8)		31 (20.5)	
Mean parity	2.6	2.2	0.05	2.3	0.18
Hormone use, n (%)					
History of combined hormonal contraceptive use	55 (73.3)	168 (84.8)	0.04	127 (85.2)	0.05
Current combined hormonal contraceptive use	0 (0)	32 (19.6)		19 (15.6)	
History of combined hormone replacement therapy	8 (10.8)	26 (13.2)	0.68	17 (11.3)	>0.99
Current combined hormone replacement therapy	2 (2.5)	9 (31.9)		6 (35.3)	
History of estrogen only	15 (20.3)	25 (12.7)	0.13	15 (10.1)	0.06
Current estrogen only	0 (0)	3 (16.6)		3 (21.4)	

BMI, body mass index.

TABLE 3. ASSOCIATION OF SYMPTOMS IN ENDOMETRIAL CANCER CASES COMPARED TO ANNUAL VISIT AND PROBLEM VISIT CONTROL GROUPS

	Cases, n (%)	AV controls, n (%)	Cases (n=75) vs. AV controls (n=203)			PV controls, n (%)	Cases (n=75) vs. PV Controls (n=151)		
			OR	95% CI	p		OR	95% CI	p
<b>Menstrual symptoms<sup>a</sup></b>									
Postmenopausal bleeding <sup>b</sup>	50 (84.8)	16 (14.4)	32.99	13.61–79.97	<0.001 <sup>c</sup>	40 (48.8)	5.83	2.54–13.40	<0.001 <sup>c</sup>
Irregular menses	35 (46.7)	74 (36.6)	1.51	0.89–2.59	0.130	71 (47.0)	0.99	0.57–1.72	0.960
Intermenstrual bleeding	15 (20.0)	34 (16.8)	1.24	0.63–2.44	0.528	30 (20.1)	0.99	0.5–1.98	0.981
Heavy menses	47 (62.7)	100 (49.3)	1.73	1.0–2.98	0.048	87 (57.6)	1.23	0.7–2.18	0.467
Prolonged menses	25 (33.8)	38 (18.9)	2.19	1.2–3.98	0.010	45 (29.8)	1.20	0.66–2.18	0.545
Bleeding after sex	8 (10.7)	12 (5.9)	1.89	0.74–4.83	0.183	21 (13.9)	0.74	0.31–1.76	0.494
<b>Nonmenstrual symptoms<sup>a</sup></b>									
Pain	48 (64.0)	59 (29.2)	4.31	2.46–7.55	<0.001 <sup>c</sup>	75 (50.34)	1.75	0.99–3.1	0.054
Pelvic pressure	31 (41.3)	20 (10.0)	6.38	3.32–12.23	<0.001 <sup>c</sup>	46 (30.87)	1.58	0.89–2.81	0.121
Urinary frequency	39 (52.0)	53 (26.4)	3.03	1.74–5.25	<0.001 <sup>c</sup>	65 (43.1)	1.43	0.82–2.5	0.204
Abnormal vaginal discharge	41 (55.4)	25 (12.4)	8.80	4.73–16.37	<0.001 <sup>c</sup>	41 (27.3)	3.3	1.85–5.91	<0.001 <sup>c</sup>
Fatigue	45 (60.0)	76 (37.6)	2.49	1.45–4.28	<0.001 <sup>c</sup>	78 (52.0)	1.38	0.79–2.43	0.255
Change in bowel habits	28 (37.3)	50 (25.0)	1.79	1.01–3.15	0.04	49 (32.5)	1.24	0.7–2.21	0.466

Symptoms listed are those that the patient reported as ever having occurred.

<sup>a</sup>Each symptom was stratified by appointment type, and the reason for the problem visit was unknown.

<sup>b</sup>Only postmenopausal women were included in this analysis.

<sup>c</sup> $p < 0.008$  to control for multiple testing on primary objective.

AV, annual gynecologic care visit; CI, confidence interval; PV, gynecologic problem-based visit; OR, odds ratio.

duration of discharge in cases compared with AV controls ( $p=0.24$ ) or PV controls ( $p=0.33$ ) or in frequency of discharge (cases vs. AV,  $p=0.06$ ; cases vs. PV,  $p=0.50$ ). There was also no difference in duration of postmenopausal bleeding among those that had reported this symptom (cases vs. AV,  $p=0.61$ ; cases vs. PV,  $p=0.22$ ).

Both menopausal status and weight may also potentially affect the prevalence of EC associated symptoms. When multivariate analysis controlling for case, menopausal, and obesity status was used, postmenopausal women were more likely to report urinary frequency in the AV controls (OR=2.48,  $p < 0.01$ ) and less likely to report bleeding after sex in the PV controls (OR=0.25,  $p < 0.01$ ) (Table 4). Obesity when controlled for case and menopausal status, on the other hand, was associated with heavy menses in the PV controls (OR=2.19,  $p=0.01$ ) and pain in the AV controls (OR=2.43,  $p=0.01$ ). Case status, however, was not predictive of heavy periods suggesting that the symptom of heavy periods is driven by obesity rather than the presence of disease (Table 4).

## Discussion

The early detection rate of EC is thought secondary to the presence of warning symptoms, such as postmenopausal bleeding that prompt evaluation of these patients. Despite this widely accepted observation of these symptoms in EC, the prevalence of such symptoms has been poorly documented in the literature. In our present study, we demonstrated that the presence of postmenopausal bleeding was predictive of EC with an OR of 32.99 in cases compared with healthy patients seen for AV and an OR of 5.83 compared with patients seen for a PV. Abnormal vaginal discharge was also strongly associated with EC, and reported in 55.4% of all EC cases with an OR of 8.80 compared with AV controls and an OR of 3.30 compared with PV controls.

Prior studies have evaluated rates of general gynecological cancer alarm symptoms in large population-based studies. Low et al. surveyed 911 women in the United Kingdom on the presence of gynecological cancer symptoms in the preceding 3 months, and found that 44% of respondents experienced at least one of the surveyed symptoms.<sup>5</sup> The most common symptoms reported were abdominal, back, or pelvic pain and increased abdominal size, and 21% of those surveyed reported three or more symptoms. With regard to potential EC-related symptoms, 1% reported postmenopausal bleeding and 5% reported abnormal vaginal discharge. Another survey conducted in a healthy Danish population showed about 80% of respondents experienced at least one gynecological alarm symptom in the preceding 4 weeks.<sup>6</sup> Again, with more nonspecific symptoms of tiredness, and abdominal bloating being the most common. Postmenopausal bleeding was reported in 2.3% of respondents, which was similar to the Low study. These studies demonstrate that the prevalence of more specific gynecological alarm symptoms is relatively rare in the general population. These data, however, are not able to address the relationship of these symptoms in those with disease versus those without disease, as there was no comparison to cancer patients.

When patients specifically present with the gynecological warning symptom of postmenopausal bleeding, several studies have investigated the associated risk of concurrent EC. These studies have shown the risk of EC to be 4%–8%.<sup>2–4,9</sup> Patient's age, BMI, presence of diabetes, and recurrent episodes of bleeding have also been shown to be predictors of EC in addition to postmenopausal bleeding.<sup>2,9–11</sup> A study by Salman et al., found age greater than 55, bleeding exceeding five pads per day, and recurrent episodes of bleeding significantly correlated with EC in postmenopausal women.<sup>10</sup> Patients with EC were also found to have, on average, a longer duration of bleeding (63.3 vs. 9.0 days,  $p < 0.01$ ). In our study, however, there was no significant difference in length of postmenopausal bleeding between the cases and controls.

TABLE 4. MULTIVARIATE ANALYSIS OF REPORTED SYMPTOM PREVALENCE

Outcome	Predictor	Annual visit			Problem visit		
		OR	95% CI	p	OR	95% CI	p
Irregular/unpredictable periods	Case	1.43	0.80–2.56	0.227	1.38	0.74–2.57	0.316
	Postmenopause	0.62	0.37–1.03	0.066	0.22	0.12–1.40	<0.001 <sup>a</sup>
	Obese	1.65	0.99–2.75	0.056	1.25	0.71–2.22	0.437
Bleeding between periods	Case	2.07	0.92–4.64	0.078	1.84	0.78–4.34	0.166
	Postmenopause	0.13	0.06–0.29	<0.001 <sup>a</sup>	0.09	0.04–0.20	<0.001 <sup>a</sup>
	Obese	1.12	0.56–2.24	0.746	1.30	0.61–2.76	0.500
Heavy periods	Case	1.60	0.89–2.87	0.116	1.49	0.79–2.80	0.216
	Postmenopause	0.69	0.42–1.16	0.161	0.28	0.15–0.53	<0.001 <sup>a</sup>
	Obese	1.85	1.11–3.06	0.017 <sup>a</sup>	2.19	1.23–3.88	0.007 <sup>a</sup>
Prolonged periods (>7 days)	Case	3.01	1.51–6.03	0.002 <sup>a</sup>	1.75	0.88–3.51	0.112
	Postmenopause	0.28	0.14–0.53	<0.001 <sup>a</sup>	0.19	0.10–0.37	<0.001 <sup>a</sup>
	Obese	1.31	0.71–2.43	0.392	1.46	0.78–2.72	0.233
Bleeding after sex	Case	3.02	1.04–8.75	0.042 <sup>a</sup>	0.99	0.39–2.54	0.986
	Postmenopause	0.25	0.09–0.69	0.008 <sup>a</sup>	0.25	0.11–0.59	0.002 <sup>a</sup>
	Obese	0.66	0.24–1.79	0.417	1.21	0.53–2.77	0.657
Bleeding after menopause	Case	29.46	12.02–72.18	<0.001 <sup>a</sup>	5.50	2.38–12.72	<0.001 <sup>a</sup>
	Obese	1.43	0.60–3.39	0.417	1.65	0.78–3.47	0.191
Pelvic pain	Case	4.35	2.33–8.12	<0.001 <sup>a</sup>	1.94	1.05–3.57	0.034 <sup>a</sup>
	Postmenopause	0.48	0.27–0.85	0.011 <sup>a</sup>	0.48	0.27–0.85	0.013 <sup>a</sup>
	Obese	2.43	1.42–4.16	0.001 <sup>a</sup>	1.52	0.87–2.63	0.138
Pelvic pressure	Case	7.05	3.39–14.66	<0.001 <sup>a</sup>	1.48	0.81–2.70	0.204
	Postmenopause	0.58	0.28–1.20	0.139	1.03	0.57–1.86	0.916
	Obese	1.43	0.72–2.87	0.309	1.28	0.72–2.26	0.396
Urinary frequency	Case	2.32	1.29–4.19	0.005 <sup>a</sup>	1.21	0.68–2.18	0.519
	Postmenopause	2.48	1.38–4.45	0.002 <sup>a</sup>	1.35	0.78–2.37	0.285
	Obese	1.87	1.07–3.26	0.028 <sup>a</sup>	1.53	0.89–2.63	0.123
Bowel habits	Case	1.40	0.77–2.56	0.275	1.11	0.60–2.04	0.744
	Postmenopause	1.30	0.74–2.30	0.363	0.96	0.53–1.72	0.884
	Obese	1.87	1.07–3.26	0.027 <sup>a</sup>	1.76	0.99–3.12	0.052
Discharge	Case	9.41	4.68–18.92	<0.001 <sup>a</sup>	3.32	1.79–6.15	<0.001 <sup>a</sup>
	Postmenopause	0.51	0.26–1.03	0.060	0.80	0.44–1.46	0.470
	Obese	1.63	0.85–3.11	0.138	1.22	0.68–2.18	0.499
Fatigue	Case	2.28	1.28–4.08	0.005 <sup>a</sup>	1.35	0.74–2.46	0.330
	Postmenopause	0.85	0.50–1.42	0.533	0.65	0.37–1.15	0.141
	Obese	1.73	1.04–2.87	0.035 <sup>a</sup>	1.82	1.05–3.14	0.032 <sup>a</sup>

All models included terms for obesity, menstrual status, and case–control status.  
<sup>a</sup>*p* < 0.008 to control for multiple testing on primary objective.

Vaginal discharge is also often referred to as a presenting symptom for EC, but there are few studies which quantify the level of risk. We found that 55.4% of cases reported the symptom of vaginal discharge. A prior study by Schmidt et al., evaluated the presence of intracavitary fluid in asymptomatic postmenopausal women finding 5.4% of these patients to have EC.<sup>12</sup> Among patients with EC, other sonographic findings such as mean thickened endometrium of greater than 12 mm were also found. Although, the association of intracavitary fluid and EC in asymptomatic women has been described, little is reported on the associated risk of abnormal vaginal discharge. Based on our study findings, in patients with persistent unexplained vaginal discharge, evaluation of the endometrial cavity with transvaginal ultrasound should be considered.

Obesity has been shown to be a prominent risk factor for the development of EC that increases proportionally with BMI.<sup>2,8,10</sup> Recently, the presence of metabolic syndrome, as well as each of its component factors (obesity, impaired

fasting glucose, high blood pressure, and high triglycerides), have also demonstrated an elevated risk for EC.<sup>13</sup> Those with an elevated BMI have also been found, in one study, to have an earlier onset of disease with average diagnosis at 56 versus 67 years in those with a normal BMI.<sup>14</sup> Given this association, it is possible that obesity may alter the symptom profile of patients with EC. In our study, obese women were more likely to report heavy menses in the PV group than nonobese participants. However, when the presence of heavy menses was compared among obese cases and obese PV controls, there was no difference seen in the prevalence of heavy menses. This signifies that the symptom of heavy menses is reflective of obesity itself and not of disease status. In an obese patient presenting with heavy menses, her chance of EC is not increased from baseline, but still warrants further evaluation.

Although the association of obesity and EC is well known among the medical community, public knowledge is more

limited. Previously, our group has shown that only 42% of women were aware that obesity affected EC risk, regardless of their individual BMIs.<sup>15</sup> In addition, public knowledge of EC-related symptoms was limited. By better characterizing the prevalence of such symptoms, as done in this study, physicians will have more informed tools in which to educate their patients. Additionally, public health initiatives can be directly targeted to women with postmenopausal bleeding and abnormal vaginal discharge who are at increased risk.

The main strength of this study is the comparison between symptoms in healthy patients to those experienced in EC cases. Additionally, patients were questioned about their symptoms at the time of their cancer diagnosis or gynecological visit. Hopefully, this short interval helped to reduce recall bias, although, there is likely still some component of this. Limitations include differences in demographic factors such as age, BMI, menopausal status, and oral contraceptive use. This was also an investigator-developed survey that was not previously validated.

### Conclusions

Our study reinforces the clinically observed association of postmenopausal bleeding and EC, as well as, highlighting the strong association of abnormal vaginal discharge and EC. Patients presenting with such symptoms require prompt evaluation and gynecological referral, and particularly, the symptom of abnormal vaginal discharge should not be overlooked.

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### Author Disclosure Statement

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### References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015;65:5–29.
2. Burbos N, Musonda P, Duncan TJ, Crocker SG, Morris EP, Nieto JJ. Estimating the risk of endometrial cancer in symptomatic postmenopausal women: A novel clinical prediction model based on patients' characteristics. *Int J Gynecol Cancer* 2011;21:500–506.
3. Bachmann LM, ter Riet G, Clark TJ, Gupta JK, Khan KS. Probability analysis for diagnosis of endometrial hyperplasia and cancer in postmenopausal bleeding: An approach for a rational diagnostic workup. *Acta Obstet Gynecol Scand* 2003;82:564–569.
4. Smith PP, O'Connor S, Gupta J, Clark TJ. Recurrent postmenopausal bleeding: A prospective cohort study. *J Minim Invasive Gynecol* 2014;21:799–803.
5. Low EL, Simon AE, Waller J, Wardle J, Menon U. Experience of symptoms indicative of gynaecological cancers in UK women. *Br J Cancer* 2013;109:882–887.
6. Balasubramaniam K, Ravin P, Larsen PV, Sondergaard J, Jarbol DE. Specific and unspecific gynecological alarm symptoms—Prevalence estimates in different age groups: A population-based study. *Acta Obstet Gynecol Scand* 2014; 94:191–197.
7. Astrup K, de Fine Olivarius N. Frequency of spontaneously occurring postmenopausal bleeding in the general population. *Acta Obstet Gynecol Scand* 2004;83:203–207.
8. Brinton LA, Berman ML, Mortel R, et al. Reproductive, menstrual, and medical risk factors for endometrial cancer: Results from a case-control study. *Am J Obstet Gynecol* 1992;167:1317–1325.
9. Gredmark T, Kivert S, Havel G, Mattsson LA. Histopathological findings in women with postmenopausal bleeding. *Br J Obstet Gynaecol* 1995;102:133–136.
10. Salman MC, Bozdag G, Dogan S, Yuce K. Role of postmenopausal bleeding pattern and women's age in the prediction of endometrial cancer. *Aust NZ J Obstet Gynaecol* 2013;53:484.
11. Feldman S, Cook F, Harlow BL, Berkowitz RS. Predicting endometrial cancer among older women who present with abnormal vaginal bleeding. *Gynecol Oncol* 1995;56:376–381.
12. Schmidt T, Nawroth F, Breidenbach M, Hoopman M, Mallmann P, Valter MM. Differential indication for histological evaluation of endometrial fluid in postmenopause. *Maturitas* 2005;50:177–181.
13. Trabert B, Wentzensen N, Felix AS, Yang HP, Sherman ME, Brinton LA. Metabolic syndrome and risk of endometrial cancer in the United States: A study in the SEER-Medicare linked database. *Cancer Epidemiol Biomarkers Prev* 2015;24:261–267.
14. Nevadunsky NS, Arsdale AV, Strickler HD, et al. Obesity and age at diagnosis of endometrial cancer. *Obstet Gynecol* 2014;124:300–306.
15. Soliman PT, Bassett RL, Wilson EB, et al. Limited public knowledge of obesity and endometrial cancer risk. *Obstet Gynecol* 2008;112:835–842.

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