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Association between body mass index and surgical menopausal symptoms in patients with early stage endometrial cancer

James C. Cripe [a,*], Tommy R. Buchanan Jr [a], Lindsay M. Kuroki [a], Leping Wan [a], Kathryn A. Mills [a], Leslie Massad [a], Andrea R. Hagemann [a], Katherine C. Fuh [a], David G. Mutch [a], Matthew A. Powell [a], Koji Matsuo [b], Premal H. Thaker [a]

[a] Washington University School of Medicine St. Louis, St Louis, MO, USA
[b] Keck School of Medicine of USC, Los Angeles, CA, USA

HIGHLIGHTS

- We describe the relationship of BMI with menopausal symptoms in women undergoing oophorectomy for endometrial cancer.
- Women with a BMI >40 had significantly less menopausal symptoms than women with BMI <30.
- Menopausal symptom type did not differ in relation to BMI.
- These data have not been previously documented and may impact preoperative counseling of patients.

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ABSTRACT

Objectives. Premenopausal women may undergo surgical menopause after staging for their endometrial cancer. Our aim was to determine the association between body mass index (BMI) and surgical menopausal symptoms.

Methods. We report a retrospective review of endometrial cancer patients whom underwent menopause secondary to their surgical staging procedure. Symptoms were classified as severe if treatment was prescribed, or mild if treatment was offered, but declined. Univariate analysis was performed with ANOVA and Chi-square tests as appropriate. Relative risks (RR) were generated from Poisson regression models.

Results. We identified 166 patients in whom the BMI (kg/m^2) distribution was as follows: 33 (19.9%) had BMI <30, 49 (29.5%) had BMI 30–39.9, 50 (30.1%) had BMI 40–49.9, and 34 (20.5%) had BMI ≥50. There were no differences in race, age, or adjuvant treatment among the groups. Overall, 65 (39.2%) women reported symptoms of surgical menopause, including 19 (11.4%) mild and 46 (27.7%) severe. Symptom type did not differ by BMI; however, the prevalence of severe menopausal symptoms decreased with increasing BMI: <30 (45.5%), 30–39.9 (30.6%), 40–49.9 (22%), and ≥ 50 (14.7%); $P = 0.002$. Multivariate analysis confirmed that symptom prevalence decreased with increasing BMI. Compared to women with a BMI of <30, those with a BMI 40–49.9 (RR = 0.39, 95% CI: 0.17–0.87) or ≥ 50 (RR = 0.24, 95% CI: 0.08–0.70) were significantly less likely to experience menopausal symptoms.

Conclusions. Women younger than 50 with BMI >40 and stage I endometrial cancer are significantly less likely than women with BMI <30 to experience menopausal symptoms after oophorectomy. This information may assist in peri-operative counseling.

1. Introduction

The incidence of endometrial cancer has increased by >50% over the last ten years and will affect a projected 63,230 women in 2018 [1]. This steady upward trend is partially related to the increasing obesity epidemic affecting 36.5% of adults in the United States [2]. Not only is endometrial cancer more common, but also it is affecting premenopausal women more frequently [3].

The 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system includes surgical removal of uterus, tubes, and ovaries with lymphadenectomy indicated depending on pre-operative and intra-operative findings [4]. Ovarian conservation remains controversial despite several national database studies suggesting this does not adversely affect survival in women with early stage endometrial

* Corresponding author at: Division of Gynecologic Oncology, Washington University School of Medicine, St. Louis, MO, USA.
E-mail address: jccripe@wustl.edu (J.C. Cripe).

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cancer [5–7]. Given the rising prevalence of endometrial cancer among premenopausal women, surgical menopause is becoming increasingly problematic when caring for these women.

Symptoms of surgical menopause may negatively impact quality of life and include vaginal dryness, mood changes, sleep disturbances, low libido, and most frequently vasomotor symptoms [8]. Data show that over a third of patients may be reluctant to undergo oophorectomy due to the possibility of immediate menopausal symptoms and the complexities of hormone replacement [9].

Multiple factors such as tobacco use, albumin levels, and antidepressant use have been associated with the frequency and severity of menopausal symptoms [8,10,11]. Although high body mass index (BMI, reported as kg/m^2) has been suggested to increase vasomotor symptoms during menopause, it is unknown whether BMI is associated with risk of surgical menopausal symptoms in patients who undergo oophorectomy as part of endometrial cancer staging [12]. To provide information to help surgeons and patients decide on an appropriate treatment strategy, our aim was to assess the association between BMI and menopausal symptoms after oophorectomy for early-stage endometrial cancer among women who are 50 years old or younger.

2. Materials and methods

After approval by the Washington University Human Research Protection office (#201612038), a cross-sectional review of surgically staged EC patients from 1/1/2000–12/31/2014 was performed from our billing records. All patients within that time frame were included who had endometrial endometrioid adenocarcinoma, stage I disease, age < 50 years, removal of both ovaries at the time of staging, and no previously documented menopausal symptoms or hormone replacement usage.

Menopausal symptoms were documented in the medical record via a patient's self-symptom assessment intake form presented and filled out by all patients seen in clinic, as well as the encounter's documented progress note. Abstracted symptoms included vasomotor symptoms, mood changes, fatigue/sleep disturbances, or sexual dysfunction/vaginal dryness. These symptoms were recorded if they occurred within 12 weeks post-operatively. This time point was set arbitrarily to contain all patients postoperative visit as some were not seen until 8–11 weeks after their surgery. Symptoms were qualitatively classified as severe if they were both present and had a treatment prescribed, mild if present but had declined treatment, or none, if no symptoms were present. Nonprescription medications such as black cohosh, soy, or the like were unable to be captured.

Univariate analysis was performed with ANOVA and Chi-square when appropriate. Relative risks (RR) were generated from Poisson regression models. Covariates for multivariate analysis included age, BMI, beta blocker use, and preoperative antidepressant use. Only 8 patients were smokers and there was not interaction on statistically modeling. A *P*-value of <0.05 was considered statistically significant. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all statistical tests.

3. Results

We identified 188 patients who underwent surgical management and were confirmed to have had stage I endometrial carcinoma. After exclusion of patients for loss to follow-up and/or ovarian conservation, 166 were evaluable with a median follow-up of 55.2 months. Mean age was 42.5 years, and mean BMI was 40.7. The majority of patients were white ($n = 140$, 84.3%). All patients underwent hysterectomy; 163 had bilateral salpingo-oophorectomy, and 3 had previous unilateral salpingo-oophorectomy and underwent completion unilateral salpingo-oophorectomy. Pelvic and para-aortic lymphadenectomy were performed in 53.0% and 46.4% of patients, respectively. Adjuvant chemotherapy and/or radiation only occurred in five patients (3.0%). Twenty-six patients were noted to have used selective serotonin reuptake inhibitors (SSRIs)/serotonin-norepinephrine reuptake inhibitors (SNRIs) pre-operatively, and only eight patients reported tobacco use. Table 1 lists clinico-demographic factors of the cohort.

Overall, 46 (27.7%) patients reported menopausal symptoms; 19 (11.4%) had mild symptoms, and 46 (27.7%) had severe symptoms. The most common symptom was vasomotor symptoms (78.5%), followed by sexual dysfunction/vaginal dryness (33.8%), mood changes (16.9%), and fatigue/sleep disturbances (9.2%).

The BMI distribution among patients was as follows: 33 (19.9%) had BMI <30, 49 (29.5%) had BMI 30–39.9, 50 (30.1%) had BMI 40–49.9, and 34 (20.5%) had BMI ≥50. There was no difference in race, age, or adjuvant treatment among these BMI groups. Symptom type did not differ by BMI; however, the prevalence of severe menopausal symptoms was inversely related to BMI: <30 (45.5%), 30–39.9 (30.6%), 40–49.9 (22%), and ≥50 (14.7%); $P = 0.005$ (Fig. 1). After controlling for age, pre-operative use of SSRIs/SNRIs/ and beta blockers, multivariate analysis confirmed that symptom prevalence decreased with increasing BMI. Specifically, compared to women with a BMI of <30, those with a BMI 40–49.9 (RR = 0.39, 95% CI: 0.17–0.87) or ≥50 (RR = 0.24, 95% CI: 0.08–0.70) were significantly less likely to experience menopausal symptoms (Table 2).

The treatments prescribed for severe symptoms included systemic estrogen ($n = 12$, 26.0%), vaginal estrogen ($n = 10$, 21.7%), and SSRI/SNRI ($n = 24$, 52.2%). Non-hormonal and systemic estrogen treatment rates did not vary by BMI; however, vaginal estrogen was recommended more frequently in patients with a BMI <40 ($P = 0.01$).

Consistent with the favorable prognostic factors of our cohort, recurrent disease was infrequent, and occurred in only 4 (2.4%) patients; 2 patients had vaginal apex lesions and 2 had pelvic sidewall masses. Salvage occurred in 3 (75%) of the recurrences, and 1 patient died of

Table 1
Clinicodemographic factors.

BMI	<30 ($n = 33$)		30–39.9 ($n = 49$)		40–49.9 ($n = 50$)		≥50 ($n = 34$)		*P*-value
Mean age (yr)	44.5 ± 3.6		42.1 ± 5.1		42 ± 5.1		42.1 ± 6.9		0.14
Race									
White	29	87.9%	40	81.6%	42	84.0%	29	85.3%	0.89
Black	3	9.1%	7	14.3%	4	8.0%	4	11.8%	0.76
Asian	1	3.0%	1	2.0%	0	0.0%	0	0.0%	0.52
Other	0	0.0%	1	2.0%	4	8.0%	1	2.9%	0.83
Stage									
IA	32	97.0%	46	93.9%	46	92.0%	33	97.1%	0.90
IB	1	3.0%	3	6.12%	4	8.0%	1	2.9%	0.69
Adjuvant therapy									
Chemo	1	3.0%	0	0.0%	0	0.0%	0	0.0%	0.26
RT	1	3.0%	0	0.0%	0	0.0%	0	0.0%	0.26
Chemo/RT	0	0.0%	2	4.1%	1	2.0%	0	0.0%	0.45
Severity of menopausal symptoms									
Severe	15	45.5%	15	30.6%	11	22.0%	5	14.7%	**0.005**
Mild	3	9.1%	7	14.3%	6	12.0%	3	8.8%	0.16
None	15	45.5%	27	55.1%	33	66.0%	26	76.5%	**0.003**
Symptom type									
Hot flashes	13	72.2%	16	72.7%	15	88.2%	7	87.5%	0.54
Mood	2	11.1%	6	27.3%	2	11.8%	1	12.5%	0.47
Fatigue/sleep disturbance	1	5.6%	3	13.6%	2	11.8%	0	0.0%	0.63
Sexual dysfunction/vaginal dryness	7	38.9%	10	45.5%	3	17.7%	2	25.0%	0.28
Recommended treatment of menopausal symptoms									
Anti-depressant	6	40.0%	9	60.0%	6	54.6%	3	60.0%	0.55
Vaginal estrogen	5	33.3%	4	26.7%	0	0.0%	1	20.0%	**0.01**
Systemic estrogen	4	26.7%	2	13.3%	5	45.5%	1	20.0%	0.34

BMI: body mass index (kg/m^2), chemo: chemotherapy, RT: radiation therapy, yr: years.
Bold values indicates statistically significance at $P < 0.05$.

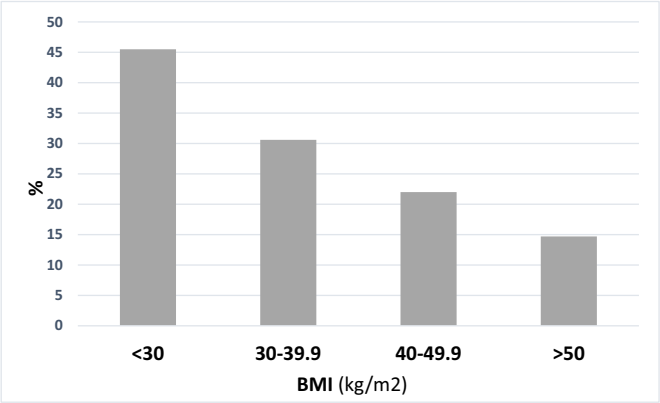

Fig. 1. Menopausal symptom prevalence.

disease. Time to recurrence was 3, 5, 11, and 38 months after surgery. Treatment regimens for recurrent disease included a combination of chemotherapy and radiation. Only 1/3 salvaged patients were treated with systemic estrogen therapy. Lastly, there were two patients with intercurrent deaths, neither of which were on hormonal therapy.

4. Conclusions

Our findings suggest that, among women aged 50 or younger who underwent oophorectomy as part of surgical treatment for endometrial cancer, BMI is inversely related to complaints of menopausal symptoms. We identified a precipitous decline in the frequency of symptoms ranging from 45.5% in women with BMI of <30 to only 14.7% in women with BMI >50, but quality of menopausal symptoms did not vary by BMI. Previously reported data is limited to patients undergoing natural menopause and those women without an underlying malignancy, but have suggested patients with a high BMI have significantly more vasomotor symptoms than women with a lower BMI [13]. An Australian study identified patients with BMI >35 have lower estradiol and estrone than those with BMI <25 [14]. Our study cohort is unique as compared to the women included in prior studies for three reasons. First, our cohort underwent surgical menopause instead of natural menopause. Second, the mean BMI of our cohort was 40, which is substantially higher than that reported in previous studies. Third, our cohort is composed of women with endometrial cancer. Thus, by focusing on premenopausal women with endometrial cancer, we may have selected for obese women with increased peripheral conversion of androgen to estrogen.

Menopausal symptoms cause a significant decrease in overall quality of life by limiting work productivity, impairing daily activities, substantially increasing healthcare utilization [15], and potentially negatively affecting personal relationships by impairing sexual function [16]. Additionally, menopausal symptoms may portend adverse cardiovascular outcomes, reduced bone health, memory loss, and increased risk of stroke and colorectal cancers [7,17–20]. Vasomotor symptoms alone are associated with elevated systolic blood pressure and increased total cholesterol [21]. Age at menopause is critically important, as each year's delay in menopause is associated with a 2% decrease in overall mortality [22]. Our data suggest that the prevalence of menopausal symptoms decreases with increasing BMI. However, a lack of menopausal symptoms may not translate to the absence of adverse cardiovascular outcomes, especially given the known detrimental cardiac effects of obesity. Additionally, women with morbid obesity, who have a suspected increase in peripheral estrogen, may not be affected by oophorectomy.

Table 2
Multivariate analysis: factors associated with menopausal symptoms.

	Relative risk	95% confidence interval
BMI		
<30	Reference	Reference
30–39.9	0.54	0.26–1.14
40–49.9	0.39	0.17–0.87
≥50	0.24	0.08–0.70
Age	0.93	0.89–0.98

BMI: body mass index (kg/m^2).

The gold standard treatment for menopausal symptoms is estrogen replacement therapy. This can help women with vasomotor symptoms, who have significantly lower levels of estradiol than those without symptoms [23]. However, although estrogen effectively manages symptoms, it has not been shown to change the long-term cardiovascular impact of menopause. Additionally, in endometrial cancer patients, the effect of estrogen therapy on cancer recurrence is a concern. The Gynecologic Oncology Group opened protocol 137, a randomized controlled trial of estrogen vs. placebo in patients with stage I and II endometrial cancer. A total of 1236 patients were enrolled with a median follow up of 35.7 months. This study had a preponderance of low risk endometrial cancers with a median age of 57 years and 88% of these were stage IA. Deeply invasive tumors or grade 3 lesions accounted for only 8% and 7% respectively. Thus, the rate of recurrence was low (2.1%), this study was closed early secondary to the concerns raised in the Women's Health Initiative study that estrogen therapy increases the risk of breast cancer and heart disease. The insufficient enrollment and premature closure prevented the author's ability to conclusively refute or support the safety of exogenous estrogen with regard to risk of endometrial cancer recurrence [24,25]. Lastly, local estrogen may be safely administered to low risk endometrial cancer survivors, however this may only effect vulvo-vaginal symptoms [26].

The decision to proceed with oophorectomy is complicated and impacted by the patient's malignancy as well as BMI. Given the concerns raised in the Women's Health initiative, as well as findings that ovarian conservation does not reduce overall survival in premenopausal endometrial cancer patients [5–7,25], it may be prudent to conserve ovaries instead of prescribing estrogen therapy after oophorectomy. However, this is with the caveat that patients have had genetic predispositions such as Lynch syndrome excluded. Conversely, oophorectomy may be supported by the suboptimal imaging that radiologists face regarding the monitoring of these patient's ovarian pathology. Radiology departments are having increasing difficulties transporting, accommodating, and obtaining adequate image quality in obese patients [27]. This is compounded by the fact that 50% of patients with polycystic ovarian syndrome are obese, necessitating further imaging [28]. Careful consideration of the risks and benefits is necessary and should take the patients social and medical into account.

A strength of our study is found in that our findings fill a void in the literature surrounding surgical menopause in endometrial cancer. We provide a comprehensive and qualitative analysis of one institution's experiences with surgical menopause in endometrial cancer patients aged 50 or younger. Additionally, our analysis controlled for factors associated with menopausal symptoms including SSRI/SNRI treatment for psychiatric complaints before surgery, and smoking. Nonetheless, we note several limitations of our study. First, our study relied on retrospective analysis of patient accounts of symptoms within the medical record and does not have long term follow-up. However, we would not expect underreporting to occur at a higher frequency among any specific group of patients with respect to BMI. Second, we recognize possible confounders (over-the-counter remedies), such as personal biases that may increase or decrease a patient's acceptance of treatment for menopausal symptoms. Third, our population was rather homogenous (84% white), and the results may not apply to other racial and ethnic groups.

In conclusion, when planning surgery for endometrial cancer in premenopausal women, the patient and her physician should discuss how women with a BMI >40 may have fewer side effects of surgical menopause than premenopausal women without obesity. Further research

should be undertaken to determine the long-term health impacts of high BMI and menopausal symptoms after surgery for endometrial cancer.

Disclosures

The authors report no conflict of interest or relevant disclosures.

Author contributions

1. J.C. Cripe, M.D.: lead author who designed the study, performed the majority of data collection and entry, and assisted with manuscript writing and editing.
2. T.R. Buchanan, M.D.: performed data collection and assisted with manuscript writing and revisions.
3. L.M. Kuroki, M.D., M.S.C.I: assisted with manuscript writing and editing.
4. L. Wan, M.P.H: assisted with statistical analysis and approval of final submitted version.
5. K.A. Mills: Assisted with manuscript writing and revisions.
6. AR Hagemann, M.D., M.S.C·I: assisted with manuscript revisions and approval of final submitted version.
7. L.S. Massad, M.D.: assisted with manuscript revisions and approval of final submitted version
8. K.C. Fuh, M.D., Ph.D.: assisted with manuscript revisions and approval of final submitted version.
9. D.G. Mutch, M.D.: assisted with manuscript revisions and approval of final submitted version.
10. M.A. Powell, M.D.: assisted with manuscript revisions and approval of final submitted version.
11. K. Matsuo, M.D.: assisted with manuscript revisions and approval of final submitted version
12. P.H. Thaker, M.D., M.S.: lead author who helped with initial study design. Assisted with manuscript revisions and approval of final submitted version.

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