GYNECOLOGY

Body mass index trumps age in decision for endometrial biopsy: cohort study of symptomatic premenopausal women

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BACKGROUND: Clinical guidelines recommend that women with abnormal uterine bleeding with risk factors have an endometrial biopsy to exclude hyperplasia or cancer. Given the majority of endometrial cancer occurs in postmenopausal women, it has not been widely recognized that obesity is a significant risk factor for endometrial hyperplasia and cancer in young, symptomatic, premenopausal women.

OBJECTIVE: We sought to evaluate the effect of body mass index on risk of endometrial hyperplasia or cancer in premenopausal women with abnormal uterine bleeding.

STUDY DESIGN: This was a retrospective cohort study in a single large urban secondary women's health service. Participants were 916 premenopausal women referred for abnormal uterine bleeding of any cause and had an endometrial biopsy from 2008 through 2014. The primary outcome was complex endometrial hyperplasia (with or without atypia) or endometrial cancer.

RESULTS: Almost 5% of participants had complex endometrial hyperplasia or cancer. After adjusting for clinical and demographic factors, women with a measured body mass index $\geq$30 kg/m^2 were 4 times more likely to develop complex hyperplasia or cancer (95% confidence interval, 1.36–11.74). Other risk factors were nulliparity (adjusted odds ratio, 3.08; 95% confidence interval, 1.43–6.64) and anemia (adjusted odds ratio, 2.23; 95% confidence interval, 1.14–4.35). Age, diabetes, and menstrual history were not significant.

CONCLUSION: Obesity is an important risk factor for complex endometrial hyperplasia or cancer in premenopausal women with abnormal uterine bleeding who had an endometrial biopsy in a secondary gynecology service. As over half of women with the outcome in this study were age <45 years, deciding to biopsy primarily based on age, as currently recommended in national guidelines, potentially misses many cases or delays diagnosis. Body mass index should be the first stratification in the decision to perform endometrial biopsy and/or to refer secondary gynecology services.

Key words: biopsy, endometrial hyperplasia, endometrial neoplasms, menorrhagia, menstruation disturbances, obesity, premenopause

Introduction

Abnormal uterine bleeding (AUB) such as heavy or irregular vaginal bleeding of any cause, is the most common reason for referral to a gynecologist,[1,2] and frequently leads to an invasive diagnostic test such as endometrial biopsy or hysteroscopy. In a large study of premenopausal women with AUB referred for an endometrial biopsy, the prevalence of complex endometrial hyperplasia or cancer was 3.0%.[3]

Endometrial hyperplasia is a precursor to endometrial cancer and is thought to result from persistent, prolonged, unopposed estrogenic stimulation of the endometrium, the most common cause being a succession of anovulatory cycles.[4] Anovulation occurs most often during the perimenopause, or in women with polycystic ovarian syndrome or obesity.[4] An important distinction in the evaluation of hyperplasia is whether or not nuclear atypia is present. Women with complex hyperplasia with atypia are at risk of progression to endometrial cancer and as many as 28% of cases will progress over time to cancer and up to 43% of cases have unrecognized concurrent carcinoma at the time of biopsy.[5,6]

Commonly recognized risk factors for endometrial cancer include age, obesity, nulliparity, infertility, and late-onset menopause. Family history of hereditary nonpolyposis colorectal cancer is another risk factor. Diabetes and hypertension are frequently associated with endometrial cancer, while smoking and use of combined oral contraceptive pill are thought to be protective.[7]

Over the past 2 decades there has been global recognition of increasing levels of obesity.[8] At the same time, there is epidemiological evidence of increased incidence of endometrial cancer. Several systematic reviews have shown an association between obesity and endometrial cancer.[9-12] However, given that the majority of endometrial cancer occurs in postmenopausal women, it has not been widely recognized that obesity is a significant risk factor for endometrial hyperplasia and cancer in young, symptomatic, premenopausal women.[13]

Developing a greater understanding of the leading risk factors for premenopausal women would lead to improved clinical pathways from primary to secondary care and improved targeting of invasive diagnostic testing. The objective of the current study was to evaluate the association of body mass index (BMI) and endometrial complex hyperplasia or cancer in premenopausal women with AUB who had an endometrial biopsy, adjusting for clinical and demographic factors. We hypothesized that obese women would be more likely to have complex hyperplasia or cancer compared to normal-weight women.

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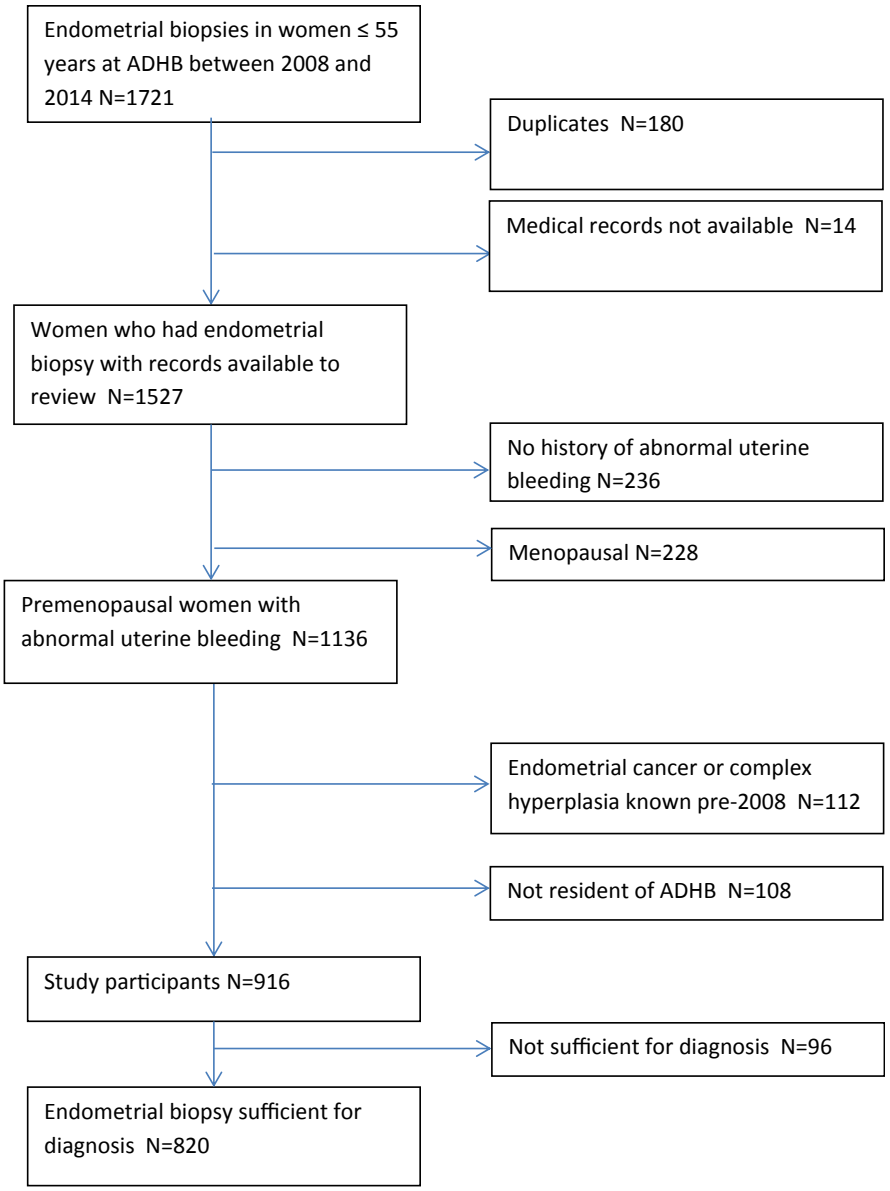
FIGURE 1
Flow chart of participants



Flow diagram of participant selection. Some participants may have had >1 exclusion criteria.
ADHB, Auckland District Health Board.
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Materials and Methods

This was a retrospective cohort study including women age ≤55 years who had an endometrial biopsy at Auckland District Health Board from 2008 through 2014. Women were included if they had a history of AUB (clinical diagnosis by the referring doctor, including structural and nonstructural causes) and were not menopausal (either recorded as menopausal in the clinical record, or amenorrhea ≥6 months, or serum follicle-stimulating hormone level >20 IU/L). Women were excluded if they were known prior to 2008 to have had endometrial cancer. Women who were not residents of Auckland District Health Board were also excluded due to the referral pattern of surrounding district health boards to Auckland for tertiary cancer services. The primary study outcome was histologic diagnosis of endometrial biopsy of complex hyperplasia, complex atypical hyperplasia, or endometrial cancer, as stated in the pathology report.[14]

Participants were identified from the hospital laboratory database of all inpatient and outpatient samples. The National Health Identifier was used to directly link with the hospital electronic medical records and clinical and demographic data were collected. The following clinical variables were collected: age, BMI, parity, self-reported use of hormone therapy, menstrual history, infertility (>12 months), medical history (smoking, diabetes, breast cancer, colorectal cancer), and family history (breast, colorectal, or endometrial cancer). Recent investigations (hemoglobin, pelvic ultrasound scan) and subsequent hysterectomy were also recorded.

Endometrial biopsy was performed by Pipelle (Pipelle De Cornier, Laboratoire CCD, Paris, France), sharp curettage, or both. If >1 biopsy was performed within 6 months, the one resulting in the most serious diagnosis was considered the final outcome. If a hysterectomy was performed within 6 months of the biopsy, the hysterectomy histology was considered the final outcome. The exception to this was in the setting where the biopsy reported hyperplasia, there was clear documentation that the patient was treated with progestogen in the interim, and the hysterectomy histology was normal. In that case, due to the known effectiveness of progestogen in treating endometrial hyperplasia,[15] then the original biopsy result was considered the final outcome.

Self-reported ethnicity was collected at hospital registration with a standard New Zealand (NZ) census question. The concept of ethnicity adopted by Statistics NZ is a social construct of group affiliation and identity. The present statistical standard for ethnicity states that ethnicity is the ethnic group or groups that people identify with or believe they belong to; thus, ethnicity is self-perceived and people can belong to >1 ethnic

group.[16] If >1 ethnicity was reported, it was prioritized using the NZ Ministry of Health protocol.[17]

Height and weight measurements used for calculating BMI were measured within 1 year of biopsy. Standard World Health Organization criteria were used to categorize BMI (normal 18.5–24.9 kg/m^2, overweight 25–29.9 kg/m^2, obese ≥30 kg/m^2).[18] Socioeconomic status was estimated using the NZ deprivation score based on recorded maternal place of residence.[19] Deprivation centiles (1–10) were condensed into quintile scores from 1 (least deprived) to 5 (most deprived).

Data analysis

We determined the overall incidence of endometrial complex hyperplasia or cancer and compared crude rates across each clinical and demographic variable using simple logistic regression. Odds ratios (OR) and 95% confidence limits were estimated for each of these associations. In all cases, a *P* value of .05 was considered statistically significant. Multivariable analysis using logistic regression was performed to assess the independent association between each variable and the outcome. Included in the multivariable model were BMI and age (for a priori reasons) and those factors significantly associated with the outcome on univariate analysis.

As ethnicity and BMI are highly correlated in this population, only 1 of these variables was able to be retained in the multivariable model. We chose BMI as: (1) it meant a smaller number of degrees of freedom (2 vs 5), and (2) the use of BMI is more generalizable to other populations. Endometrial thickness was missing in one third of participants, hence we produced multivariable models both excluding and including endometrial thickness. Further sensitivity analysis was performed using the outcome of complex atypical hyperplasia or cancer. Data analysis was performed in software (SAS, Version 9.4; SAS Institute Inc, Cary, NC).

Based on a power of 80%, a level of significance of 5%, and an estimated prevalence of complex hyperplasia or cancer 3.0% and of obesity 30% (in the previous NZ study),[3] the current study with a sample of 840 subjects had the power to detect a relative risk of 1.89.

This study was approved on Oct. 5, 2012, by the University of Auckland Human Participants Ethics Committee (Ref. 8651).

TABLE 1
Characteristics of participants

	BMI <30		BMI ≥30	
	N = 465	%	N = 451	%
Demographic characteristics				
Age, y				
Mean ± SD	43.7 ± 6.4		42.0 ± 7.2	
<40	87	18.7	137	30.4
40–44	139	29.9	119	26.4
45–49	163	35.0	137	30.4
50–55	73	15.7	57	12.6
Ethnicity				
European	158	34.0	82	18.2
Māori	36	7.7	80	17.8
Pacific	18	3.9	213	47.3
Indian	83	17.8	35	7.8
Asian	112	24.1	22	4.9
Other	58	12.5	18	4.0
NZ deprivation score				
1–2	44	12.6	16	4.9
3–4	65	18.7	52	15.9
5–6	78	22.4	56	17.1
7–8	87	25.0	88	26.9
9–10[a]	74	21.3	115	3
Weight, kg				
Mean ± SD	65.9 ± 10.2		104.8 ± 24.5	
Clinical characteristics				
Menstrual history				
Mean duration of AUB, y (mean ± SD)	3.4 ± 4.1		3.8 ± 5.4	
Menstrual cycle regularity				
Regular	203	44.7	157	35.4
Irregular	209	46.0	254	57.2
Menstrual cycle duration, d				
<7	211	47.0	170	38.6
7–14	83	18.5	78	17.7
>14	53	11.8	80	18.2
Intermenstrual bleeding				
Yes	131	28.8	82	18.6

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TABLE 1
Characteristics of participants *(continued)*

	BMI <30		BMI ≥30	
	N = 465	%	N = 451	%
Hormonal therapy (current, recent)				
COCP	29	6.2	15	3.3
Progestogen	112	24.1	170	37.7
Tamoxifen	3	0.6	2	0.4
Pregnancy history				
Nulliparity	69	14.8	67	14.9
Infertility	20	4.5	33	7.6
Medical history				
Diabetes	26	5.7	63	14.0
Breast cancer	8	1.7	7	1.6
Colorectal cancer	1	0.2	1	0.2
Smoking (current)	50	10.9	92	20.7
Family history of cancer				
Endometrial	10	2.2	14	3.1
Breast	21	4.5	24	5.3
Colorectal	19	4.1	10	2.2
Anemia				
Yes	148	32.9	202	46.6
Pelvic ultrasound scan				
Submucous fibroid	35	7.5	18	4.0
Polyp	33	7.1	32	7.1
Endometrial thickness, mm				
Mean	16.5 ± 44.6		26.0 ± 126.5	
≥12 mm	117	38.0	156	49.8

Proportion of women with missing characteristics: NZ deprivation score (26.3%); menstrual cycle regularity (10.1%) and duration (26.4%); intermenstrual bleeding (6.8%); hormonal therapy (8.4%); parity (11.4%); infertility (21.6%); smoking (15.5%); anemia (9.3%); and endometrial thickness (32.2%).

AUB, abnormal uterine bleeding; *BMI*, body mass index; *COCP*, combined oral contraceptive pill; *NZ*, New Zealand.

[a] Lowest fifth of socioeconomic status.

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Results

The study cohort comprised 916 women who met the inclusion and exclusion criteria (Figure 1). Half of the women were obese. Obese women were more likely to be <40 years old, of Māori and Pacific ethnicity, and residing in areas of high deprivation. Characteristics of participants are shown in Table 1.

In the whole cohort, 85% of women had a Pipelle, 22% had sharp curettage, and 7% had both. Endometrial biopsy results are shown in Table 2. Of 840 women with sufficient tissue for diagnosis, 41 women (4.9%) were diagnosed with endometrial complex hyperplasia, complex atypical hyperplasia, or cancer. This is significantly higher than the incidence reported in the previous NZ study ($P = .035$).

OR for the association of demographic and clinical factors with complex hyperplasia or cancer are shown in Table 3. Women of Indian and Pacific ethnicity had significantly higher odds of having complex hyperplasia or cancer compared to European women (OR, 3.72; 95% confidence intervals [CI], 1.07−13.00, and OR, 6.21; 95% CI, 2.11−18.32, respectively). A more in-depth investigation of the relationship of ethnicity to BMI found that we were unable to distinguish between Pacific ethnicity and BMI, due to the high prevalence of obesity in the Pacific sample (92.2%).

Other factors associated with an increased risk of complex hyperplasia or cancer were nulliparity (OR, 2.51; 95% CI, 1.25−5.05), anemia (OR, 2.38; 95% CI, 1.25−4.56), and thickened endometrium on ultrasound scan (OR, 4.04; 95% CI, 1.69−9.65). We assessed the relationship of age using a generalized additive model and found the relationship to be cubic in nature with the highest risk association with the youngest women (mid-20s to mid-30s) and the oldest women (Figure 2). The overall association of age fitted in this form did not quite reach statistical significance ($P = .063$). Diabetes, hypertension, and menstrual history showed no effect.

The multivariable analyses are found in Table 4. After adjusting for age, anemia, and nulliparity, obese women had significantly higher odds of having complex hyperplasia or cancer compared to women with normal BMI (adjusted OR, 4.00; 95% CI, 1.36−11.74), while overweight women showed no increased risk. Nulliparous women were at increased risk (adjusted OR, 3.08; 95% CI, 1.43−6.64), as were women with anemia (adjusted OR, 2.23; 95% CI, 1.14−4.35). Age remained nonsignificant.

In a sensitivity analysis including endometrial thickness in the model, the adjusted OR for the above variables did not change much, and women with endometrium thickness ≥12 mm had significantly higher odds of having complex hyperplasia or cancer (adjusted OR, 4.20; 95% CI, 1.58−11.15). In a sensitivity analysis including only complex atypical hyperplasia or cancer as the outcome, the point estimates of the OR did not differ in any meaningful way from those in Table 4 (data not shown).

Comment

This large retrospective cohort study has reported a 4.9% incidence of endometrial complex hyperplasia, complex atypical hyperplasia, or cancer in premenopausal women with AUB who underwent endometrial biopsy. Obese women were 4 times more likely than normal-weight women to have complex hyperplasia or cancer. Other significant risk factors were nulliparity, anemia, and thickened endometrium on ultrasound scan; age was not a significant risk factor.

The increased incidence of complex hyperplasia or cancer in our hospital from 3.0% (1995 through 1997)[3] to 4.9% (2008 through 2014) is most likely related to an increase in obesity in women in NZ from 21% in 1997 to 30% in 2013 through 2014.[20] Obesity rates in NZ are third highest of the Organization for Economic Co-operation and Development countries, close behind the United States, which is second highest.[21] In NZ, 71% of Pacific women are obese, compared to 48% of Māori women, 28% European, and 14% Asian.[20] Given the overall obesity rate in this study of 49%, and a univariate OR of 3.76, the population-attributable risk associated with obesity in this study is 48%. This shows the potential impact on complex hyperplasia or cancer that could be achieved by reducing obesity rates. These findings are also consistent with the increasing endometrial cancer rates from 2002 through 2012, from an age-standardized rate of 12.2 in 2002 to 16.2 per 100,000 in NZ,[22] and from 24.9–27.5 per 100,000 in the United States.[23]

Our findings confirm the increased risk of endometrial cancer with increased BMI in previously published reports.[9-11] In the only meta-analysis of endometrial cancer in women who were premenopausal at time of diagnosis, for the studies that reported on women with BMI ≥30 kg/m^2 the pooled OR was 5.25 (95% CI, 4.00–6.90).[12] None of these reviews included endometrial hyperplasia as an outcome.

The main strength of this study is its cohort design. This is the more appropriate and more robust study design to answer the question of risk factors for

TABLE 2
Results of endometrial biopsy where tissue sample was sufficient for diagnosis (N = 840)

	N	%
Endometrial adenocarcinoma	12	1.4
Complex hyperplasia with atypia	9	1.1
Complex hyperplasia without atypia	20	2.4
Disordered proliferative endometrium/prolonged proliferative phase/simple hyperplasia	172	20.5
Atrophy/inactive endometrium	109	13.0
Exogenous progesterone effect	68	8.1
Normal	350	41.7
Other, including metaplasia, polyp	100	11.9

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TABLE 3
Demographic and clinical factors associated with endometrial complex hyperplasia or cancer

	Cases, N, or mean (SD)	Controls, N, or mean (SD)	Odds ratio (95% confidence interval)
Demographic characteristics			
Age fitted as cubic term, y	42.0 (8.4)	42.9 (6.8)	$\chi^2 = 7.29$, $P = .063$
Ethnicity			
European	4	312	1.00
Asian	4	130	1.82 (0.45–7.38)
Indian	7	111	3.72 (1.07–13.00)
Māori	4	112	2.11 (0.52–8.58)
Pacific	22	209	6.21 (2.11–18.32)
NZ deprivation score [missing = 244]			
1–2	1	59	1.0
3–4	5	112	2.63 (0.30–23.04)
5–6	4	130	1.81 (0.20–16.58)
7–8	7	169	2.44 (0.29–20.26)
9–10	10	179	3.29 (0.41–26.26)
Body mass index			
<25 kg/m^2	6	251	1.00
25–29.9 kg/m^2	4	204	1.21 (0.34–4.38)
≥30 kg/m^2	31	420	3.76 (1.31–10.80)
Clinical characteristics			
Duration of AUB, y	4.6 (3.1)	3.5 (4.8)	1.04 (0.96–1.12)
Cycle regularity [missing = 21]			
Regular	12	348	1.00
Irregular	24	440	1.58 (0.78–3.21)

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TABLE 3
Demographic and clinical factors associated with endometrial complex hyperplasia or cancer *(continued)*

	Cases, N, or mean (SD)	Controls, N, or mean (SD)	Odds ratio (95% confidence interval)
Cycle length, d			
<7	17	364	1.00
7–14	4	157	0.55 (0.18–1.65)
>14	8	125	1.37 (0.58–3.25)
Intermenstrual bleeding [missing = 24]			
No	34	648	1.00
Yes	7	207	0.64 (0.28–1.48)
Current use of hormonal therapy			
No	29	599	1.00
Yes	12	277	0.90 (0.45–1.78)
Parity			
>0	29	752	1.00
0	12	124	2.51 (1.25–5.05)
Infertility			
No	36	791	
Yes	5	48	2.29 (0.86–6.10)
Diabetes [missing = 133]			
No	32	666	1.00
Yes	7	82	1.78 (0.76–4.15)
Smoking			
Never/non/past	37	725	1.00
Current	4	138	0.54 (0.19–1.57)
Family history of breast cancer			
No	37	818	1.00
Yes	4	42	2.11 (0.72–6.18)
Family history of colorectal cancer [missing = 92]			
No	32	692	1.00
Yes	1	28	0.77 (0.10–5.86)
Investigations			
Anemia			
No	16	518	1.00
Yes	24	326	2.38 (1.25–4.56)
Endometrial thickness			
<12 mm	7	341	1.00
≥12 mm	21	253	4.04 (1.69–9.65)

Numbers of women of "other" ethnicity, with personal history of breast or colorectal cancer, and with family history of endometrial cancer were too small to perform univariate analysis.

AUB, abnormal uterine bleeding; *NZ*, New Zealand.

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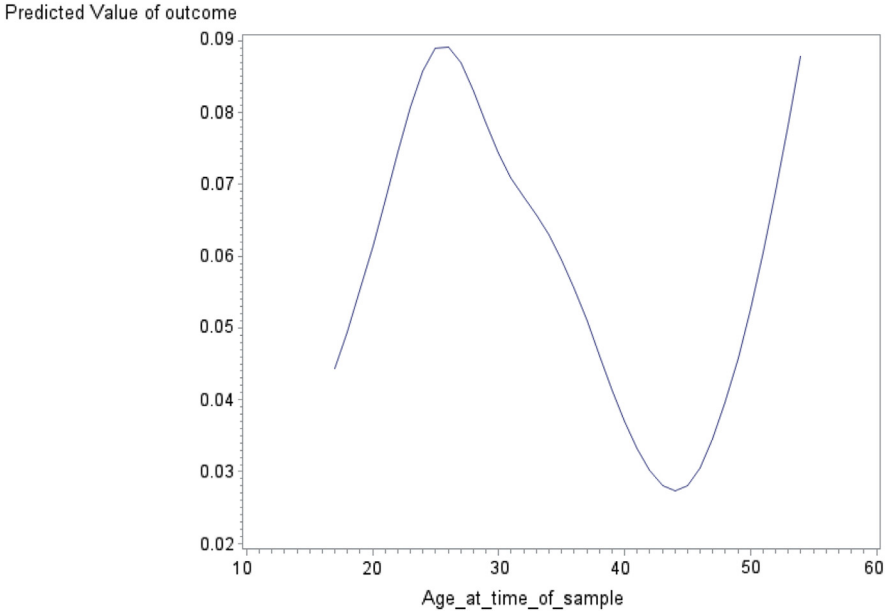
complex hyperplasia or cancer in premenopausal women presenting with AUB, rather than case-control design of evaluating premenopausal women with and without endometrial pathology to explore the association with obesity. BMI was the primary variable of interest, and was measured around the time of the biopsy, in contrast to many other studies where self-reported BMI was used, which is not as accurate.[24] In addition, we were able to adjust for several demographic and clinical variables known to be associated with the outcome. To our knowledge, this is the first cohort study of premenopausal women with AUB with biopsy-proven endometrial hyperplasia or cancer, comparing obese to nonobese women.

Limitations of this study include that data were collected retrospectively from the electronic medical records of women referred to a secondary gynecology service at a single urban hospital. Ideally, a prospective cohort study of women presenting with AUB in the community setting could be performed to determine the true incidence of complex hyperplasia or cancer, however, this would be challenging given the large number of practices that would be involved. As with all observational research, there may be unmeasured and unknown confounders not included in the analysis that could contribute to the findings. In addition, some variables found to be nonsignificant may be due to small numbers, for example, young healthy women are not usually screened for diabetes. The diagnosis of atypical complex hyperplasia has low reproducibility,[4] and histology was not reviewed by a pathologist for the purposes of this study; however, this makes our findings more generalizable, and further strengthens our argument to include BMI to stratify risk. These findings may not be generalizable to all women with AUB, rather only those referred to a gynecologist and who had an endometrial biopsy; in our setting, about one third of women referred for AUB had an endometrial biopsy. These findings may also not be generalizable to populations with a different ethnic mix, given different possible genetic risks. However, we believe these findings are

FIGURE 2
Distribution of age in women with endometrial complex hyperplasia or cancer



Generalized additive model showing risk of endometrial complex hyperplasia or cancer with age.

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generalizable to a population of women in a country with high rates of obesity, and similar pattern of referral from primary to secondary services.

These findings could be used to inform current guidelines for the investigation of women with AUB. The US and Canadian guidelines on AUB recommend biopsy in women age >45 years or >40 years, respectively, or in younger women with risk factors for endometrial cancer, including obesity.[25,26] The 2007 National Institute for Health and Care Excellence guidelines recommend biopsy if indicated, for example, in cases of persistent intermenstrual bleeding, or in women aged ≥45 years who experience treatment failure or ineffective treatment.[13] The 1998 NZ guidelines recommend that women age ≥45 years, or weight ≥90 kg, have an endometrial biopsy.[27] All of these guidelines could now be updated to suggest that endometrial biopsy be performed in women with BMI ≥30 kg/m^2 (or other clinical risk factors, eg, nulliparity or anemia).

Although age may be an important risk factor for endometrial cancer in perimenopausal and postmenopausal women, age does not appear in our study to be a risk factor in premenopausal women. Thus, we suggest that BMI be used as the primary deciding factor to further investigate AUB with an invasive test. In our study, the approach of using a BMI threshold, instead of age, would have reduced the number of women in our population needing biopsies by half. Another potential benefit is detecting endometrial complex hyperplasia or cancer in younger women at an earlier stage in disease, allowing for more conservative treatment. ■

TABLE 4
Multivariable model of risk factors for endometrial complex hyperplasia or cancer

	Adjusted odds ratios (95% confidence intervals)	Sensitivity analysis (including endometrial thickness[a])
BMI 25–29.9 kg/m^2	1.20 (0.31–4.62)	0.69 (0.11–4.41)
BMI ≥30 kg/m^2	4.00 (1.36–11.74)	4.19 (1.13–15.48)
Anemia	2.23 (1.14–4.35)	2.16 (0.91–5.12)
Nulliparity	3.08 (1.43–6.64)	4.95 (1.89–12.92)
Endometrial thickness ≥12 mm		4.20 (1.58–11.15)
Age as cubic form	χ^2 (df = 3) = 5.88, P = .12	χ^2 (df = 3) = 6.30, P = .10
Area under curve	75.5%	84.0%

BMI, body mass index; *df*, degrees of freedom.

[a] Endometrial thickness missing in 32% of women.

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