GYNECOLOGY

Prevalence, characteristics, and risk factors of occult uterine cancer in presumed benign hysterectomy

Vrunda B. Desai, MD; Jason D. Wright, MD; Cary P. Gross, MD; Haiqun Lin, MD, PhD; Francis P. Boscoe, PhD; Lindsey M. Hutchison, MS; Peter E. Schwartz, MD; Xiao Xu, PhD

BACKGROUND: Occult uterine cancer at the time of benign hysterectomy poses unique challenges in patient care. There is large variability and uncertainty in estimated risk of occult uterine cancer in the literature and prior research often did not differentiate/include all subtypes.

OBJECTIVES: To thoroughly examine the prevalence of occult uterine cancer in a large population-based sample of women undergoing hysterectomy for presumed benign indications and to identify associated risk factors.

STUDY DESIGN: Using the New York Statewide Planning and Research Cooperative System database, we identified 229,536 adult women who underwent an inpatient or outpatient hysterectomy for benign indications during the period October 1, 2003 to December 31, 2013 at civilian hospitals and ambulatory surgery centers throughout the state. Diagnosis of corpus uteri cancer within 28 days after the index hysterectomy was determined using linked state cancer registry data. We estimated the prevalence of occult uterine cancer (overall and by subtype) and developed and validated risk prediction models using a random split sample approach.

RESULTS: Overall, 0.96% (95% confidence interval: 0.92—1.00%) of the women had occult uterine cancer, including 0.75% (95% confidence interval: 0.71—0.78%) with endometrial carcinoma and 0.22% (95% confidence interval: 0.20—0.23%) with uterine sarcoma. The prevalence of leiomyosarcoma was 0.15% (95% confidence interval: 0.13—0.17%). Seventy-one percent of the endometrial carcinomas and 58.0% of the uterine sarcomas were at localized stage. The risk for occult uterine cancer ranged from 0.10% in women aged 18—29 years to 4.40% in women aged ≥75 years; and varied from 0.14% in women undergoing hysterectomy for endometriosis to 0.62% for uterine fibroids and 8.43% for postmenopausal bleeding. The risk of occult uterine cancer was also significantly associated with race/ethnicity, obesity, comorbidity, and personal history of malignancy. Prediction models incorporating these risk factors had high negative predictive values (99.8% for endometrial carcinoma and 99.9% for uterine sarcoma) and good rule-out accuracy despite low positive predictive value.

CONCLUSIONS: In women undergoing hysterectomy for presumed benign indications, 0.96% had unexpected uterine cancer. Patient characteristics such as age, surgical indication, and medical history may help guide risk stratification.

Key words: endometrial carcinoma, hysterectomy, leiomyosarcoma, occult uterine cancer, risk prediction, uterine sarcoma

More than 600,000 women undergo hysterectomy each year, making it one of the most common gynecologic procedures in the United States.[1] Suspected presence of uterine cancer can have profound impact on surgical planning by influencing choice of surgical approach (eg, total vs subtotal hysterectomy) and surgical team (eg, involvement of gynecologic oncologists).[2] Some patients, however, have occult (preoperatively unrecognized) uterine cancer, which can pose unique challenges in care. They may require reoperation for surgical staging or removal of additional anatomy (cervix, adnexal organs, lymph nodes, and omentum) if not performed at initial hysterectomy. Uncontained laparoscopic power morcellation, if used at initial hysterectomy, may also inadvertently disseminate cancerous cells into the abdominopelvic cavity, jeopardizing prognosis.[3,4]

Unfortunately, current knowledge on the prevalence of and risk factors for occult uterine cancer is still limited. Prior research was mostly based on medical record reviews from selected institutions with small sample sizes and nonrepresentative samples, leading to large variability and uncertainty in estimated prevalence (eg, a wide range of 0—3.17% for unexpected uterine cancer).[5—8] Conversely, studies at larger scales often relied on claims data and diagnosis codes to identify occult cancers, lacking histopathologic detail to confirm or adequately characterize the malignancy (eg, inability to distinguish cancer subtypes).[9,10] Moreover, existing data tend to focus on uterine sarcoma, overlooking endometrial carcinoma which is the more prevalent type of uterine cancer[11]; and rigorous assessment of risk factors has been sparse owing to the small number of patients with occult uterine cancer in prior studies. These limitations and knowledge gaps, along with limited screening tests available, have hindered our ability in managing occult uterine cancer in hysterectomies.

To better inform risk stratification in patient care, we constructed a large, population-based sample of women undergoing hysterectomy for presumed benign indications in New York State with linkage to cancer registry data, and examined the prevalence of occult uterine cancer (including all major subtypes) and associated tumor characteristics. Moreover, we thoroughly evaluated

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AJOG at a Glance

Why was this study conducted?

- Understanding the magnitude of risk and risk factors for occult uterine cancer at the time of benign hysterectomy is essential for appropriate patient management.

Key findings

- In a large sample of 229,536 women undergoing hysterectomy for presumed benign indications, 0.75% had endometrial carcinoma and 0.22% had uterine sarcoma (including 0.15% with leiomyosarcoma).
- The risk for occult uterine cancer differed significantly by patient age, surgical indication, and comorbidities.
- Prediction models using relevant patient characteristics had high negative predictive values and good rule-out accuracy.

What does this add to what is known?

- This study provides population-based estimates for risk of occult uterine cancer.
- In addition to uterine sarcoma, presence of occult endometrial carcinoma also warrants attention.
- The risk prediction models may help identify patients at low risk for occult uterine cancer and inform future development of decision aids.

differences in risk of occult uterine cancer across different patient subgroups (by age, surgical indication, and surgical route) and developed risk prediction models based on patients' preoperative characteristics.

Materials and Methods

Data sources and study population

This study used data from the 2003−2013 New York Statewide Planning and Research Cooperative System (SPARCS)—an all-payer data system capturing all inpatient and outpatient encounters at civilian hospitals as well as hospital-based and free-standing ambulatory surgery centers throughout the state.[12] For each encounter, the SPARCS data provided detailed information on patient sociodemographic and clinical characteristics, such as age, sex, race/ethnicity, admitting and discharge diagnosis, and procedure codes and dates. A unique personal identifier and date of birth allowed for longitudinal linkage of data within the same patient. Using the SPARCS data, we identified all hysterectomies performed for adult women during the period October 1, 2003 to December 31, 2013 based on International Classification of Diseases Ninth Revision (ICD-9) procedure codes and Current Procedural Terminology codes (Supplemental Table 1). A 9-month period prior to surgery was used to measure medical histories.

To identify occult uterine cancer, we further acquired data from the New York State Cancer Registry on all women diagnosed with corpus uteri cancer in 2003-2015.[13] Additional data were also available on women diagnosed with cancer of the cervix uteri or fallopian tube/uterine ligaments in this time period. For each of these patients, the cancer registry data included her complete diagnosis history (ie, all cancers ever diagnosed) and diagnosis date and detailed characteristics of each cancer. We linked these cancer registry data to hysterectomy encounters in the SPARCS database using each patient's unique identifier and date of birth. This study was approved by Yale University Human Investigation Committee.

To study hysterectomies performed for presumed benign indications, we excluded patients with the following: (1) admitting diagnosis of any cancer, (2) discharge diagnosis indicating personal history of gynecologic malignancy, (3) encounters in the previous 9 months indicating a diagnosis of gynecologic cancer or cancer metastasis to female genital organs, or (4) documentation of corpus uteri, cervix uteri, or fallopian tube/uterine ligaments cancer in the cancer registry prior to date of hysterectomy. Patients with an admitting diagnosis of ascites or neoplasm of uncertain behavior/unspecified nature or with a history of endometrial hyperplasia (admitting diagnosis or in previous 9 months) were also excluded, as they were often suspected of having cancer. To focus on a gynecologic patient population, we further excluded hysterectomies performed for obstetric conditions or diseases of the digestive system. Sensitivity analyses were performed by additionally excluding patients who underwent a radical hysterectomy or had any diagnosis of metastatic cancer in the 9 months before index hysterectomy. Supplemental Figure 1 provides more details regarding our sample inclusion and exclusion criteria.

Outcome measures

We defined a patient as having uterine cancer if she had International Classification of Diseases for Oncology 3rd Edition (ICD-O-3) site code 54.x or 55.x (excluding histology code 9050−9055, 9140, or 9590−9992).[14] In addition, we required an ICD-O-3 behavioral code of malignancy (ie, excluding in situ disease). Uterine cancer newly diagnosed within 28 days after an index hysterectomy was defined as "occult" cancer, with sensitivity analyses conducted using alternative cutoffs at 6 and 24 months, respectively.

For each identified occult uterine cancer, we characterized its subtype, stage, grade, and tumor size based on data from the cancer registry. Uterine cancer included 2 major types: endometrial carcinoma and uterine sarcoma. Within each type, we further distinguished more specific subtypes (eg, adenocarcinoma, leiomyosarcoma) based on ICD-O-3 histology codes (Supplemental Table 2).[11,15,16] To minimize missing data, we categorized cancer stage as localized, regional, distant, or unknown by reconciling information from the American Joint Committee on Cancer stage variable and Surveillance,

Epidemiology, and End Results Program stage variable. Grade was categorized as 1−4 or unknown; and tumor size was classified as <2 centimeters, 2−5 centimeters, >5 centimeters, or unknown.

Patient characteristics

For each index hysterectomy, we ascertained patient age, race/ethnicity, surgical indication, and surgical route. We determined surgical indication based on ICD-9 admitting diagnosis code and classified it into categories (eg, uterine fibroid, menstrual disorders, and genital prolapse) (Supplemental Table 1). We classified surgical route (eg, total abdominal hysterectomy, laparoscopic supracervical hysterectomy) based on ICD-9 and Current Procedural Terminology procedure codes (Supplemental Table 1).

In addition, to characterize patients' medical history and comorbidities, we used ICD-9 discharge diagnosis codes from encounters in the 9 months before index hysterectomy, as well as from the index hysterectomy itself (excluding diagnosis codes for gynecologic cancer, as they might be newly diagnosed after hysterectomy). We required that the diagnosis code be either from the index admission or from at least 1 inpatient encounter or 2 outpatient encounters (>30 days apart) in the past 9 months.[17] This enabled us to measure the following binary indicators: (1) genetic susceptibility to malignant neoplasm of the breast, endometrium, ovary, and other female genital organ, respectively; (2) comorbidities including tobacco use, history of other cancer (breast cancer, colon cancer, melanoma, cancer of urinary organs, other solid tumor, and lymphoma, respectively), and 18 measures of benign chronic conditions adapted from the Elixhauser index (eg, hypertension, diabetes, and obesity);[18] and (3) family history of malignant neoplasm of breast, ovary, other female genital organs, and gastrointestinal tract, respectively. We selected these variables based on clinical relevance and availability of data.

Statistical analysis

We summarized patient and tumor characteristics using descriptive statistics, and reported prevalence of occult uterine cancer (overall and by subtype) using point estimates and 95% confidence intervals (CIs). The CIs were calculated using exact binomial method if there were fewer than 5 cases of occult cancer or based on normal approximation otherwise. We analyzed data in the overall sample, as well as by surgical indication, route, and age category.

We further developed a predictive model for patients' risk of occult endometrial carcinoma and occult uterine sarcoma, respectively, using a random split sample approach (randomly selecting two thirds of the sample for model development while using the remaining sample for validation). In model development, we used a Poisson regression to estimate the risk ratio of having occult cancer associated with various patient characteristics.[19] Age, race/ethnicity, surgical indication, comorbidities, and genetic susceptibility to and family history of malignant neoplasm were candidate risk factors. Variables that were statistically significant at the $P < .10$ level in bivariate analysis were included in a backward selection process in multivariable regression to determine the final list of risk factors retained in the model (cutoff P value = .05).

We evaluated the performance of these predictive models in the validation sample. First, the models predicted each patient's probability of having occult cancer. We then used the Youden index to determine the optimal threshold of the predicted probability for indicating occult cancer,[20] and classified each patient as having or not having occult cancer. By comparing this predicted occult cancer status with the cancer registry data, we calculated the models' sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), overall accuracy, area under receiver operating characteristic (ROC) curve, and clinical utility index for rule-in and rule-out accuracy.[21] For clinical utility index, a value of 0.64−0.80 was considered good and a value ≥0.81 was considered excellent.[21] All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

Patient characteristics

A total of 229,536 adult women met sample eligibility criteria. Their median age was 47 years (interquartile range: 42−52) (Table 1). Uterine fibroid (38.9%), menstrual disorders (20.3%), and genital prolapse (13.8%) were the most common indications. Forty-two percent of the women underwent a total abdominal or total laparoscopic hysterectomy, while 28.8% had a vaginal or laparoscopic-assisted vaginal hysterectomy.

Prevalence of occult uterine cancer

In this sample, 2207 patients had occult uterine cancer, resulting in an overall prevalence of 0.96% (95% CI: 0.92−1.00%; Table 2). When distinguished by subtype, 1716 had endometrial carcinoma (0.75%, 95% CI: 0.71−0.78%), and 495 had uterine sarcoma (0.22%, 95% CI: 0.20−0.23%) including 346 who had leiomyosarcoma (0.15%, 95% CI: 0.13−0.17%). (Four patients had both endometrial carcinoma and uterine sarcoma.) Sensitivity analyses excluding radical hysterectomies, excluding patients with any diagnosis of metastatic cancer in the past 9 months, or expanding the time window for measuring occult uterine cancer to 6 months and 24 months after index hysterectomy produced similar estimates (Supplemental Table 3).

The risk of occult uterine cancer varied by surgical indication, age, and surgical route (Table 2). Endometrial carcinoma was found in 0.13% (95% CI: 0.05−0.21%) of women undergoing hysterectomy for endometriosis, 0.33% (95% CI: 0.29−0.37%) for uterine fibroids, and 7.92% (95% CI: 7.08−8.77%) for postmenopausal bleeding. When stratified by age, the risk for occult endometrial carcinoma ranged from 0.10% (95% CI: 0.02−0.29%) in women aged 18−29 years to 3.93% (95% CI: 3.47−4.38%) in women aged ≥75 years. Likewise, the risk for occult endometrial carcinoma was 0.18% (95% CI: 0.12−0.24%) in women undergoing laparoscopic supracervical hysterectomy vs 1.35% (95% CI: 1.25−1.45%) in women who underwent a total abdominal hysterectomy. Risk for

TABLE 1
Sample characteristics of patients (n = 229,536)

Characteristic	n (%)
Age, median (interquartile range)	47 (42–52)
Race/ethnicity	
Non-Hispanic white	131,303 (57.2)
Non-Hispanic black	39,225 (17.1)
Hispanic	24,623 (10.7)
Asian	6031 (2.6)
Other	10,443 (4.5)
Unknown	17,911 (7.8)
Primary payer	
Medicare	21,518 (9.4)
Medicaid	17,118 (7.5)
Private insurance	177,758 (77.4)
Other payer	1561 (0.7)
Self-pay	6270 (2.7)
Unknown	5311 (2.3)
Surgical indication	
Uterine fibroid	89,262 (38.9)
Other benign neoplasm of uterus	266 (0.1)
Menstrual disorders	46,488 (20.3)
Genital prolapse	31,567 (13.8)
Endometriosis	8401 (3.7)
Ovarian cyst	6036 (2.6)
Postmenopausal bleeding	3913 (1.7)
Other menopausal disorders	986 (0.4)
Cervical abnormalities	2444 (1.1)
Benign neoplasm of ovary	1789 (0.8)
Inflammatory diseases of female pelvic organs	1425 (0.6)
Other female genital disorders	19,439 (8.5)
Abdominal mass/pain	11,085 (4.8)
Other	6435 (2.8)
Surgical route	
Total abdominal hysterectomy	49,677 (21.6)
Total laparoscopic hysterectomy	15,906 (6.9)
Total abdominal or laparoscopic hysterectomy[a]	30,299 (13.2)
Vaginal or laparoscopic-assisted vaginal hysterectomy	66,211 (28.8)
Abdominal supracervical hysterectomy	44,708 (19.5)
Laparoscopic supracervical hysterectomy	20,794 (9.1)
Radical hysterectomy	1515 (0.7)
Hysterectomy with unspecified approach	426 (0.2)

Percentages may not add to 100 owing to rounding.

[a] Prior to October 1, 2006, ICD-9 procedure code could not distinguish total abdominal vs total laparoscopic hysterectomy.

Desai et al. Occult uterine cancer in hysterectomy. Am J Obstet Gynecol 2019.

occult uterine sarcoma had a similar pattern.

Histopathologic characteristics

Among women with occult endometrial carcinoma, most had localized disease (71.3%) and grade 1–2 tumor (63.8%) (Table 3). Thirty-five percent had tumors ≤5 centimeters, while 48.2% had unknown tumor size. Adenocarcinoma was the most common subtype (89.2%).

In contrast, women with unexpected uterine sarcoma had more severe disease (Table 3). Twenty-one percent had distant stage, 54.1% had grade 3–4 tumor, and 61.8% had tumors larger than 5 centimeters. Leiomyosarcoma accounted for 69.9% of the occult uterine sarcomas.

Risk factors

The multivariable prediction models confirmed surgical indication and age as significant risk factors (Figure 1, A and B). For instance, compared to women undergoing hysterectomy for fibroids, those who had hysterectomy for genital prolapse were 0.29 (95% CI: 0.22–0.39) times as likely to have occult endometrial carcinoma and 0.01 (95% CI: 0.001–0.05) times as likely to have occult uterine sarcoma. Moreover, the risk of occult uterine cancer was significantly higher in older women (eg, adjusted risk ratio for age 60–64 years vs 45–49 years = 7.08, 95% CI: 5.34–9.39, for endometrial carcinoma; and 7.06, 95% CI: 4.44–11.21, for uterine sarcoma).

Non-Hispanic black women were less likely than non-Hispanic white women to have occult endometrial carcinoma, possibly owing to more frequent evaluation of uterine fibroids among black women, whereas diabetes, hypertension, obesity, and renal failure were associated with a higher risk for occult endometrial carcinoma (Figure 1A). For occult uterine sarcoma, the risk was higher in patients with hypertension, blood loss or deficiency anemia, weight loss, and personal history of malignancy (Figure 1B).

When evaluated in the validation sample, the model for endometrial carcinoma had a sensitivity of 73.7%, specificity of 86.0%, and area under the

TABLE 2
Prevalence of occult uterine cancer in adult women undergoing hysterectomy for presumed benign indications

Patient characteristics	Sample size	Proportion (%) of patients with occult cancer (95% CI)			
				Uterine sarcoma	
		All uterine cancer	Endometrial carcinoma	All uterine sarcoma	Leiomyosarcoma
Overall sample	229,536	0.96 (0.92–1.00)	0.75 (0.71–0.78)	0.22 (0.20–0.23)	0.15 (0.13–0.17)
By surgical indication					
Uterine fibroid	89,262	0.62 (0.57–0.67)	0.33 (0.29–0.37)	0.30 (0.26–0.33)	0.21 (0.18–0.24)
Other benign neoplasm of uterus	266	3.01 (0.96–5.06)	2.26 (0.47–4.04)	0.75 (0.09–2.69)	0.75 (0.09–2.69)
Menstrual disorders	46,488	0.40 (0.34–0.46)	0.31 (0.26–0.36)	0.09 (0.06–0.11)	0.06 (0.04–0.09)
Genital prolapse	31,567	0.40 (0.33–0.47)	0.38 (0.32–0.45)	0.01 (0.00–0.03)	0.01 (0.00–0.03)
Endometriosis	8401	0.14 (0.06–0.22)	0.13 (0.05–0.21)	0.01 (0.00–0.07)	0.01 (0.00–0.07)
Ovarian cyst	6036	1.04 (0.79–1.30)	0.93 (0.69–1.17)	0.12 (0.03–0.20)	0.03 (0.00–0.12)
Postmenopausal bleeding	3913	8.43 (7.56–9.30)	7.92 (7.08–8.77)	0.51 (0.29–0.73)	0.43 (0.23–0.64)
Other menopausal disorders	986	1.01 (0.39–1.64)	0.91 (0.32–1.51)	0.10 (0.00–0.56)	0.01 (0.00–0.56)
Cervical abnormalities	2444	1.68 (1.17–2.19)	1.64 (1.13–2.14)	0.04 (0.00–0.23)	0.04 (0.00–0.23)
Benign neoplasm of ovary	1789	0.50 (0.18–0.83)	0.50 (0.18–0.83)	0.00 (NA)	0.00 (NA)
Inflammatory diseases of female pelvic organs	1425	0.56 (0.17–0.95)	0.42 (0.08–0.76)	0.14 (0.02–0.51)	0.07 (0.00–0.39)
Other female genital disorders	19,439	1.38 (1.21–1.54)	1.12 (0.97–1.27)	0.27 (0.19–0.34)	0.18 (0.12–0.24)
Abdominal mass/pain	11,085	4.00 (3.63–4.36)	3.27 (2.94–3.61)	0.73 (0.57–0.89)	0.49 (0.36–0.62)
By age, years					
18–29	3021	0.10 (0.02–0.29)	0.10 (0.02–0.29)	0.00 (NA)	0.00 (NA)
30–34	8867	0.16 (0.08–0.24)	0.11 (0.04–0.18)	0.05 (0.01–0.12)	0.03 (0.01–0.10)
35–39	23,599	0.17 (0.11–0.22)	0.12 (0.08–0.17)	0.04 (0.02–0.07)	0.03 (0.01–0.05)
40–44	51,740	0.26 (0.22–0.31)	0.16 (0.12–0.19)	0.11 (0.08–0.13)	0.06 (0.04–0.09)
45–49	62,052	0.42 (0.37–0.47)	0.28 (0.23–0.32)	0.14 (0.11–0.17)	0.09 (0.07–0.11)
50–54	33,237	1.03 (0.92–1.14)	0.69 (0.60–0.78)	0.35 (0.29–0.41)	0.24 (0.19–0.29)
55–59	14,453	2.21 (1.97–2.45)	1.66 (1.45–1.87)	0.55 (0.43–0.67)	0.47 (0.36–0.58)
60–64	10,911	3.00 (2.68–3.32)	2.47 (2.17–2.76)	0.53 (0.40–0.67)	0.38 (0.27–0.50)
65–69	8603	3.12 (2.75–3.48)	2.72 (2.38–3.06)	0.40 (0.26–0.53)	0.27 (0.16–0.38)
70–74	6077	3.14 (2.70–3.58)	2.88 (2.46–3.30)	0.26 (0.13–0.39)	0.21 (0.10–0.33)
≥75	6976	4.40 (3.92–4.88)	3.93 (3.47–4.38)	0.50 (0.34–0.67)	0.32 (0.18–0.45)
By surgical route					
Total abdominal hysterectomy	49,677	1.79 (1.67–1.91)	1.35 (1.25–1.45)	0.45 (0.39–0.51)	0.31 (0.26–0.36)
Total laparoscopic hysterectomy	15,906	1.06 (0.90–1.22)	0.96 (0.81–1.11)	0.09 (0.05–0.14)	0.08 (0.03–0.12)
Vaginal or laparoscopic-assisted vaginal hysterectomy	66,211	0.47 (0.42–0.52)	0.43 (0.38–0.48)	0.03 (0.02–0.05)	0.02 (0.01–0.03)
Abdominal supracervical hysterectomy	44,708	0.51 (0.45–0.58)	0.31 (0.26–0.36)	0.20 (0.16–0.24)	0.14 (0.10–0.17)
Laparoscopic supracervical hysterectomy	20,794	0.27 (0.20–0.34)	0.18 (0.12–0.24)	0.09 (0.05–0.13)	0.06 (0.03–0.10)

CI, confidence interval; *NA*, not applicable.

Desai et al. Occult uterine cancer in hysterectomy. Am J Obstet Gynecol 2019.

TABLE 3
Characteristics of occult uterine cancer identified in adult women undergoing hysterectomy for presumed benign indications

Tumor characteristic	Endometrial carcinoma (n = 1716[a,b]) n (%)	Uterine sarcoma[b] All uterine sarcoma (n = 495) n (%)	Uterine sarcoma[b] Leiomyosarcoma (n = 346) n (%)
Stage			
Localized	1224 (71.3)	287 (58.0)	200 (57.8)
Regional	326 (19.0)	85 (17.2)	49 (14.2)
Distant	149 (8.7)	106 (21.4)	82 (23.7)
Unknown	17 (1.0)	17 (3.4)	15 (4.3)
Grade			
1	735 (42.8)	45 (9.1)	6 (1.7)
2	359 (20.9)	56 (11.3)	22 (6.4)
3	289 (16.8)	97 (19.6)	79 (22.8)
4	87 (5.1)	171 (34.5)	137 (39.6)
Unknown	246 (14.3)	126 (25.5)	102 (29.5)
Tumor size, centimeters			
<2	259 (15.1)	13 (2.6)	8 (2.3)
2–5	350 (20.4)	37 (7.5)	19 (5.5)
>5	280 (16.3)	306 (61.8)	234 (67.6)
Unknown	827 (48.2)	139 (28.1)	85 (24.6)
Cancer subtype			
Adenocarcinoma	1530 (89.2)	NA	NA
Adenosarcoma	19 (1.1)	NA	NA
Carcinosarcoma	76 (4.4)	NA	NA
Other endometrial carcinoma	91 (5.3)	NA	NA
Leiomyosarcoma	NA	346 (69.9)	346 (100)
Low-grade endometrial stromal sarcoma	NA	64 (12.9)	NA
High-grade endometrial stromal sarcoma	NA	62 (12.5)	NA
Other uterine sarcoma	NA	23 (4.6)	NA

Percentages may not add to 100 owing to rounding.

NA, not applicable.

[a] In 2 of these patients, they each had 2 diagnoses of occult endometrial carcinoma (with different histology codes) on the day of index hysterectomy. For these 2 patients, we reported tumor characteristics associated with the more aggressive histology type; [b] Four patients had both endometrial carcinoma and uterine sarcoma.

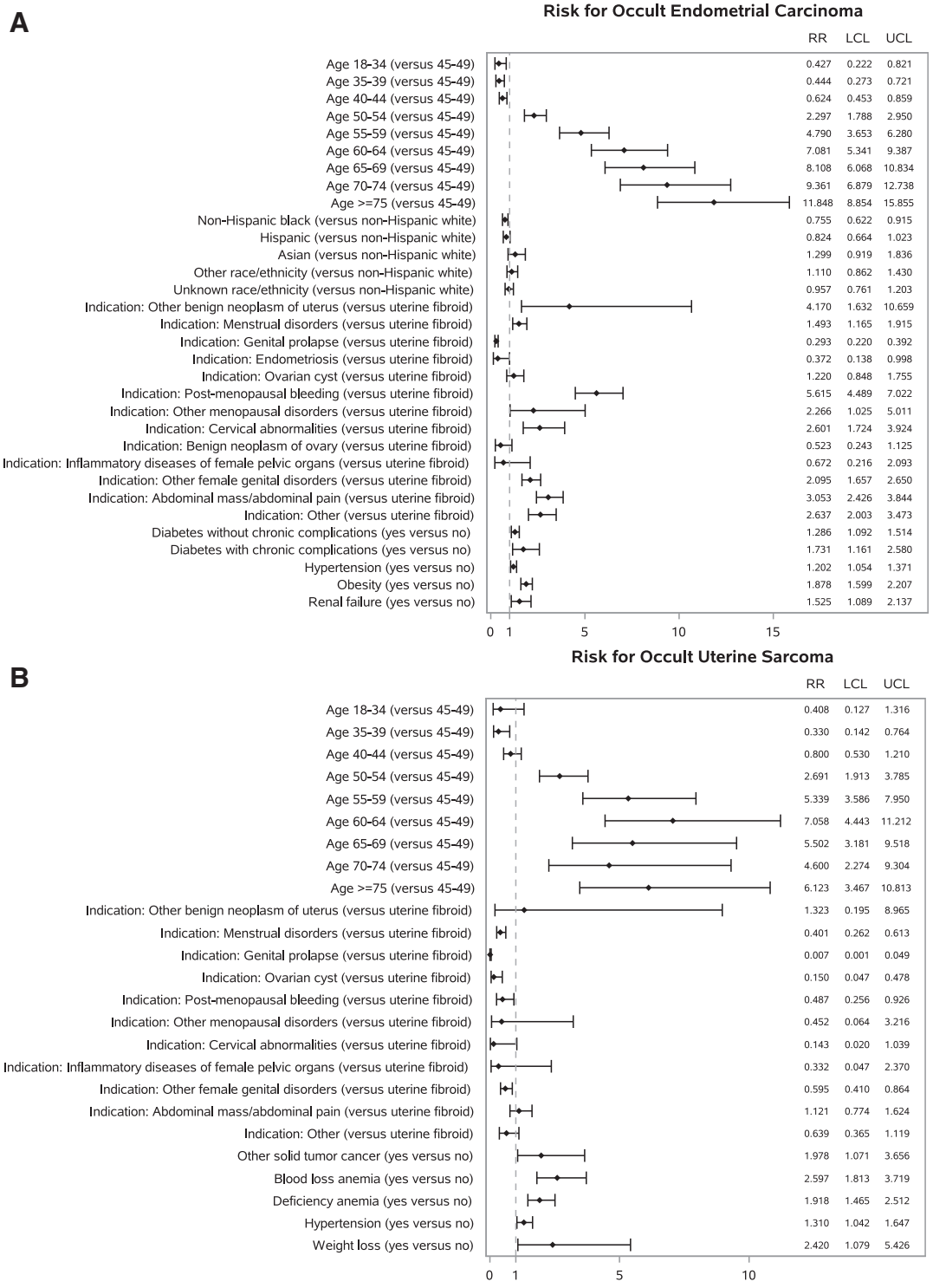
Desai et al. Occult uterine cancer in hysterectomy. Am J Obstet Gynecol 2019.

ROC curve of 0.85; and the model for uterine sarcoma attained a sensitivity of 70.4%, specificity of 75.2%, and area under ROC curve of 0.80 (Table 4). Both models had high NPV (99.8% for endometrial carcinoma and 99.9% for uterine sarcoma) and good clinical utility index score for ruling out the disease, supporting their potential use in identifying women at low risk for occult uterine cancer. However, since occult uterine cancer was rare, these models had low PPV.

Comments

In a large population-based sample of women undergoing hysterectomy for presumed benign indications, we found that 0.75% of them had occult endometrial carcinoma and 0.22% had occult uterine sarcoma (including 0.15% with occult leiomyosarcoma). The risk for occult uterine cancer differed by patient age, surgical indication, and surgical route. Several other patient characteristics were also identified that may inform preoperative risk assessment.

FIGURE 1
Adjusted association between patient characteristics and the risk of having occult uterine cancer, development sample (n = 153,032)



Estimated risk of occult uterine cancer varied substantially in previous research. For instance, among 23 studies published between April 1, 2014 and April 15, 2017, the estimated risk ranged from 0% to 0.51% for unexpected leiomyosarcoma and from 0% to 1.48% for uterine sarcoma.[3] The U.S. Food and Drug Administration (FDA) synthesized

TABLE 4
Performance of the risk prediction models, validation sample (n = 76,504)

Model performance	Endometrial carcinoma	Uterine sarcoma
Sensitivity, n/total n (%)	424/575 (73.7)	119/169 (70.4)
Specificity, n/total n (%)	65,322/75,929 (86.0)	57,429/76,335 (75.2)
Positive predictive value, n/total n (%)	424/11,031 (3.8)	119/19,025 (0.6)
Negative predictive value, n/total n (%)	65,322/65,473 (99.8)	57,429/57,479 (99.9)
Overall accuracy, n/total n (%)	65,746/76,504 (85.9)	57,548/76,504 (75.2)
Clinical utility index − rule in	0.03	0.004
Clinical utility index − rule out	0.86	0.75
Area under the receiver operating characteristic curve	0.85	0.80

Desai et al. Occult uterine cancer in hysterectomy. Am J Obstet Gynecol 2019.

evidence from the literature and reported a risk of 1 in 498 women (0.20%) for occult leiomyosarcoma and 1 in 352 (0.28%) for occult uterine sarcoma in its initial statement in 2014,[22] and a risk of 0.09−0.20% for leiomyosarcoma and 0.17−0.45% for uterine sarcoma in an updated assessment in 2017.[3] Meta-analysis performed by the Agency for Healthcare Research and Quality (AHRQ) estimated that 0.021% (95% credible interval: 0−0.094%) of women in prospective studies and 0.085% (95% credible interval: 0.047−0.127%) in retrospective studies had unexpected leiomyosarcoma.[4] These estimates, however, focused on women with fibroids. In our study, the risk of occult leiomyosarcoma and uterine sarcoma was 0.21% and 0.30%, respectively, in the subset of women undergoing hysterectomy for fibroids, which are on par with the FDA estimates but higher than the AHRQ estimates. One possible explanation is that in addition to hysterectomies, the FDA and AHRQ assessments included myomectomies where the risk for occult uterine cancer is lower because patients tend to be younger and healthier.[23,24] In particular, 56.7% of the prospective studies and 31.9% of the retrospective studies included in the AHRQ analysis focused on myomectomies.[4]

Our study also extends this literature by examining the risk of occult endometrial carcinoma in hysterectomies. Although most attention has centered on sarcomas owing to their poor prognosis, endometrial carcinoma is more common and warrants careful consideration as well. In our study, three quarters of the occult uterine cancers were endometrial carcinoma. Meanwhile, techniques for identifying endometrial carcinoma (eg, transvaginal ultrasonography, endometrial biopsy) are more effective than those available for identifying uterine sarcomas. Thus initiatives to reduce unexpected endometrial carcinoma may be one promising area for improvement. These initiatives can benefit from additional research examining reasons for the unexpected malignancies (eg, owing to inadequate preoperative assessment or ineffectiveness of existing techniques) and comparative effectiveness of alternative evaluation strategies (eg, different endometrium sampling method).[25,26]

The risk factors and prediction models identified in our study may facilitate patient risk stratification. Consistent with prior research,[3,9,10,24,27] we found age and surgical indication as 2 important risk factors. Race/ethnicity, obesity, comorbidity, and personal history of malignancy were also pertinent factors. Differences in occult cancer risk across surgical routes, however, may be confounded by patient characteristics (eg, younger women with lower risk for occult cancer were more likely to undergo subtotal hysterectomy, and women with genital prolapse who have lower risk for occult cancer frequently undergo vaginal hysterectomy). Turning knowledge on risk factors into effective decision aids may be one fruitful area of investigation. The prediction models in our study reflect a preliminary step in this direction. For instance, for patients with different age, race/ethnicity, and

A, Risk for occult endometrial carcinoma. **B,** Risk for occult uterine sarcoma. Notes: (1) The 2 youngest age categories (18−29 years and 30−34 years) were combined owing to the small number of patients with occult uterine cancer in these age categories. (2) Because no patients with endometriosis or benign neoplasm of the ovary in the development sample had occult uterine sarcoma, they were combined with other female genital disorders in the risk prediction model for occult uterine sarcoma. (3) "Other solid tumor cancer" referred to cancer of solid tumor other than breast, colon, melanoma, and urinary organs. (4) Area under receiver operating characteristic curve was 0.87 and 0.82 for the risk prediction model for occult endometrial carcinoma and occult uterine sarcoma, respectively.

LCL, lower confidence limit of the 95% confidence interval; *RR*, risk ratio; *UCL*, upper confidence limit of the 95% confidence interval.

Desai et al. Occult uterine cancer in hysterectomy. Am J Obstet Gynecol 2019.

indication profiles, the models can predict their likelihood of having occult uterine cancer (examples are provided in Supplemental Table 4). Research to further validate and improve these models using other databases and patient samples will be important for developing rigorous risk assessment tools for use by providers and patients in clinical care. However, given the high NPV and low PPV, these models may be more useful in ruling out occult cancers rather than confirming them.

We recognize several limitations of this study. First, our data reflect patient population and clinical practice in 1 single state. The findings may not generalize to other places in the country. Second, a 10-year study period may mask changes in practice and hence prevalence of occult cancer. However, when stratified by years, we found similar rates of occult endometrial carcinoma (0.71% in 2003−2008 and 0.79% in 2009−2013) and uterine sarcoma (0.20% in 2003−2008 and 0.23% in 2009−2013). Third, we relied on retrospective data to identify hysterectomies performed for benign indications. Since not all preoperative suspicions for malignancy can be coded and identified in claims data, we might overestimate the risk of occult cancer. Indeed, it has been shown that retrospective studies generally report higher prevalence of occult uterine cancer than prospective studies.[4,28] Likewise, we measured medical history and comorbidities using hospital discharge records and a 9-month look-back window. As claims data have limited accuracy in capturing certain diseases[29,30] and not all patients had hospital encounters over the past 9 months, we might misclassify or underestimate some conditions.

In summary, using statewide data from New York, we found that the overall risk of occult uterine cancer was 0.96% in women undergoing hysterectomy for presumed benign indications. Preoperative risk factors such as age and surgical indication may be used to guide risk stratification and surgical planning. Efforts to enhance preoperative evaluation and develop effective risk assessment tools may facilitate future patient care. ■

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Author and article information

From the Departments of Obstetrics, Gynecology and Reproductive Sciences (Drs Desai, Schwartz, and Xu) and Internal Medicine (Dr Gross), Yale School of Medicine, New Haven, CT; CooperSurgical Inc, Trumbull, CT (Dr Desai); Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, New York, NY (Dr Wright); Yale Cancer Outcomes, Public Policy and Effectiveness Research Center, New Haven, CT (Drs Gross and Xu); Department of Biostatistics, Yale School of Public Health, New Haven, CT (Dr Lin); and New York State Cancer Registry, New York State Department of Health, Albany, NY (Dr Boscoe and Ms Hutchison).

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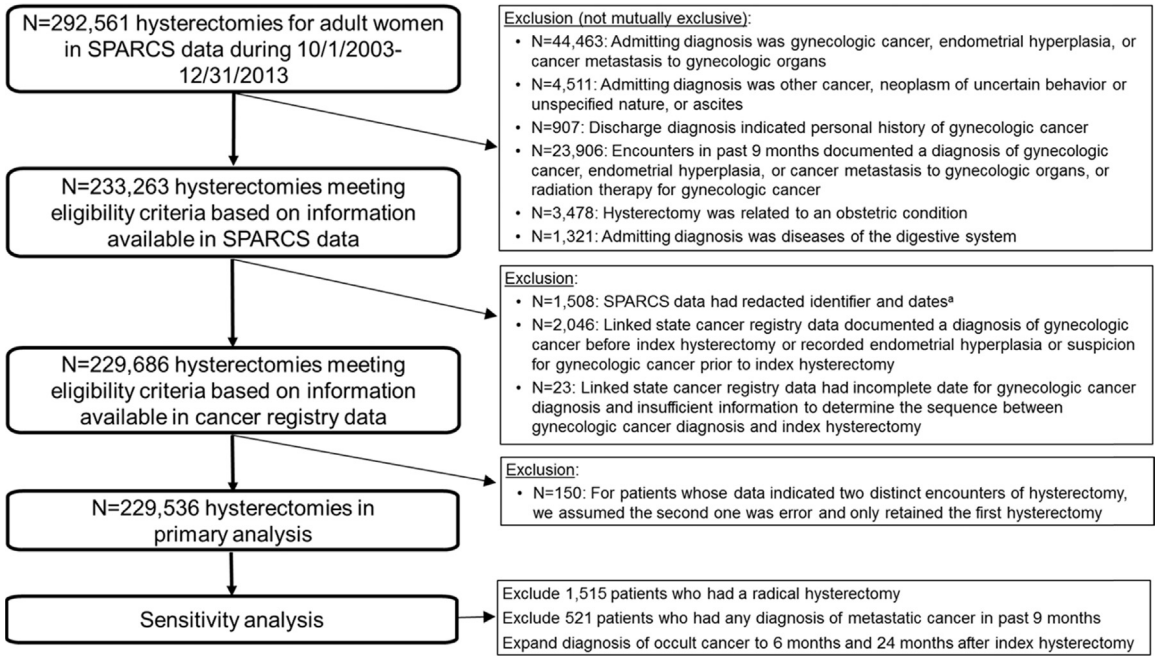
Corresponding author: Xiao Xu, PhD. xiao.xu@yale.edu

SUPPLEMENTAL FIGURE 1
Sample selection flow diagram



[a]To protect patient confidentiality, identifiers and dates were redacted in SPARCS data if an encounter was abortion- or HIV-related. Therefore, these encounters could not be linked to cancer registry data.

SPARCS, New York Statewide Planning and Research Cooperative System.

Desai et al. Occult uterine cancer in hysterectomy. Am J Obstet Gynecol 2019.

SUPPLEMENTAL TABLE 1
International Classification of Diseases Ninth Revision and Current Procedural Terminology codes used to identify hysterectomies, select sample, and define surgical indication

Condition or procedure	CPT procedure code	ICD-9 procedure code	ICD-9 diagnosis code
Hysterectomy			
Total abdominal hysterectomy	58150, 58152	68.49	NA
Total laparoscopic hysterectomy	58570, 58571, 58572, 58573	68.41	NA
Total abdominal/laparoscopic hysterectomy	NA	68.4[a]	NA
Vaginal or laparoscopic-assisted vaginal hysterectomy	58260, 58262, 58263, 58267, 58270, 58290, 58291, 58292, 58293, 58294, 58550, 58552, 58553, 58554	68.51, 68.59	NA
Abdominal supracervical hysterectomy	58180	68.39	NA
Laparoscopic supracervical hysterectomy	S2078, 58541, 58542, 58543, 58544	68.31	NA
Radical hysterectomy	58200, 58210, 58275, 58280, 58285, 58548, 58951, 58953, 58954, 58956	68.6, 68.61, 68.69, 68.7, 68.71, 68.79	NA
Other hysterectomy	51925	68.9	NA

Desai et al. Occult uterine cancer in hysterectomy. Am J Obstet Gynecol 2019. *(continued)*

SUPPLEMENTAL TABLE 1

International Classification of Diseases Ninth Revision and Current Procedural Terminology codes used to identify hysterectomies, select sample, and define surgical indication *(continued)*

Condition or procedure	CPT procedure code	ICD-9 procedure code	ICD-9 diagnosis code
Gynecologic cancer	NA	NA	179–184.x, 233.1–233.3x, 795.06, 795.16, V10.40–V10.44
Cancer metastasis to female genital organs	NA	NA	198.6, 198.82
Other cancer, neoplasm of uncertain behavior or unspecified nature, or ascites	NA	NA	140.x–176.x, 188.x–197.x, 198.0–198.5, 198.7, 198.81, 198.89, 199.x–209.x, 230.x–232.x, 233.0, 233.7–233.9, 234.x, 235.x–239.x, 258.0x, V10.0–V10.3, V10.5–V10.9, 789.5x
Endometrial hyperplasia	NA	NA	621.3x
Personal history of gynecologic cancer	NA	NA	V10.40–V10.44
Radiation therapy for gynecologic cancer	55920, 57155, 57156, 58346	NA	NA
Obstetric conditions[b]	59000-59899, 59135, 59525, 01962, 01963	72.x–75.x	630-679.x, V22.x–V24.x, V27.x, V28.x
Diseases of the digestive system	NA	NA	520.x–579.x
Cancer metastasis to sites other than female genital organs	NA	NA	196.x–198.5, 198.7, 198.81, 198.89, 209.7x, 789.51
Surgical indication			
Uterine fibroid	NA	NA	218.x
Other benign neoplasm of uterus	NA	NA	219.x
Menstrual disorders	NA	NA	625.3, 626.0–626.6, 626.8, 626.9
Genital prolapse	NA	NA	618.x
Endometriosis	NA	NA	617.x
Ovarian cyst	NA	NA	620.0–620.2
Postmenopausal bleeding	NA	NA	627.1
Other menopausal disorders	NA	NA	256.31, 256.39, 627.0, 627.2–627.4, 627.8–627.9, V07.4
Cervical abnormalities	NA	NA	622.1–622.12, 795.00–795.05, 795.07–795.09, V13.22
Benign neoplasm of ovary	NA	NA	220.x
Inflammatory diseases of female pelvic organs	NA	NA	614.x, 615.x, 616.x, 625.71
Other female genital disorders	NA	NA	619.x, 620.3–620.9, 621.0–621.2, 621.4–621.9, 622.0, 622.2–622.9, 623.x, 624.x, 625.0–625.2, 625.4–625.70, 625.79–625.9, 626.7, 628.x, 629.x, V13.23, V13.24, V55.7, V72.3–V72.32,
Abdominal mass/pain	NA	NA	789.0x, 789.3x, 789.6x

CPT, Current Procedural Terminology, *ICD-9*, International Classification of Diseases Ninth Revision; *NA*, not applicable.

[a] Prior to October 1, 2006, ICD-9 procedure code did not distinguish total abdominal vs total laparoscopic hysterectomy; [b] The following diagnosis-related group codes were also used to identify obstetric condition–related encounters: 370–375 (in October 2003 – September 2007 data) and 765–768 and 774–775 (in October 2007 – December 2013 data).

Desai et al. Occult uterine cancer in hysterectomy. Am J Obstet Gynecol 2019.

SUPPLEMENTAL TABLE 2
International Classification of Diseases for Oncology 3rd Edition site and histology codes for defining uterine cancer

Cancer type	Site code	Histology code
Uterine cancer	54.x, 55.x	Excluding 9050–9055, 9140, or 9590–9992
Endometrial carcinoma	54.x, 55.x	8000–8790, 8933, 8950, 8951, 8980–8981, 9700–9701
Adenocarcinoma	54.x, 55.x	8050, 8140–8147, 8160–8162, 8180–8221, 8250–8506, 8520–8550, 8560, 8570–8573, 8940–8941
Carcinosarcoma	54.x, 55.x	8980, 8981
Adenosarcoma	54.x, 55.x	8933
Uterine sarcoma	54.x, 55.x	8800–8932, 8934–8941, 8959–8974, 8982–9136, 9141–9582
Leiomyosarcoma	54.x, 55.x	8890, 8891, 8896
Low-grade endometrial stromal sarcoma	54.x, 55.x	8931
High-grade endometrial stromal sarcoma	54.x, 55.x	8930, 8935

Desai et al. Occult uterine cancer in hysterectomy. Am J Obstet Gynecol 2019.

SUPPLEMENTAL TABLE 3
Prevalence of occult uterine cancer in sensitivity analyses

		Proportion (%) of patients with occult cancer (95% CI)			
				Uterine sarcoma	
Patient characteristics	Sample size	All uterine cancer	Endometrial carcinoma	All uterine sarcoma	Leiomyosarcoma
Exclude patients who had a radical hysterectomy	228,021	0.93 (0.89–0.96)	0.72 (0.68–0.75)	0.21 (0.19–0.23)	0.14 (0.13–0.16)
Exclude patients who had any diagnosis of metastatic cancer in the past 9 months	229,015	0.96 (0.92–1.00)	0.75 (0.71–0.78)	0.21 (0.20–0.23)	0.15 (0.13–0.17)
Define occult uterine cancer as diagnosis within 6 months after index hysterectomy	229,536	0.96 (0.92–1.00)	0.75 (0.71–0.78)	0.22 (0.20–0.24)	0.15 (0.13–0.17)
Define occult uterine cancer as diagnosis within 24 months after index hysterectomy	229,536	0.97 (0.93–1.01)	0.75 (0.72–0.79)	0.22 (0.20–0.24)	0.15 (0.14–0.17)

CI, confidence interval.
Desai et al. Occult uterine cancer in hysterectomy. Am J Obstet Gynecol 2019.

SUPPLEMENTAL TABLE 4

Predicted risk for occult uterine cancer in patients with specified clinical profiles

	Occult endometrial carcinoma		Occult uterine sarcoma	
Example patient clinical profile[a]	Predicted risk[b] (95% CI)	Below/above threshold[c]	Predicted risk[b] (95% CI)	Below/above threshold[d]
45-year-old non-Hispanic black woman presenting with uterine fibroid	0.0015 (0.0011–0.0019)	Below	0.0014 (0.0010–0.0019)	Below
60-year-old non-Hispanic white woman presenting with genital prolapse	0.0040 (0.0031–0.0053)	Below	0.0001 (0.0000–0.0005)	Below
33-year-old Hispanic woman presenting with abdominal pain	0.0021 (0.0010–0.0042)	Below	0.0006 (0.0002–0.0021)	Below
56-year-old non-Hispanic black woman presenting with ovarian cyst	0.0086 (0.0058–0.0128)	Borderline[e]	0.0011 (0.0003–0.0035)	Borderline[e]
66-year-old non-Hispanic white woman presenting with postmenopausal bleeding	0.0887 (0.0717–0.1097)	Above	0.0037 (0.0018–0.0078)	Borderline[e]
51-year-old Hispanic woman presenting with other menopausal disorders	0.0084 (0.0037–0.0188)	Borderline[e]	0.0017 (0.0002–0.0122)	Borderline[e]

CI, confidence interval.

[a] For simplicity, we assumed no comorbid conditions in these examples; [b] Predicted probability of having occult endometrial carcinoma (or occult uterine sarcoma) based on the risk prediction models reported in Figure 1 of the manuscript and the specified patient clinical profile. Predicted risk takes values ranging from 0 to 1; [c] Based on the Youden index, the optimal threshold of the predicted probability for indicating occult endometrial cancer was 0.0090; [d] Based on the Youden index, the optimal threshold of the predicted probability for indicating occult uterine sarcoma was 0.0023; [e] The 95% CI included the threshold value.

Desai et al. Occult uterine cancer in hysterectomy. Am J Obstet Gynecol 2019.