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Prevalence of occult endometrial carcinoma in patients with endometrial intraepithelial neoplasia who underwent hysterectomy

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Abstract

Objectives To determine the prevalence of occult endometrial carcinoma in patients with endometrial intraepithelial neoplasia (EIN) post-hysterectomy and identify pre-hysterectomy risk factors predictive of occult carcinoma.

Methods This retrospective study included patients diagnosed with EIN between 2007 and 2021 who underwent hysterectomy as primary treatment. An expert gynecologic pathologist reviewed pathological slides. Data collected from medical records included demographic and gynecologic information, sonographic findings, and surgical and pathological outcomes. The prevalence of occult endometrial carcinoma was calculated. Descriptive statistics evaluated carcinoma incidence, and logistic regression analysis identified independent risk factors.

Results A total of 113 patients were evaluated. The median time to hysterectomy was 9.1 weeks (range 5.8–12.8 weeks). Post-hysterectomy, 36 patients (31.8%) were diagnosed with endometrial carcinoma, all endometrioid type. Of these, 88.9% were stage I per the International Federation of Gynecology and Obstetrics classification system, and 11.1% were at high risk for nodal metastasis. Predictive factors for occult carcinoma included the intraoperative gross lesion size (2 cm or larger and less than 2 cm) and endometrial aspiration. Adjusted odds ratios were 6.723 (95% CI 2.338 to 19.333) for lesions 2 cm or larger, 3.381 (95% CI 1.128 to 10.132) for lesions less than 2 cm, and 2.752 (95% CI 1.092 to 6.936) for endometrial aspiration.

Conclusions Occult endometrial carcinoma was identified in 31.8% of patients with a pre-hysterectomy EIN diagnosis. The significant predictors were endometrial aspiration and the presence of a gross lesion during surgery.

Keywords Cancer, EIN, Endometrial intraepithelial neoplasia, Endometrium, Occult endometrial carcinoma

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Introduction

Endometrial intraepithelial neoplasia (EIN) is recognized as a precancerous lesion of the endometrium. This condition was previously designated "complex atypical hyperplasia" according to the 1994 World Health Organization classification, which was adapted from Kurman's classification. The EIN classification was established by the World Health Organization in 2003 and was upheld through the 2020 edition. It has been endorsed by both the American College of Obstetricians and Gynecologists and the Royal College of Obstetricians and Gynecologists [1–5]. Studies have demonstrated that the prevalence of occult endometrial carcinoma among patients with EIN who undergo hysterectomy ranges from 27 to 53%. The current standard treatment for EIN is total hysterectomy. Surgeons may also consider bilateral salpingo-oophorectomy, particularly for patients at greater risk of occult carcinoma. However, these patients might face prolonged hormonal exposure due to surgical menopause [3–5].

Preoperative identification of patients with EIN who are at increased risk for occult endometrial carcinoma can substantially enhance counseling and inform surgical decisions. Such identification can influence the consideration of additional procedures such as bilateral salpingo-oophorectomy or the assessment of lymph node metastasis. Conversely, recognizing patients at low risk for occult carcinoma can facilitate the selection of uterus-preserving treatments, thereby optimizing reproductive and oncological outcomes.

Several studies have reported predictive factors for occult endometrial carcinoma. These factors include age (using a cutoff of 50 years), diabetes mellitus, body mass index, transvaginal ultrasonography assessments of endometrial thickness, endometrial tissue biopsy techniques, and specific pathological characteristics [6–9]. The current study aimed to determine the prevalence of occult endometrial carcinoma in hysterectomy specimens and to identify pre-hysterectomy risk factors predictive of occult carcinoma.

Materials and methods

Following approval from the Siriraj Institutional Review Board (COA numbers Si 281/2020 and Si 581/2024), a retrospective chart review was conducted. Human Ethics and Consent to Participate declarations were not applicable and the study were accordance with the principles outlined in the Declaration of Helsinki. The medical records of women who were diagnosed with EIN between 2007 and 2021 and subsequently underwent hysterectomy with or without bilateral salpingo-oophorectomy at Siriraj Hospital.

All pathological slides were reviewed by an experienced gynecologic pathologist (S.H.) to confirm the diagnosis of EIN. The diagnoses of EIN were based on various methods of endometrial tissue collection, including endometrial aspiration, sampling, fractional curettage, or hysteroscopy. Patients were excluded if their pathology reviews did not confirm EIN, if they did not undergo hysterectomy, or if their medical information was incomplete. Demographic data, imaging results, pathology findings, operative records, and pathology reports were extracted and recorded.

High-risk carcinoma, which indicates regional lymph node dissection, was defined according to the following three criteria:

- The International Federation of Gynecology and Obstetrics (FIGO) defines high-risk carcinoma as (i) grade 1 endometrioid with > 50% myometrial invasion, (ii) grade 2 or 3 endometrioid with myometrial invasion, or (iii) non-endometrioid types [8].
- The Gynecologic Oncology Group (GOG) 167 defines high-risk carcinoma as (i) any grade with myometrial invasion, or (ii) grade 2 or grade 3 endometrioid or non-endometrioid carcinoma [10].
- The Mayo criteria classify high-risk carcinoma as (i) grade 1 or grade 2 endometrioid > 2 cm, (ii) > 50% myometrial invasion, or (iii) grade 3 endometrioid or non-endometrioid [6, 11].

Statistical analyses were performed using PASW Statistics, version 18 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were utilized for continuous demographic data, which are presented as the means and standard deviations or as medians and ranges. Categorical data are reported as numbers and percentages. Stepwise logistic regression analysis identified factors predicting occult endometrial carcinoma in hysterectomy specimens, with variables with $p < 0.05$ included in the multivariable analysis. The results are reported using odds ratios (ORs) and 95% confidence intervals (CIs). A p value < 0.05 was considered to indicate statistical significance.

Results

One hundred and thirty patients were eligible, but 15 were excluded due to choosing medical treatment, and 2 were re-diagnosed with benign endometrial hyperplasia. A total of 113 patients were enrolled in the study. The demographic, clinical, and pathological characteristics of the patients are detailed in Table 1. Patient ages ranged from 27 to 71 years, with a median age of 48.0 years (interquartile range [IQR] 39.0–54.0 years). The median body mass index was 28.60 kg/m^2 (IQR 23.36–35.11 kg/m^2). The median parity was 1 (IQR 0–2); 56 patients were nulliparous, 17 had one parity (P1), 28 had two parities (P2), and 12 had three parities (P3). Transvaginal sonography was performed before endometrial tissue biopsy in

Table 1 Patient demographics and clinical data for 113 patients diagnosed with endometrioid intraepithelial neoplasia who underwent hysterectomy

Variables	*N* (%)
Age, y	
< 50	64 (56.6)
≥ 50	49 (43.4)
BMI, kg/m^2	
< 30	63 (55.8)
≥ 30	50 (44.2)
Parity	
Nulliparous	56 (49.6)
Multiparous	57 (50.4)
Menopause status	
Premenopausal	83 (73.5)
Postmenopausal	30 (26.5)
Breast cancer	3 (2.7)
Diabetes mellitus	17 (15.0)
Hypertension	26 (23.0)
Endometrial thickness by transvaginal sonography	
Not evaluated	43 (38.1)
< 1 cm	14 (12.4)
1 to < 2 cm	22 (19.5)
≥ 2 cm	34 (30.1)
Endometrial biopsy methods	
Endometrial sampling	62 (54.9)
Fractional curettage	47 (41.6)
Hysteroscopy resection or biopsy	4 (3.5)
Intraoperative tumor size	
No lesion	56 (49.6)
< 2 cm	27 (23.9)
≥ 2 cm	33 (29.2)
Operations	
Hysterectomy	7 (6.0)
Hysterectomy plus BS	22 (19.0)
Hysterectomy plus BSO	61 (54.0)
Hysterectomy plus BS/BSO plus LNS	23 (19.8)
Pathology tumor size	
No gross lesion	42 (37.2)
Gross lesion ≤ 2 cm	33 (29.2)
Gross lesion > 2 cm	38 (33.6)
Pathology from hysterectomy specimen	
Normal endometrium	19 (16.8)
Endometrioid intraepithelial neoplasia	58 (51.3)
Endometrioid endometrial carcinoma	36 (31.9)

Abbreviations: BMI, body mass index; BS, bilateral salpingectomy; BSO, bilateral salpingo-oophorectomy; LNS, pelvic with or without para-aortic lymph nodes sampling

Table 2 Clinicopathological features of 36 patients with concurrent endometrial carcinoma

Variables	*N* (%)
Intraoperative tumor size	
No lesion	8 (22.2)
< 2 cm	11 (30.6)
≥ 2 cm	17 (47.2)
Pathology tumor size	
No gross lesion	6 (14.3)
Gross lesion < 2 cm	9 (27.3)
Gross lesion ≥ 2 cm	21 (55.3)
Grading	
Grade 1	32 (88.9)
Grade 2	3 (8.3)
Grade 3	1 (2.8)
Myometrial invasion	
No	21 (86.7)
Invasion ≤ 1/2	12 (10.6)
Invasion > 1/2	3 (2.7)
High-risk per FIGO criteria	4 (11.1)
High-risk per GOG 167 criteria	16 (44.4)
High-risk features per Mayo criteria	21 (58.3)
Lymph-vascular space invasion	1 (0.9)
Cervical stromal invasion	1 (0.9)
Tubal involvement, *n* = 36	3
Ovarian metastasis, *n* = 27	2
Pelvic lymphadenectomy, *n* = 23	
Negative	22
Positive	1
Para-aortic lymphadenectomy, *n* = 14	
Negative	14
Positive	0
FIGO stages	
IA	31 (86.1)
No myometrial invasion	10
Myometrial invasion < 50%	21
IB	1 (2.8)
IIIA	3 (8.3)
IIIC1	1 (2.8)
Adjuvant treatment	
None	31 (86.1)
Radiation	1 (2.8)
Chemotherapy	4 (11.1)

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; GOG, Gynecologic Oncology Group

70 cases. The median time to hysterectomy was 9.1 weeks (range 5.8–12.8 weeks). Post-hysterectomy, 36 patients (31.8%) were diagnosed with endometrial carcinoma.

The tumor characteristics of the 36 patients diagnosed with carcinoma are presented in Table 2. Histopathological examination revealed all carcinomas to be of the endometrioid type, with 32 tumors classified as grade 1, three as grade 2, and one as grade 3. Of these patients, 32 were classified as stage I according to the 2023 FIGO classification. Four patients presented with stage III disease: one had metastasis to the fallopian tube, one to both the tubal and ovarian regions, one to the tubal and pelvic nodes, and one to the ovary. Among the 113 patients with EIN, 3.5% (4 patients) were classified as high risk by the FIGO criteria, 14.1% (16 patients) by the GOG criteria, and 18.5% (21 patients) by the Mayo criteria. Specific

Table 3 Predictive factors for occult endometrial carcinoma in patients with endometrioid intraepithelial neoplasia who underwent hysterectomy

Variables	ECA *N* (%)	OR (95% CI)	*P* value	aOR (95% CI)	*P* value
Age, y					
< 50, *n* = 64	23 (35.9)	Reference	0.289		
≥ 50, *n* = 49	13 (26.9)	0.644 (0.285–1.453)			
BMI (kg/m^2)					
≤ 30, *n* = 63	15 (23.8)	Reference	0.041		
> 30, *n* = 50	21 (42.0)	2.317 (1.034–5.194)			
< 23, *n* = 25	7 (28.0)	Reference	0.639		
≥ 23, *n* = 88	29 (33.0)	1.264 (0.475–3.367)			
Parity					
Multiparous, *n* = 56	13 (22.8)	Reference			
Nulliparous, *n* = 57	23 (41.1)	1.801 (1.017–3.189)	0.037		
Menopausal status					
Premenopausal, *n* = 83	29 (34.9)	Reference	0.242		
Postmenopausal, *n* = 33	7 (23.3)	0.567 (0.217–1.478)			
Diabetes mellitus					
No, *n* = 96	30 (31.3)	Reference	0.742		
Yes, *n* = 17	6 (35.3)	1.200 (0.406–3.549)			
Hypertension					
No, *n* = 87	26 (29.9)	Reference	0.412		
Yes, *n* = 26	10 (38.5)	1.466 (0.588–3.657)			
Endometrium thickness					
< 2 cm, *n* = 36	9 (25.0)	Reference	0.236		
≥ 2 cm, *n* = 34	13 (38.2)	1.857 (0.667–5.168)			
Endometrial biopsy methods					
FC/hysteroscopy, *n* = 51	11 (21.6)	Reference	0.036	Reference	0.032
ES, *n* = 62	25 (40.3)	2.457 (1.063–5.682)		2.752 (1.092–6.936)	
Intraoperative gross lesion					
No gross lesion, *n* = 56	10 (17.9)	Reference		Reference	
Gross lesion < 2, *n* = 38	15 (39.5)	3.867 (1.320-11.327)	0.014	3.381 (1.128–10.132)	0.030
Gross lesion ≥ 2, *n* = 19	11 (57.9)	5.977 (2.264–16.503)	0.001	6.723 (2.338–19.333)	< 0.001

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; ECA, endometrium carcinoma; ES, endometrial sampling; FC, fractional curettage; OR, odds ratio; TVS, transvaginal sonography

analysis of the 36 patients with carcinoma revealed that the proportions of high-risk classifications were notably greater: 11.1% according to FIGO, 44.4% according to GOG, and 68.3% according to the Mayo criteria.

The univariable analysis revealed that the variables associated with occult endometrial carcinoma were endometrial aspiration, intraoperative tumor size, nulliparity, and a body mass index greater than 30 kg/m^2 (Table 3). The multivariable analysis determined that endometrial aspiration and intraoperative lesion size were independent predictors of occult carcinoma.

Discussion

The significance of EIN lies not only in its role as a precursor lesion but also in its association with occult endometrial carcinoma. The high prevalence of these carcinomas underscores the risk of preoperatively undiagnosed malignancy in patients diagnosed with EIN. Some patients undergo hysterectomy, with or without salpingo-oophorectomy, which was deemed inappropriate in certain cases. This situation may be especially concerning for those desiring uterus-preserving treatments. The risk of occult carcinoma can influence the decision to opt for hysterectomy over medical management for EIN. This study uniquely contributes to the understanding of occult endometrial carcinoma by identifying independent predictive factors such as endometrial sampling and intraoperative gross tumor volume, which can inform more accurate clinical decision-making.

Our investigation identified a 31.8% prevalence of occult endometrial carcinoma among patients with preexisting EIN, a figure that aligns with previously reported rates ranging from 27–53%.[5–8,10] The variability in these rates may be attributed to differences in demographic and ethnic backgrounds among the populations sampled. Physicians should consider these proportions when

choosing the treatment modality or surgical procedure. Additionally, while our 31.8% prevalence is consistent with reported rates, our study uniquely identifies independent predictive factors, such as endometrial sampling and intraoperative gross tumor volume, in a population with specific clinical features, thus filling a gap in the existing literature.

Notably, all occult carcinomas identified in our cohort were of the endometrioid type, suggesting that EIN is a precursor to endometrioid endometrial carcinoma. A sizeable majority (88.9%) of these carcinomas were classified as stage I, consistent with prior findings [5, 9, 12–14]. Standard surgical treatment for endometrial carcinoma includes extrafascial hysterectomy and bilateral salpingo-oophorectomy, with selective lymph node dissection recommended in patients with high-risk carcinoma to have nodal metastasis. The current study highlights considerable variability in the delineation of high-risk carcinoma, depending on the classification criteria employed. Unlike prior studies that may use differing criteria for high-risk classification, our research utilizes consistent methodology, demonstrating the need for clearer standardization in defining high-risk carcinoma to guide surgical decision-making.

Previous studies have identified pre-hysterectomy factors that can predict occult carcinoma in patients diagnosed with EIN, such as preoperative sonography assessing endometrial stripe thickness, endometrial biopsy techniques, and intraoperative tumor size. Transvaginal sonography is a valuable tool for evaluating patients with abnormal uterine bleeding, particularly in assessing endometrial carcinoma risk through endometrial thickness measurements. For example, Vetter et al.'s study involving 169 women with EIN reported that an endometrial thickness cutoff of ≥ 2 cm was an independent predictor for occult carcinoma, with an adjusted OR of 4.0 (95% CI 1.6 to 10.1). Additionally, they reported that 44% of EIN patients exhibited tumor characteristics indicative of lymph node metastasis based on the Mayo criteria [6]. However, our findings suggest that sonography alone may overlook occult carcinomas in EIN patients. Thus, combining sonography with additional diagnostic methods, such as endometrial biopsy or curettage, may improve diagnostic accuracy and guide appropriate management decisions.

Similarly, Abt et al.'s study of 378 women with EIN using endometrial thickness cutoffs of ≥ 1.5 cm and ≥ 2 cm yielded adjusted ORs of 1.6 (95% CI 1.1–2.3) and 1.9 (95% CI 1.3–2.8), respectively. They revealed that 31% of women diagnosed with carcinoma were classified as high risk according to the Mayo criteria [14]. In contrast, the present investigation found no significant association between endometrial thickness and occult carcinoma. This lack of association may be due to the relatively small sample size (70 women undergoing sonography), which might not have provided sufficient statistical power to validate the predictive value of sonographic measurements. While transvaginal sonography remains a widely used predictive tool, our study highlights discrepancies in endometrial thickness measurements, underscoring the need for tailored sonographic assessments, particularly in populations with specific clinical features or risk factors. A larger cohort may offer the statistical power required to validate the predictive value of sonographic measurements. Future studies with expanded populations and multicenter designs are necessary to confirm our findings and ensure generalizability.

Endometrial biopsy emerged as an independent predictor of occult carcinoma in this study, corroborating findings from previous research. A study comparing endometrial biopsy to dilatation and curettage in women with complex atypical hyperplasia revealed markedly different rates of occult carcinoma: 45.9% for endometrial biopsy versus 26.8% for dilatation and curettage ($p < 0.001$).[8] In another study, the risk of occult carcinoma was twice as high in women who underwent endometrial sampling than in those who had dilatation and curettage-based biopsy techniques (OR 2.0, 95% CI 1.4 to 2.9) [7]. These findings suggest that curettage-based techniques offer greater accuracy than endometrial aspiration in detecting carcinoma within the EIN cohort. This increased accuracy is likely due to the more comprehensive tissue sample obtained through curettage.

Our findings further affirm the importance of biopsy techniques, particularly dilatation and curettage, in detecting occult carcinoma. While endometrial biopsy is less invasive, its lower accuracy compared to curettage suggests that a sequential approach may offer optimal diagnostic precision. Performing curettage after an initial biopsy can confirm pathology and improve preoperative decision-making. Although endometrial biopsy emerged as a significant predictive factor in our study, our results uniquely highlight differences in aspiration accuracy and sample variability. These findings suggest that a combined approach, incorporating both biopsy and curettage, could enhance diagnostic accuracy for occult carcinoma and guide more effective treatment planning.

A larger intraoperative tumor size has been robustly identified as an independent predictor of occult carcinoma. Theoretically, larger tumor sizes in endometrial carcinoma correlate with increased rates of lymph node metastasis, as stated by the Mayo criteria [11]. Although this factor often aligns with the sonographic assessment of endometrial thickness, it becomes critically important when preoperative sonography is not conducted. During hysterectomy, intraoperative examination of the uterine cavity is essential not only for detecting occult carcinoma but also for assessing the risk of nodal involvement. Our

identification of tumor size as a predictive factor further emphasizes the importance of intraoperative gross examination, particularly when preoperative imaging is unavailable or inconclusive.

A key strength of this study was its review of pathology specimens from a substantial number of patients, which was performed by a gynecologic pathologist using EIN terminology. However, the clinical outcomes of patients diagnosed with endometrial carcinoma have yet to be reported. While our study benefits from a rigorous pathological review and the use of EIN terminology, the relatively small sample size is a limitation that may restrict the generalizability of certain findings. This underscores the importance of validating our results in larger, more diverse cohorts to strengthen their clinical applicability.

There is currently no precise risk stratification system for predicting occult carcinoma and nodal involvement. Some studies have evaluated molecular markers, such as the loss of phosphatase and tensin homologs, mismatch repair deficiency, or p53 expression, as potential predictors of increased risk for occult carcinoma [12]. To better guide lymphadenectomy decisions, future research should prospectively evaluate various methods for enhancing the prediction of occult carcinoma. These methods include measuring endometrial thickness using vaginal sonography at different cutoff points, conducting Doppler flow studies, and repeating endometrial biopsies via fractional curettage or hysteroscopy. Additionally, the use of immunohistochemistry and the assessment of frozen section accuracy are crucial for predicting occult carcinoma and evaluating nodal metastasis risk. Further refinements in diagnostic tools, such as combining sonographic and biopsy findings with molecular markers like p53 expression or mismatch repair deficiency, may provide a more comprehensive risk stratification system for occult carcinoma. Future research should prioritize the development and validation of multimodal diagnostic frameworks to improve clinical decision-making.

Conclusions

Occult endometrial carcinoma was identified in 31.8% of preoperatively diagnosed EIN patients who underwent hysterectomy, with endometrial sampling and intraoperative gross tumor volume emerging as independent predictors. This study provides critical data on the prevalence and risk factors associated with occult carcinoma in EIN patients, emphasizing the diagnostic challenges encountered in clinical practice. The findings highlight the importance of adopting a multimodal diagnostic approach to enhance diagnostic accuracy and support more informed clinical decision-making for patients with EIN.

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Author contributions
All the authors contributed to the study design. W.T., S.H., and I.R. collected the data. W.T., S.K., and I.R. were responsible for the data analysis and interpretation. W.T. drafted the manuscript, while S.K. and I.R. revised it for important intellectual content. All authors approved the final version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics norm or standard
The research was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Human ethics and consent to participate declarations
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Consent to participate
Since no individual participants were involved, there was no need for a consent to participate.

Competing interests
The authors indicate no potential conflicts of interest.

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