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Prevalence of Endometrial Cancer in Patients with Endometrioid Intraepithelial Neoplasia Histology

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ABSTRACT

Objectives: The primary objective was to ascertain the prevalence of concurrent endometrial cancer among patients initially diagnosed with endometrial intraepithelial neoplasia (EIN). The secondary objective was to assess the characteristics and risk factors associated with occult endometrial cancer in EIN patients.

Materials and Methods: This retrospective study analyzed cases spanning from 2015 to 2019 of patients diagnosed with EIN through various endometrial biopsy methods, including endometrial sampling, fractional curettage, or hysteroscopic biopsy. Demographic information and histological findings from hysterectomy specimens were collected to determine the prevalence of concurrent endometrial cancer. In the conservative group, patients were categorized as not having concurrent cancer if malignancy was not found in the 12-month follow-up period. Descriptive statistics were employed to evaluate the prevalence of concurrent endometrial cancer in EIN patients, alongside demographic and clinical characteristics. Multivariable logistic regression analysis was utilized to explore the association between demographics and clinical factors with concurrent endometrial cancer.

Results: A total of 130 EIN patients were included. The mean age of patients diagnosed with concurrent endometrial cancer was 47.02 (standard deviation (SD) 13.2) years and 52.23 (SD 10.9) years for those without endometrial cancer. The prevalence of concurrent endometrial cancer in EIN patients was 23.1%, (95% confidence interval 16.1 - 31.2). The prevalence of concurrent endometrial cancer in the surgical group was 32.5% and in the conservative group was 8%. All patients diagnosed with concurrent endometrial cancer exhibited uterine-confined disease, with no diagnoses of stage III or IV disease.

Conclusion: Approximately one-third to one-fourth of EIN patients diagnosed via endometrial sampling were found to have concurrent endometrial cancer. Notably, all patients diagnosed with concurrent endometrial cancer exhibited uterine-confined disease. We recommend using this data for counseling patients who have EIN in both surgical and conservative cases.

Keywords: atypical endometrial hyperplasia, concurrent endometrial cancer, endometrial carcinoma, endometrioid intraepithelial neoplasia (EIN), occult cancer.

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ความชุกของมะเร็งเยื่อบุโพรงมดลูก ในผู้ป่วยที่มีผลตรวจเยื่อบุโพรงมดลูกเป็น Endometrioid Intraepithelial Neoplasia (EIN)

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บทคัดย่อ

วัตถุประสงค์*: วัตถุประสงค์หลักเพื่อศึกษาความชุกของมะเร็งเยื่อบุโพรงมดลูกในผู้ป่วยที่มีผลการตรวจชิ้นเนื้อจากโพรงมดลูกเป็น Endometrioid Intraepithelial Neoplasia (EIN) วัตถุประสงค์รอง เพื่อประเมินลักษณะและปัจจัยเสี่ยงในผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกในผู้ป่วยที่มีผลการตรวจชิ้นเนื้อจากโพรงมดลูกเป็น EIN*

วัสดุและวิธีการ*: เป็นการศึกษาแบบย้อนหลัง ตั้งแต่ปี พ.ศ.2558 ถึง 2562 โดยรวบรวมผู้ป่วยที่มีผลการตรวจชิ้นเนื้อจากโพรงมดลูกเป็น EIN ซึ่งจะเก็บทั้งการสุ่มตัดชิ้นเนื้อจากโพรงมดลูก (endometrial biopsy) การขูดมดลูกแบบแยกส่วน (Fractional curettage) และการส่องกล้องตัดชิ้นเนื้อในโพรงมดลูก (Hysteroscopic biopsy) โดยเก็บข้อมูลพื้นฐานของผู้ป่วยและใช้ผลพยาธิวิทยาของชิ้นเนื้อที่ได้จากการตัดมดลูกมาวิเคราะห์ว่ามีมะเร็งซ่อนอยู่หรือไม่ ในกลุ่มที่ได้รับการรักษาแบบธำรงภาวะเจริญพันธุ์ จะถือว่าไม่มีมะเร็งซ่อนอยู่เมื่อตรวจติดตามไปมากกว่า 1 ปี แล้วไม่พบหลักฐานว่ามีมะเร็งซ่อนอยู่ ข้อมูลพื้นฐานของผู้ป่วย รวมทั้งข้อมูลทางคลินิก และผลทางพยาธิวิทยาจะถูกรวบรวมและนำมาวิเคราะห์หาความชุกของการมีมะเร็งเยื่อบุโพรงมดลูกซ่อนอยู่ และความสัมพันธ์ของปัจจัยกับการมีมะเร็งเยื่อบุโพรงมดลูกซ่อนอยู่*

ผลการศึกษา*: การศึกษานี้รวบรวมผู้ป่วยที่มีผลการตรวจโพรงมดลูกเป็น EIN จำนวน 130 ราย อายุเฉลี่ยของผู้ป่วยกลุ่มที่มีมะเร็งซ่อนอยู่คือ 47.02 ปี (SD 13.2) และกลุ่มที่ไม่มีมะเร็งซ่อนอยู่คือ 52.23 ปี (SD 10.9) ความชุกของการมีมะเร็งซ่อนอยู่ คือ ร้อยละ 23.1 (95%CI : 16.1-31.2) โดยความชุกของการมีมะเร็งซ่อนอยู่ในกลุ่มที่ได้รับการตัดมดลูก คือ ร้อยละ 32.5 และกลุ่มที่ได้รับการรักษาแบบธำรงภาวะเจริญพันธุ์ คือ ร้อยละ 8 ผู้ป่วยที่มีมะเร็งซ่อนอยู่ทั้งหมดนั้นยังไม่มีการ กระจายออกนอกตัวมดลูก และไม่พบผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกระยะที่ 3-4 ในการศึกษานี้*

สรุป*: หนึ่งในสาม ถึง หนึ่งในสี่ของผู้ป่วยที่มีผลการตรวจเยื่อบุโพรงมดลูกเป็น EIN จะมีมะเร็งเยื่อบุโพรงมดลูกซ่อนอยู่ และในกลุ่มนั้น รอยโรคจะยังอยู่ในตัวมดลูก ข้อมูลดังกล่าวเป็นข้อมูลสำคัญที่ควรให้แก่ผู้ป่วยก่อนเริ่มรักษาทั้งในกลุ่มที่ตัดมดลูก*

และ กลุ่มที่รักษาด้วยวิธีธำรงภาวะเจริญพันธุ์

***คำสำคัญ**: ภาวะเยื่อบุโพรงมดลูกหนาตัวชนิด Atypical endometrial hyperplasia, การพบมะเร็งร่วม, มะเร็งเยื่อบุโพรงมดลูก, ภาวะเยื่อบุโพรงมดลูกหนาตัวชนิด Endometrioid intraepithelial neoplasia (EIN), การมีมะเร็งซ่อนอยู่*

Introduction

Endometrial cancer is the most common gynecologic cancer in developed countries. The incidence of endometrial cancer has continuously increased[1]. Endometrioid intraepithelial neoplasia (EIN) in the World Health Organization (WHO) classification of endometrial hyperplasia, is considered a precursor of endometrial cancer. Endometrial hyperplasia is a disorder induced by prolonged unopposed endogenous or exogenous estrogen exposure[2,3].

The pathology of endometrial hyperplasia is defined by an increase in gland and stroma ratio that resulting in abnormal architecture and cytologic features of the endometrial gland. Endometrial hyperplasia is diagnosed using various criteria. According to the WHO 1994 classification, endometrial hyperplasia is classified as simple hyperplasia without atypia, complex hyperplasia without atypia, simple hyperplasia with atypia, and complex hyperplasia with atypia. In 2000, the International Endometrial Collaborative Group proposed the EIN classification, which the International Society of Gynecologic Pathologists later accepted in 2014. The WHO 2014 classification divided hyperplasia into benign hyperplasia and atypical hyperplasia (AH)/EIN. Therefore, the EIN classification is becoming more popular because it is easier to use and has more defined criteria for interpreting data[3-5].

Occult endometrial cancer has been detected in several patients following curettage, endometrial sampling, or hysterectomy subsequently to the EIN diagnosis. Previous studies have been reported variable rates of occult endometrial cancer in patients with EIN, ranging from 17 to 52%[6,7]. EIN can be managed with hormonal therapy or hysterectomy, which is less aggressive than the treatment of endometrial cancer. Standard treatment of endometrial cancer typically involves surgical staging for determining cancer stage and may include radiation or chemotherapy[8,9].

In Thailand, endometrial hyperplasia has been characterized utilizing diverse classification due to transition in terminology from the WHO 1994 classification to the EIN classification. Furthermore, variations in classification utilization among pathologists have been observed due to individual preferences. Research endeavors exploring the prevalence of occult endometrial cancer in endometrial hyperplasia or EIN biopsies in Asia have been limited, with most focusing solely on endometrial hyperplasia classification[10-12]. Therefore, the primary objective of this study was to ascertain the prevalence of concurrent endometrial cancer in patients initially diagnosed with EIN, while the secondary objective was to evaluate the characteristics and risk factors associated with occult endometrial cancer in EIN patients.

Materials and Methods

This retrospective cohort study was conducted at King Chulalongkorn Memorial Hospital (KCMH), a university hospital in Bangkok, Thailand. The study protocol was approved by the Research Ethics Committee of the Faculty of Medicine, Chulalongkorn University. Data collection commenced following the

institutional review board approved the protocol (IRB No. 557/64).

Data spanning from 2015 to 2019 were gathered. All specimens obtained through endometrial sampling including endometrial biopsy, fractional curettage or hysteroscopic biopsy, were reviewed. Pathological results indicative of any type of endometrial hyperplasia or EIN were included in the study.

All patients diagnosed with endometrial hyperplasia and EIN at KCMH between 2015 and 2019 were recruited. In our institution, most of the endometrial hyperplasia cases were reported according to the WHO 1994 classification. EIN classification has been used since 2018. Endometrial hyperplasia included simple hyperplasia without atypia, complex hyperplasia without atypia, simple hyperplasia with atypia, and complex hyperplasia with atypia from WHO 1994 classification. Pathological slides initially classified under the WHO 1994 classification were re-classified as per the EIN classification by two pathologists (N.P. and C.A.). Any discordant results were jointly reviewed, and a consensus diagnosis was reached. Slides initially classified under the EIN classification were also reviewed to confirm the diagnosis of EIN. The pathologists were blinded to the initial diagnosis and all slides were re-categorized as less than EIN, EIN, and malignancy.

The study population comprised patients identified with EIN following slide review by pathologists. Data collected included demographic information, risk factors, treatment options, pathological diagnosis following hysterectomy, and details of follow-up visits.

Final diagnosis was determined based on the final pathological findings of hysterectomy specimens in surgical cases. Conservative cases encompassed patients requiring fertility preservation or those who declined surgical interventions for other reasons. For conservative cases, treatment included oral progestin or levonorgestrel intrauterine devices (IUDs) were offered. Patients declining surgery, oral progestin and levonorgestrel IUDs were offer closed follow-up option. Endometrial sampling was conducted every 3 to 6 months for conservative cases, with the absence of malignancy in consecutive samples over a minimum 12-month follow-up period indicative of no occult malignancy. Patients with insufficient information or unavailable slides for review were excluded from the study.

Statistical analysis was performed using SPSS version 22 (SPSS Inc, Chicago, IL, USA). Descriptive analyses were employed to assess the prevalence of concurrent endometrial cancer in EIN patients. Demographic data were presented as frequency, percentage, mean, and standard deviation (SD) as appropriate. Between groups comparisons (with and without occult malignancy) utilized independent t-tests for continuous variables and a chi-square tests or Fisher's exact tests for categorical variables. Logistic regression analyses were conducted to evaluate the association between demographics and clinical factors with concurrent endometrial cancer, presenting odds ratios (ORs) and 95% confidence intervals (95% CIs). Parameters for multivariable analysis were derived from the literature review, incorporating demographics and clinical factors exhibiting statistical significance ($p < 0.05$) in the univariable model. Statistical significance was set at p value < 0.05. Sample size calculation was based on data from a previous study[7], with 94 participants deemed necessary to provide adequate power for addressing the primary research question.

Results

Between 2015 and 2019, a total of 374 patients were diagnosed with endometrial hyperplasia according to the WHO 1994 classification, while 52 patients were diagnosed with EIN using the EIN classification from endometrial sampling, fractional curettage and hysteroscopic biopsy. Six patients from the WHO classification were excluded due to missing pathological slides. For the remaining 368 patients who were previously classified with the WHO classification, their slides were reviewed and re-

categorized into three categories: less than EIN, EIN, and malignancy. Upon evaluation, 21.1% (78/368 patients) were diagnosed with EIN, while 67.7% (249/368 patients) were categorized as less than EIN, and 11.1% (41/368 patients) were diagnosed with endometrial cancer (Fig. 1). Among the 78 patients reclassified as EIN, 52.6% (41/78 patients) had previously been diagnosed with simple hyperplasia without atypia, 11.5% (9/78 patients) with simple hyperplasia with atypia, 20.5% (16/78 patients) with complex hyperplasia without atypia, and 15.4% (12/78 patients) with complex hyperplasia with atypia. Of the 52 patients previously diagnosed with EIN, all were confirmed as EIN. Consequently, 130 patients with EIN were included in the study (Fig. 1).

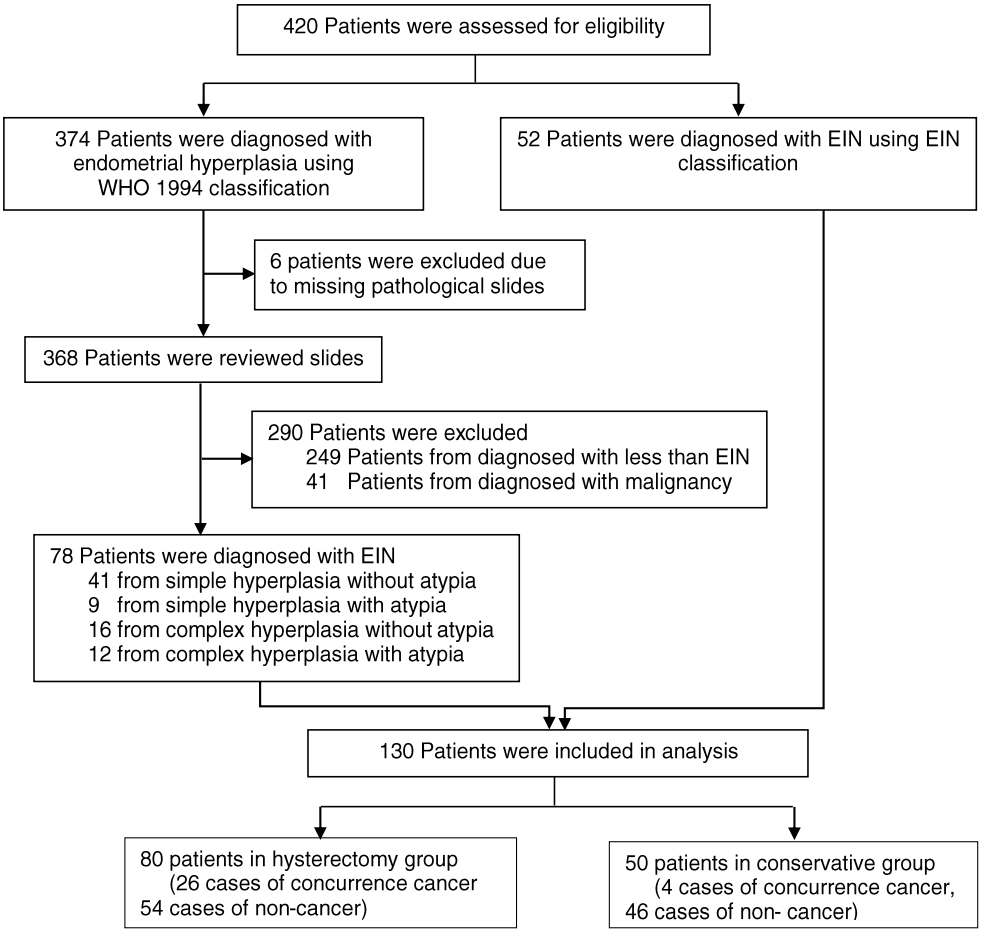

Fig. 1. Study Flow.
EIN: Endometrioid Intraepithelial Neoplasia

Among the 130 EIN patients, 80 underwent hysterectomy while 50 received conservative treatment. Following the final results, 30 out of 130 patients (23.1% (95%CI 16.1-31.2) were diagnosed with concurrent endometrial carcinoma, with the remaining 100 patients showing no concurrent endometrial carcinoma. Of the 80 patients in the surgical group, 26 had concurrent cancer, compared to 4 out of 50 in the conservative group. The mean age of the patients in the concurrent endometrial cancer group was 47.02 years (SD 13.2) compared to 52.23 years (SD 10.9) for those without endometrial

cancer. While body mass index (BMI) did not statistically significant differences between the cancer and non-cancer groups, there was a tendency towards higher proportions of overweight and obesity individuals in the former group. Most patients in both groups were premenopausal women (60% and 77.0%, respectively). The majority of the patients had no underlying medical conditions. Patients with underlying medical conditions included hypertension, diabetes, dyslipidemia, breast cancer, and polycystic ovarian syndrome (PCOS) were not different between the two groups. Three patients with underlying breast cancer were taking tamoxifen at the time of EIN diagnosis (Table 1).

Table 1. Baseline characteristics of the study participants (n = 130).

Characteristics		Concurrent endometrial cancer		p value
		Yes n (%) = 30 (23.1)	No n (%) = 100 (76.9)	
Age (mean (SD), years)		47.02 (13.2)	52.23 (10.9)	0.03**
BMI	Underweight (< 18.5 kg/m^2)	1 (3.3)	4 (4.0)	0.18
	Normal (18.5-24.9 kg/m^2)	8 (26.7)	38 (38.0)	
	Overweight (25-29.9 kg/m^2)	15 (50.0)	26 (26.0)	
	Obese class I (30-34.9 kg/m^2)	2 (6.7)	18 (18.0)	
	Obese class II (35-39.9 kg/m^2)	3 (10.0)	8 (8.0)	
	Obese class III (≥ 40 kg/m^2)	1 (3.3)	6 (6.0)	
Parity	Nulliparous	17 (56.7)	55 (55.0)	0.87
	Multiparous	13 (43.3)	45 (45.0)	
Menopausal status	Premenopause	18 (60.0)	77 (77.0)	0.06
	Postmenopause	12 (40.0)	23 (23.0)	
Underlying disease	No	20 (66.7)	54 (54.0)	0.96
	Hypertension	2 (6.7)	12 (12.0)	
	Diabetes	3 (10.0)	7 (7.0)	
	Dyslipidemia	2 (6.7)	9 (9.0)	
	Breast cancer	2 (6.7)	5 (5.0)	
	Polycystic ovarian syndrome	0 (0.0)	2 (2.0)	
Medication	No	20 (66.7)	70 (70.0)	0.76
	Tamoxifen	1 (3.3)	2 (2.0)	
	non-hormonal medication†	9 (30.0)	28 (28.0)	
Treatment	Hysterectomy	26 (86.7)	53 (53.0)	< 0.01
	Conservative treatment	4 (13.3)	47 (47.0)	
Methods of tissue collection	Endometrial sampling	16 (53.3)	41 (41.0)	0.30
	Fractional curettage	12 (40.0)	55 (55.0)	
	Hysteroscopic biopsy	2 (6.7)	4 (4.0)	

* Chi-square or Fisher Exact test, ** Independent t-test, † non-hormonal medication was a current medication that patients were taken regularly without the hormone estrogen
SD: standard deviation, BMI: body mass index

Most tissues were obtained via fractional curettage and endometrial biopsy. Demographic data of surgical cases and conservative cases are presented in Table 2, indicating that the patients in the conservative group were younger than those in the surgical group (43.66 vs 51.07 years old). Additionally, the percentage of menopausal status was lower in the conservative group compared to the surgical group (14% vs 35%).

All concurrent endometrial cancer cases were diagnosed as uterine-confined disease, with no diagnoses of stage III or IV. Ten concurrent endometrial cancer cases were associated with high-risk features, including stage IB, stage II, and pathological grade 2 and 3 (Table 3).

Age, menopausal status, parity, underlying medical conditions, and BMI were considered potential confounders in multivariable analysis. Patients over the age of 60 were independently associated with concurrent endometrial cancer, adjusted OR 4.37 (95%CI 1.04-18.29) (p = 0.04), when compared to patients under 40 years old. Association between menopausal status, parity, underlying disease, and BMI with concurrent endometrial cancer was not found (Table 4).

Table 2. Demographic data of the surgical group and the conservative group.

Demographic data	Surgical group n = 80	Conservative group n = 50
Age (mean (SD))	51.07 (10.25)	43.66 (12.01)
BMI (mean (SD))	27.23 (6.08)	29.23 (7.09)
Underlying disease (n (%))		
Yes	44 (55)	30 (60)
No	36 (45)	20 (40)
Menopause (n (%))	28 (35)	7 (14)
Concurrent malignancy (n (%))	26 (32.50)	4* (8)

In the conservative group, concurrent malignancy was found in 3 out of 43 oral progestin cases, 0 out of 2 levonorgestrel levonorgestrel intrauterine devices (IUDs) cases and 1 out of 5 closed observe cases.

SD: standard deviation, BMI: body mass index

Table 3. Uterine cancer staging and FIGO grade in patients with concurrent endometrial cancer (n = 30).

Stage	FIGO grade			Total n (%)
	Grade 1	Grade 2	Grade 3	
IA	20	6	0	26 (86.7)
IB	3	0	0	3 (10.0)
II	0	0	1	1 (3.3)
Total n (%)	23 (76.7)	6 (20.0)	1 (3.3)	

FIGO: International Federation of Gynecology and Obstetrics

Table 4. Multivariable logistic regression analysis of the association between demographics and clinical factors with concurrent endometrial cancer (n = 130).

Variable		Adjusted odds ratio (95% confidence interval)	p value
Age (mean (SD))	< 40 years	Reference	-
	40-59 years	1.82 (0.56-5.90)	0.31
	≥ 60 years	4.37 (1.04-18.29)	0.04
Menopausal status		2.23 (0.93-5.30)	0.06
Multiparity		0.93 (0.41-2.12)	0.87
Underlying disease	No	Reference	-
	Yes	0.58 (0.25-1.38)	0.22
BMI	Normal (18.5-24.9 kg/m^2)	Reference	-
	Underweight (< 18.5 kg/m^2)	1.18 (0.11-12.08)	0.88
	Overweight and Obese (≥ 25 kg/m^2)	1.72 (0.69-4.27)	0.24

BMI: body mass index

Discussion

The prevalence of concurrent endometrial cancer among patients with EIN histology in our study was 23.1% (95%CI 16.1-31.2), which was lower than the reported in European country and the United States[6, 7, 13], yet higher than the research published

between 1992-2005, which reported rate of approximately 9-18%[14, 15]. A meta-analysis encompassing 15 trials, 1496 patients, found the prevalence of concurrent endometrial cancer in patients diagnosed with endometrial hyperplasia was 32.1%, although the data exhibited high heterogeneity (I^2 = 87.6%)[13]. Notably, our study comprised two distinct subgroups: surgical and conservative groups. In the surgical group, the prevalence of concurrent endometrial cancer was 32.5%, mirroring the findings from papers in Europe and the United States[6, 7, 13]. Conversely, the prevalence of concurrent malignancy in the conservative group was markedly lower at 8% (4 out of 50), suggesting potential impacts of patient selection and treatment intervention. Patients in the conservative group tended to be younger than those in the surgical group. Additionally, treatment interventions such as oral progestin or levonorgestrel IUDs may influence pathologic findings in final histology. Furthermore, the follow-up endometrial sampling technique at the 12-months follow-up period, utilizing endometrial biopsy or curettage, may present a reduced chance of detecting concurrent malignancy compared to histologic results from hysterectomy specimens. Therefore, caution is warranted in interpreting this result.

In our study, some patients received conservative treatment. The reasons for choosing conservative treatment include young age and still have fertility desire. In the conservative group follow-up endometrial biopsy was performed every 3-6 months. The patient was considered to have no occult malignancy if no malignancy was found from endometrial sampling in at least 12 months in follow-up. This follow-up scheme aligned with the approach in the study by Baak et al[14], where endometrial curettage or biopsy was utilized for diagnosing concurrent endometrial cancer in conservative cases. Patients with endometrial hyperplasia who underwent conservative treatment in the study by Baak et al were monitored for 12 months, similar to our study[14].

We analyzed age, menopausal status, parity, underlying disease, and BMI to assess their association with concurrent endometrial cancer. Patients aged over 60 years were independently associated with concurrent cancer (adjusted OR 4.37 (95%CI 1.04-18.29), p = 0.04) compared to patients under 40 years old. However, menopausal status, parity, underlying disease, and BMI were not independently associated with concurrent endometrial cancer. These findings were partly different from the previous research by Kender et al and Trimble et al that reported age and atypia histology have a higher risk of concurrent endometrial cancer and high-risk cancer[7, 16]. However, our sample size was not calculated for detecting all the aspects of risk factors and associations in secondary objective, necessitating further research with adequate sample size to address these associations comprehensively.

Given the retrospective nature of our study, limitations exist, such as potential limitations in data quality, including slide degradation due to storage techniques. Missing data also poses a limitation. However, we made efforts to mitigate these limitations by meticulously evaluating slides from the WHO 1994 classification to establish a new EIN classification. The pathologists were blinded to the prior pathologic results to ensure the accuracy of the information. This study contributed to the limited body of research on the Asian population's prevalence of cancer in patients with EIN histology.

Conclusion

Approximately one-third to one-fourth of patients diagnosed with EIN via endometrial sampling had concurrent endometrial cancer. EIN in patients over 60 years old was independently associated with concurrent cancer. Notably, all patients diagnosed with concurrent endometrial cancer exhibited uterine-confined disease. We recommend counseling patients with EIN in both surgical and conservative cases using these data.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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