Original Research

The impact of pre-existing polycystic ovary syndrome on endometrial cancer recurrence

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Summary

Purpose: Polycystic ovary syndrome (PCOS) is a risk factor for the development of endometrial cancer (EC). To the present authors' knowledge, no study has clarified whether pre-existing PCOS is a prognostic factor for post-surgical EC recurrences. The aim of this study was to determine whether pre-existing PCOS is a risk factor for the recurrence of EC even after the surgical treatment of EC in premenopausal women. *Materials and Methods:* The authors performed a retrospective cohort study on premenopausal EC patients aged 50 years or younger who underwent surgery at this hospital between 2009 and 2013. The median follow-up period was 65.5 months. *Results:* Of 46 patients with EC, nine (19.6%) had PCOS. Four of the nine PCOS patients developed recurrence of EC, three of whom died of the disease, whereas only one of 37 patients who did not have PCOS developed EC recurrence (44.4% and 2.7%, respectively; $p = 0.003$). Univariate analysis showed that the progression-free and overall survival of the patients with pre-existing PCOS was worse than that of patients without pre-existing PCOS ($p = 0.008$ and $p = 0.029$, respectively). Multivariate analysis revealed that PCOS was a poor prognostic factor for progression-free survival and a marginal poor prognostic factor for overall survival ($p = 0.011$ and $p = 0.061$, respectively). *Conclusions:* Pre-existing PCOS was a risk factor for recurrence in premenopausal post-operative patients with EC aged 50 years or younger.

Key words: Polycystic ovary syndrome; Endometrial neoplasm; Recurrence; Premenopause; Insulin resistance.

Introduction

Polycystic ovary syndrome (PCOS) and endometrial cancer (EC) are common diseases affecting women, which share common risk factors, such as obesity and insulin resistance (IR) [1-4]. PCOS per se is a risk factor for EC occurrence [5-11], and women diagnosed with PCOS are three- to four-times more likely to develop EC than the general population [12, 13]. The fundamental mechanisms underlying the association between EC and PCOS have not yet been determined, although it is currently believed that IR-related factors, such as elevated insulin, insulin-like growth factor, estrogen, and sex hormone-binding globulin levels, are involved in the stimulation of cellular proliferation and carcinogenesis [14].

To the present authors' knowledge, no study has clarified whether pre-existing PCOS is a prognostic factor for postsurgical EC recurrences. Pillay *et al.* demonstrated that cyclin D1-expressing tumors are more prevalent in patients with polycystic ovaries than in those without [10]. Considering that cyclin D1 is associated with a poorer prognosis [15], we assume that pre-existing PCOS is a risk factor for EC recurrence after surgical treatment.

Understanding that pre-existing PCOS is a risk factor for post-surgical recurrence is clinically relevant because endocrine therapy targeting PCOS could be a supportive therapy for prevention of EC recurrence if some endocrine conditions associated with PCOS are risk factors for EC recurrence. Furthermore, recognition of pre-existing PCOS as a risk factor for EC recurrence would be beneficial for determining follow-up and adjuvant strategies following surgical treatment.

To clarify the impact of pre-existing PCOS on the recurrence of EC, the present authors compared the recurrence ratio of surgically treated EC between patients with and those without pre-existing PCOS.

Materials and Methods

Premenopausal women (aged 50 years or younger) with EC who underwent surgery at Chiba University Hospital between 2009 and 2013 were eligible for participation in this study. Patient data were collected from chart review. The serum levels of sex hormones were determined before initiation of EC treatment. A 75-g oral glucose tolerance test (OGTT) was performed if necessary. Insulin resistance (IR) was assessed using Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) [16]. A HOMA-IR score $\geq$ 2.5 was considered to indicate insulin resistance. There were 85 EC patients aged 50 years or younger during the study period. Of these, 46 met the inclusion criteria and 39 were excluded because of insufficient data (n = 12), menopausal status (n = 4), or no hysterectomy (n = 23) (Figure 1).

Table 1. — *Patient characteristics.*

Factor	PCOS+ n = 9	PCOS- n = 37	Total n = 46	p
Age (years) (median, range)	36 (27–42)	42 (29–50)	41.5 (27–50)	0.002
BMI (kg/m^2) (median, range)	36.2 (18.5–44.1)	26.3 (18.6–42.1)	27.2 (18.5–44.1)	0.051
Child birth	3 (33.3%)	18 (48.6%)	21 (45.7%)	0.478
Hypertension	2 (22.2%)	8 (21.6%)	10 (21.7%)	1
Diabetes mellitus	3 (33.3%)	6 (16.2%)	9 (19.6%)	0.348
Oligoovulation or anovulation	7 (77.8%)	8 (21.6%)	15 (32.6%)	0.003
Hyperandrogenism	6 (66.7%)	5 (13.5%)	11 (23.9%)	0.003
PCO	7 (77.8%)	3 (8.1%)	10 (21.7%)	< 0.001
LN metastasis (Positive)	2 (22.2%)	5 (13.5%)	7 (15.2%)	0.609
Myometrial invasion ($\geq$ 1/2)	3 (33.3%)	5 (13.5%)	8 (17.4%)	0.176
LVSI (Positive)	2 (22.2%)	9 (24.3%)	11 (23.9%)	1
Type II	2 (22.2%)	3 (8.1%)	5 (10.9%)	0.248
Stage I	5 (55.6%)	28 (75.7%)	33 (71.7%)	0.246
Stage IV	2 (22.2%)	2 (5.4%)	4 (8.7%)	0.167

PCOS: polycystic ovary syndrome; BMI: body mass index; PCO: polycystic ovaries; LN: lymph node; LVSI: lymphovascular space involvement, PCOS+: patients with pre-existing PCOS; PCOS-: patients without pre-existing PCOS
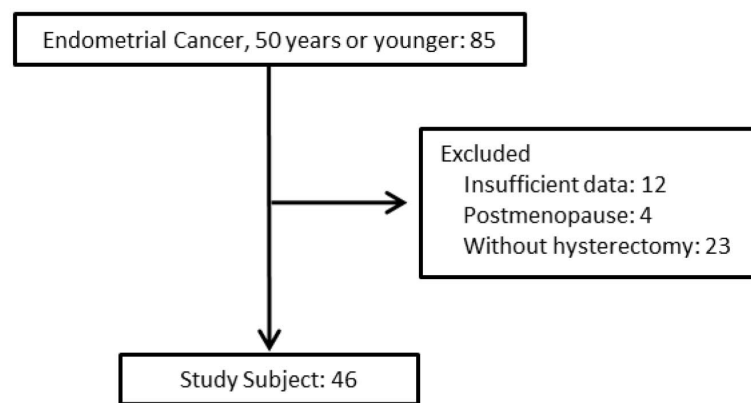

Figure 1. — Patient selection.

Of 46 patients, 41 were hysterectomized according to the guidelines of the Japan Society of Gynecologic Oncology (2009 edition) [17]. The remaining five patients underwent hysterectomy after treatment failure of fertility-sparing therapy using medroxyprogesterone acetate alone or a combination of medroxyprogesterone acetate and metformin, administered as part of an institutional clinical trial [18].

PCOS is diagnosed on the basis of the following Rotterdam criteria [19, 20]: oligoovulation or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries. A diagnosis of PCOS is made when at least two of the three criteria are met.

Patient characteristics were analyzed using continuous and categorical variables. Student's *t*-test or the Mann-Whitney *U*-test was used to assess the statistical significance of continuous variables. A logistic regression analysis, a two-sided Fisher's exact test or a chi-square test was used to assess the statistical significance of categorical variables. Progression-free survival (PFS) was defined as the time from the date of treatment initiation to the date of EC progression, last contact, or death from any cause, whichever occurred first. Overall survival (OS) was defined as the time from the date of initiation of treatment to the date of last contact or death from any cause. Log-rank tests were performed to determine possible prognostic factors using Kaplan-Meier methods. For multivariate analyses, Cox regression modeling was performed to identify independent prognostic factors. $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS version 21.

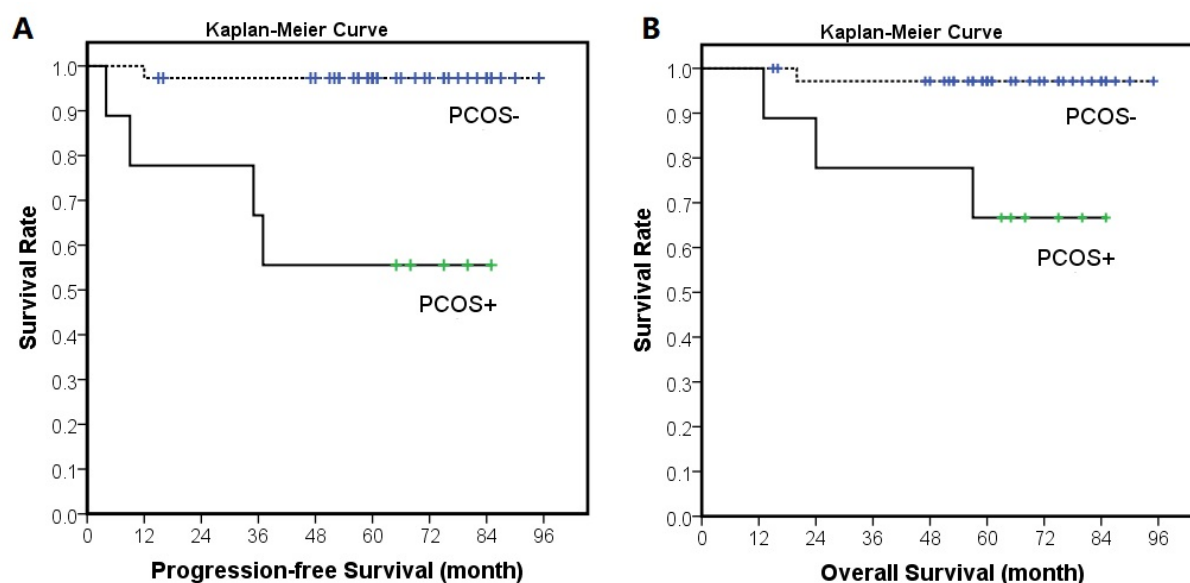This study was approved by the Institutional Review

A

B

Figure 2. — A) Kaplan-Meier curve of progression-free survival of patients with or without PCOS. The progression-free survival of patients with PCOS was significantly worse than that of those without PCOS (log-rank test, $p < 0.001$). B) Kaplan Meier curve of overall survival of patients with or without PCOS. The overall survival of patients with PCOS was significantly worse than that of those without PCOS (log-rank test, $p < 0.005$).

Table 2. — *Serum hormonal values of the patients.*

Factor	Median		p
	PCOS+	PCOS-	
	(n = 8)	(n = 29)	
BS 0 min (mg/dL)	103	103	0.631
BS 60 min (mg/dL)	200.5	154	0.053
BS 120 min (mg/dL)	144	121	0.06
IRI 0 min (μU/mL)	19.15	8.69	0.051
IRI 60 min (μU/mL)	106.4	70.8	0.042
IRI 120 min (μU/mL)	105.15	53.9	0.005
HOMA-IR	5.26	2.207	0.077
HOMA-IR $\geq$ 2.5	75.0% (6/8)	34.5% (10/29)	0.055

PCOS: polycystic ovary syndrome; BS: blood sugar; IRI: immunoreactive insulin; HOMA-IR: homeostasis model assessment of insulin resistance. PCOS+: patients with pre-existing PCOS; PCOS-: patients without pre-existing PCOS

Board of Chiba University and was conducted in accordance with the principles set forth in the Declaration of Helsinki (1964 and later versions).

Results

Of 46 patients, nine (19.6%) had pre-existing PCOS (PCOS+ patients) before treatment initiation. The PCOS+ patients were younger and tended to be more obese than the patients pre-existing without PCOS (PCOS- patients; Table 1). Of the PCOS+ patients, three were in their 20 s; four, in their 30 s; and two, in their 40 s. Seven of the nine PCOS+ patients (78%) had a body mass index (BMI) greater than 30 kg/m^2, while ten of the 37 PCOS- patients (27%) had a BMI greater than 30 kg/m^2 (7/9 [77.8%] *vs.* 10/37 [27.0%], odds ratio: 9.450, 95%CI: 1.674 – 53.351, $p = 0.011$). There were no differences in the history of childbirth, hypertension, or diabetes mellitus between the PCOS+ and PCOS- patients.

There was no difference in the incidence of type II EC between the PCOS+ and PCOS- groups (2/9 [22.2%] *vs.* 3/37 [8.1%], odds ratio: 3.238, 95%CI: 0.454 – 23.114, $p = 0.241$). Distributions of histological subtypes of type II cancer were, however, different between the two groups: endometrioid carcinoma G3 (n = 1) and mixed carcinoma (endometrioid carcinoma G2 plus serous carcinoma, n = 1) were observed only among PCOS+ patients, whereas serous carcinoma (n = 2) and undifferentiated carcinoma (n = 1) were observed only among PCOS- patients. Distribution of the clinical stage was not different between the two groups: the number of patients with Stages I, II, III, and IV were five, one, one, and two among PCOS+ patients and 28, three, four, and two among PCOS- patients, respectively (chi-square test, $p = 0.417$).

Patients with first-degree relatives who had a history of colorectal cancer were fewer among PCOS+ patients (0/9, 0%) than among PCOS- patients (6/37, 16%), but the difference was not significant ($p = 0.327$, two-sided Fisher's exact test). Furthermore, two of the PCOS- pa-

Table 3. — *Univariate and multivariate analyses of the patients on PFS.*

Factor	Yes vs. No	Univariate			Multivariate		
		HR	range	*p*	HR	range	*p*
PCOS	9 vs. 37	19.59	2.185–175.635	0.008	19.025	1.938–186.732	0.011
Oligoovulation or anovulation	15 vs. 31	3.342	0.558–20.013	0.186			
Hyperandrogenism	11 vs. 35	2.219	0.371–13.29	0.383			
PCO	10 vs. 36	5.707	0.953–34.176	0.056			
LN metastasis	7 vs. 39	4.767	0.79–28.779	0.089	4.325	0.435–43.057	0.212
Myometrial invasion $\geq$ 1/2	8 vs. 38	3.47	0.579–20.807	0.173	0.807	0.076–8.522	0.858
LVSI	11 vs. 35	2.219	0.371–13.29	0.383			
Type II	5 vs. 41	2.211	0.247–19.802	0.478			

PFS: progression free survival; HR: hazard ratio; C.I.: confidence interval; PCOS: polycystic ovary syndrome; PCO: polycystic ovaries; LN: lymph node; LVSI: lymphovascular space involvement.

tients had a history of colorectal cancer. Five patients had initiated hormone therapy as their primary treatment, followed by surgery after recurrence (one PCOS+ patient and four PCOS- patients). Although the fasting blood sugar level was the same, glucose loading-induced blood sugar and immunoreactive insulin levels were higher in PCOS+ patients than in PCOS- patients (Table 2). PCOS+ patients were almost twice as likely to have IR (a HOMA-IR score $\geq$ 2.5) compared with PCOS- patients (6/8 [75.0%] *vs.* 10/29 [34.5%], odds ratio: 5.70, 95% CI: 0.967 – 33.600, *p* = 0.054). The median follow-up period was 65.5 (range, 15–95) months.

Recurrence of EC was observed in four of nine PCOS+ patients compared with one of 37 PCOS- patients (44.4% and 2.7%, respectively; *p* = 0.003, two-sided Fisher's exact test). Kaplan-Meier curves of PFS and OS showed poorer prognoses for PCOS+ patients than for PCOS- patients (*p* < 0.001 and *p* < 0.005, respectively; log-rank test) (Figures 2A and 2B). Univariate analysis revealed that both PFS and OS of PCOS+ patients were significantly shorter than those of PCOS- patients (*p* = 0.008 and *p* = 0.029, respectively) (Tables 3 and 4). Multivariate analysis showed that PCOS was an independent poor prognostic factor for PFS (*p* = 0.011) (Table 3) and a marginally significantly poor prognostic factor for OS (*p* = 0.061) (Table 4).

The number of patients who died of EC was three and one among PCOS+ and PCOS- patients, respectively; the one PCOS- patient had advanced disease, while two of the three PCOS+ patients had early diseases (Stages I and II) (Table 5). One PCOS+ patient who died of early-stage disease was 29 years of age with Stage 1A endometrioid G1 cancer. She had disease progression (pelvic lymph node metastasis, bone metastasis) within four months of medroxyprogesterone-acetate therapy for fertility preservation, and the occurrence of anaplastic dedifferentiation was pathologically confirmed. Another PCOS+ patient who died of early-stage EC was 33

years of age with Stage II endometrioid G1 cancer. She underwent an emergency hysterectomy for a massive uterine hemorrhage followed by adjuvant chemotherapy, and was lost to follow-up. She appeared again two years later with a complaint of lumbago due to bone and lymph node metastases.

Discussion

The present authors found that PCOS was associated with a poorer prognosis even after removal of the uterus and the ovary. Thus, PCOS must affect EC recurrence in a manner other than through the ovary. Actually, PCOS was associated with IR and obesity, suggesting that the metabolic milieu of PCOS contributes to EC recurrence.

In the present study, the present authors applied the diagnostic criteria for PCOS (the Rotterdam criteria) strictly by reviewing clinical charts to analyze the relationship between PCOS and the prognosis. The results showed that PCOS is an independent poor prognostic factor for PFS as well as OS. Thus, PCOS may be a risk factor for EC recurrence in surgically treated premenopausal patients with EC. In fact, it is notable that half of the six early-stage (Stages I and II) PCOS+ patients with EC had recurrence at distant sites (lung or bone), whereas distant metastasis from early-stage EC is generally reported in 6–9% of women without PCOS [21-24]. Thus, the distant recurrence ratio observed in PCOS+ patient seems high.

The present authors assumed that IR and its related endocrine milieu are involved in PCOS-mediated worsening of the prognoses in patients with EC. If this is true, then the IR targeting therapy might alleviate EC progression [4]. The authors previously demonstrated that metformin improves IR and inhibits EC recurrence long after medroxyprogesterone therapy for fertility preservation [18]. Therefore, metformin might be a promising candidate for adjuvant treatment of surgically treated

Table 4. — *Univariate and multivariate analyses of the patients on OS.*

		OS					
		Univariate			Multivariate		
Factor	Yes vs. no	HR	range	p	HR	range	p
PCOS	9 vs. 37	12.438	1.293–119.63	0.029	9.882	0.9–108.533	0.061
Oligoovulation or anovulation	15 vs. 31	2.129	0.3–15.133	0.45			
Hyperandrogenism	11 vs. 35	3.233	0.455–22.95	0.241			
PCO	10 vs. 36	3.568	0.502–25.35	0.204			
LN metastasis	7 vs. 39	8.941	1.215–65.777	0.031	6.046	0.544–67.256	0.143
Myometrial invasion $\geq$ 1/2	8 vs. 38	5.159	0.726–36.672	0.101	1.141	0.092–14.1	0.918
LVSI	11 vs. 35	3.269	0.459–23.268	0.237			
Type II	5 vs. 41	2.555	0.266–24.573	0.417			

OS: overall survival; HR: hazard ratio; C.I.: confidence interval; PCOS: polycystic ovary syndrome; PCO: polycystic ovaries; LN: lymph node; LVSI: lymphovascular space involvement.

Table 5. — *Characteristics of patients experiencing recurrence.*

Age (years)	PCOS	Total TST (ng/mL)	Irregular Menstruation	PCO	Gravid/ Parous	Primary Symptom	Histology	BMI (kg/m^2)	IRI (μU/mL)	HOMA-IR	Stage	Metastatic sites	Outcome
29	Yes	0.52	Oligoovulation *	Yes *	0 / 0	infertility	Endometrioid G1	18.5	3.1	0.71	I	LN, Bone	DOD
33	Yes	0.92 *	None	Yes *	0 / 0	AGB	Endometrioid G1	40.7	19.6	4.89	II	LN, Bone	DOD
39	Yes	1.00 *	Oligoovulation *	N/A (meta)	1/1	AGB	Endometrioid G3	38.0	7.6	1.80	IV	Lung, LN, Peritoneum	DOD
27	Yes	0.65	Oligoovulation *	Yes *	0 / 0	Hypermenorrhea	Endometrioid G1	44.1	34.9	9.82	I	Lung	AWD
48	No	0.54	None	No	2/2	AGB	Endometrioid G1	26.0	NA	NA	IV	Vagina, Lung, LN	DOD

*PCOS: polycystic ovary syndrome; TST: testosterone; PCO: polycystic ovaries; AGB: abnormal genital bleeding; BMI: body mass index; IRI: immunoreactive insulin; HOMA: Homeostatic Model Assessment of Insulin Resistance; N/A: not available; meta: metastasis; G1: grade 1; G3: grade 3; diff., differentiation; DOD: died of disease: AWD, alive with disease. *Meets the criteria for PCOS [Total TST *: total testosterone value exceeded the institutional upper limit (0.78 ng/mL)].*

premenopausal PCOS+ patients with EC.

There are several limitations to the current study. First, because of the small sample size, the authors cannot exclude the possibility of alpha-error in terms of recurrence. Second, from the study population, the authors excluded the patients who underwent fertility-sparing therapy successfully and those who did not undergo hysterectomy. This indicates that the present study population is biased to patients with a higher risk for recurrence, in whom fertility-sparing therapy was not indicated or fertility-sparing therapy had failed. Thus, the present results should not be extrapolated to all early-stage EC patients but to the subgroup of early-stage EC patients who undergo surgery as primary or secondary treatment. Third, although the authors attempted to use stringent criteria to identify PCOS+ patients, the authors might have missed some PCOS patients because the number of ovarian antral follicles tends to decrease as age advances, leading to normal-appearing ovaries.

In conclusion, PCOS may be a poor prognostic factor for postoperative recurrence in early-stage EC patients, which lasts after the menopausal period, probably in a manner other than that involving the ovaries. Larger studies are warranted to confirm the present findings on the prognosis of PCOS.

Authors' contributions

Conceptualization of the study: T.U., A.M., M.S. Database creation and data collection: T.U. Analysis and interpretation of the data: T.U., A.M., M.S. Original draft preparation: T.U. Manuscript review: T.U., A.M., M.S. Approval of the manuscript: all the authors

Ethics approval and consent to participate

Participant of patients in this study was obtained through an opt-out methodology. The institutional review board of Chiba University approved the study, code 2204.

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Conflict of interest

The authors declare no conflicts of interest.

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