Demographic, Clinical, and Prognostic Factors of Ovarian Clear Cell Adenocarcinomas According to Endometriosis Status

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Objectives: Women with endometriosis carry an increased risk for ovarian clear cell adenocarcinomas (CCCs). Clear cell adenocarcinoma may develop from endometriosis lesions. Few studies have compared clinical and prognostic factors and overall survival in patients diagnosed as having CCC according to endometriosis status.

Methods: Population-based prospectively collected data on CCC with coexisting pelvic (including ovarian; n = 80) and ovarian (n = 46) endometriosis or without endometriosis (n = 95) were obtained through the Danish Gynecological Cancer Database. χ^2 Test, independent-samples *t* test, logistic regression, Kaplan-Meier test, and Cox regression were used. Statistical tests were 2 sided. *P* values less than 0.05 were considered statistically significant.

Results: Patients with CCC and pelvic or ovarian endometriosis were significantly younger than CCC patients without endometriosis, and a higher proportion of them were nulliparous (28% and 31% vs 17% (*P* = 0.07 and *P* = 0.09). Accordingly, a significantly higher proportion of women without endometriosis had given birth to more than 1 child. Interestingly, a significantly higher proportion of patients with ovarian endometriosis had pure CCCs (97.8% vs 82.1%; *P* = 0.001) as compared with patients without endometriosis. Overall survival was poorer among CCC patients with concomitant ovarian endometriosis (hazard ratio, 2.56 [95% confidence interval, 1.29–5.02], in the multivariate analysis.

Conclusions: Age at CCC diagnosis and parity as well as histology differ between CCC patients with and without concomitant endometriosis. Furthermore, CCC patients with concomitant ovarian endometriosis have a poorer prognosis compared with endometriosis-negative CCC patients. These differences warrant further research to determine whether CCCs with and without concomitant endometriosis develop through distinct pathogenic pathways.

Key Words: Endometriosis, Clear cell carcinomas, Ovarian cancer

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Endometriosis is defined by the presence of endometrium (glands and stroma) outside the corpus uteri. The prevalence is estimated to be 5% to 10% among fertile women and 25% to 50% of women with infertility.[1] Endometriosis is often associated with pelvic pain and infertility. Endometriosis is a benign disease, although it shares similarities to malignant diseases such as attachment, damage, and invasion of target tissue and local and distant foci formation.[2,3]

Ovarian clear cell adenocarcinomas (CCCs) account for 5% to 25% of all epithelial ovarian cancer (EOC) worldwide. It represents distinct molecular, clinical, and pathological characteristics as compared with other EOC subtypes.

It is believed that a subgroup of CCC develops from endometriotic precursor lesions[4–7] because patients with endometriosis carry a 3-fold increased risk for developing CCC and co-occurrence of endometriosis and CCC in the same ovary is observed in 36% to 50% of patients. The frequency of malignant transformation of endometriosis into OC has been estimated to be 0.7% to 1.6%.[8] However, not all CCC patients have evidence of endometriosis at the time of diagnosis, and it has been speculated that CCC patients with and without endometriosis may develop through different pathogenic pathways.

The current prospective nationwide study was undertaken to investigate and compare demographics, risk factor profiles, prognostic factors, histology, and overall survival rates of Danish CCC patients with or without a diagnosis of endometriosis.

MATERIALS AND METHODS

The Danish Gynaecological Cancer Database

This nationwide case-control study is based on prospectively collected data from the Danish Gynaecological Cancer Database (DGCD), which is an Internet-based clinical database. The database holds information on 97% of Danish patients diagnosed as having ovarian, corpus, or cervix cancer since January 1, 2005. Reporting to the DGCD is compulsory for all gynecological, pathological, and oncological departments in Denmark that are participating in the diagnosis and treatment of these cancers.[9] Lifelong follow-up of patients is possible through linkage via personal identification number to the Danish Hospital Discharge register, which contains data on death and discharge diagnoses among others.

Study Population

The study included all patients registered in the DGCD with a diagnosis of CCC (n = 179) in the period from 2005 to 2013. Patients with unknown endometriosis status (n = 3) and primary CCC patients diagnosed before 2005 (n = 1) were excluded. The CCC patients were divided into 3 groups: (1) patients with concomitant ovarian endometriosis (n = 46), (2) CCC patients with pelvic endometriosis including the 46 CCC patients with concomitant ovarian endometriosis (n = 80), and (3) patients with no concomitant endometriosis (n = 95). Thus, in subanalysis on CCC with concomitant ovarian endometriosis, CCC patients with concomitant pelvic endometriosis other than ovarian were excluded (n = 35). All tumors were evaluated by a pathologist specialized in gynecological pathology using the *WHO Classification of Tumors of the Breast and Female Genital Organs* from 2004. Adenocarcinomas composed of an admixture of different types were classified according to the major type. Tumors with clear cell features in a background of serous or endometrioid adenocarcinomas were classified as serous or endometrioid adenocarcinomas and were not included in the present study. Clear cell adenocarcinoma associated with ovarian endometriosis (histologic diagnosis) was defined as follows: (1) presence of CCC and endometriosis in the same ovary or (2) presence of CCC in one ovary and endometriosis in the contralateral ovary. Concomitant pelvic endometriosis (histologic diagnosis) was defined as follows: presence of CCC in either ovary and/or coexisting endometriosis at any site of the pelvis (eg, peritoneal endometriosis). Patients were followed up from the date of first visit under the diagnosis of ovarian cancer to date of death or last follow-up (November 2015), whichever came first.

Data on endometriosis status and histologic subtypes other than clear cell carcinomas were derived from the Danish Patobank, a national database that holds data from all pathoanatomical examinations performed in Denmark.

Exposure Assessment

Exposure variables were identified in the DGCD. The demographic variables included were mean age at diagnosis (in years), body mass index (BMI) groups (<18.5, 18.5–<25, 25–<30, 30–<35, and ≥35 kg/m^2), cigarette smoking (ever vs never), Eastern Cooperative Oncology Group performance status (PS), and comorbidity at the time of diagnosis (yes vs no). Reproductive characteristics were evaluated including nulliparous (yes vs no), parity (0, 1, ≥2), mean age at menarche (in years) and mean age at natural menopause (in years), and having a previous hysterectomy (yes vs no), unilateral or bilateral oophorectomy, or salpingectomy (yes vs no). Variables related to primary operation such as visible residual tumor after primary debulking surgery (yes vs no), lymphadenectomy (yes vs no), and preoperative carcinosis (carcinosis before cytoreduction; yes vs no) were registered by the surgeon at the time of operation. The preoperative carcinosis variables were introduced on January 1, 2008. Patients registered before this date do not have information on preoperative carcinosis status.

Statistical Analysis

Comparison between parameters has been computed using the independent-samples *t* test for continuous variables (eg, age). Categorical variables (eg, stage disease; American Society of Anesthesiologists score and performance score; comorbidity including other cancers; cardiovascular, endocrine [including diabetes], rheumatologic, and mental disorders [yes versus no]) and BMI groups were evaluated by using χ^2 test, as appropriate, for category size. Standard univariate and multivariate analyses were performed using binary logistic regression. Survival estimates were plotted using the Kaplan-Meier method. Prognostic variables were examined using multivariate Cox regression analyses.

Overall survival was calculated from the date of surgery to the date of death or November 2015, whichever came first.

All statistical tests were 2 sided. *P* values less than 0.05 were considered statistically significant.

Statistical analyses were performed using SPSS Statistical software (version 19.0; SPSS, Inc, Chicago, IL).

RESULTS

One hundred seventy-five patients with a diagnosis of CCC in DGCD were included for the overall analyses. Of these, 80 (45.7%) patients had a concomitant pelvic diagnosis of endometriosis (including ovarian endometriosis), 46 (26.3%) had only concomitant ovarian endometriosis, and 95 (54.3%) had no sign of endometriosis at histologic examination of the specimens.

Patients with ovarian and pelvic endometriosis–associated CCC were significantly younger than patients without concomitant endometriosis (54.6 and 57.3 years vs 62.9 years; $P < 0.002$ and $P < 0.0001$). No difference was observed regarding stage at diagnosis, BMI, smoking habits comorbidity PS, or family history of breast or ovarian cancer (Table 1).

Fewer women with CCC with endometriosis had given birth compared with women diagnosed as having CCC without endometriosis. The rates of nulliparity were 31.1%, 28.2%, and 17.2% for women with ovarian, pelvic, or no endometriosis, respectively ($P = 0.07$ and $P = 0.09$; Table 2). Accordingly, the proportion of CCC patients who had more than 1 child vs no children were lower among CCC patients with pelvic or ovarian endometriosis as compared with CCC patients without endometriosis (odds ratios [ORs], 0.44 [95% confidence interval {CI}, 0.20–0.96] and 0.36 [95% CI, 0.15–0.89]; Table 2). Having a history of oophorectomy or salpingectomy (unilateral or bilateral) was higher among patients with pelvic or ovarian endometriosis, whereas the rate hysterectomy was lower as compared with CCC patients without an endometriosis diagnosis. However, these differences did not reach a significant level. Age at menarche and menopause did not differ between the 3 groups (Table 2).

Table 3 demonstrates the histologic characteristics of CCC according to endometriosis status. The proportion of CCC patients without endometriosis at any location who had a serous component in addition to their CCC histology (including tumors with more than one different histologic component) was significantly higher as compared to CCC with concomittant pelvic endometriosis (10.5 % vs 0 %

TABLE 1. ORs of primary ovarian CCCs with a concomitant diagnosis of pelvic (CCC + endometriosis) or ovarian (CCC + ovarian endometriosis) endometriosis as compared with primary ovarian CCCs without a diagnosis of endometriosis (CCC no endometriosis) according to demographic and clinical characteristics, adjusted for stage, age, and performance score

	CCC + Pelvic Endometriosis	CCC + Ovarian Endometriosis	CCC No Endometriosis	Pelvic vs No Endometriosis		Ovarian vs No Endometriosis	
				OR (95% CI)	*P*	OR (95% CI)	*P*
No. patients	80	46	95				
Age, mean (SD), y	57.2 (11.4)	54.0 (10.4)	62.9 (11.4)		<0.001*		<0.0001*
	n (%)	n (%)	n (%)				
BMI, kg/cm^2					NS		NS
<18.5	3 (3.9)	1 (2.3)	5 (5.6)	1.28 (0.25–6.71)		1.06 (0.09–12.46)	
>18.5–25	36 (46.8)	17 (39.5)	43 (48.3)	Ref		Ref	
>25–35	34 (44.2)	23 (53.5)	35 (39.3)	0.98 (0.49–1.98)		1.38 (0.57–3.32)	
>35	4 (5.2)	2 (4.7)	6 (6.7)	0.48 (0.09–2.36)		0.46 (0.05–4.34)	
Smoking					NS	0.47	NS
Never	40 (56.3)	25 (61.0)	51 (60.0)	Ref		Ref	
Ever	31 (43.7)	16 (39.0)	34 (40.0)	1.01 (0.51–2.02)		0.73 (0.31–1.74)	
Comorbidity					NS		NS
No	49 (63.6)	33 (75.0)	51 (54.8)	Ref		Ref	
Yes	28 (36.4)	11 (25.0)	41 (45.2)	0.94 (0.46–1.93)		0.64 (0.26–1.57)	
Performance score					NS		NS
1	47 (58.8)	32 (69.6)	56 (58.9)	Ref		Ref	
2	24 (30.0)	11 (23.9)	23 (24.2)	1.56 (0.72–3.35)		1.06 (0.41–2.7)	
3	5 (6.3)	1 (2.2)	13 (13.7)	0.79 (0.24–2.64)		0.26 (0.03–2.27)	
4 + 5	4 (5.0)	2 (4.3)	3 (3.2)	2.36 (0.45–12.4)		2.26 (0.27–19.04)	

Endometriosis was defined at endometriosis in the ipsilateral or contralateral ovary at the time of diagnosis. Pelvic endometriosis was defined as endometriosis in the pelvis including ovarian endometriosis.

NS, not significant; Ref, reference.

TABLE 2. ORs of primary ovarian CCCs with a concomitant diagnosis of pelvic (CCC + pelvic endometriosis) or ovarian (CCC + ovarian endometriosis) endometriosis as compared with primary ovarian CCCs without a diagnosis of endometriosis (CCC no endometriosis) according to reproductive factors

	CCC + Pelvic Endometriosis	CCC + Ovarian Endometriosis	CCC No Endometriosis	Pelvic vs No Endomtriosis		Ovarian vs No Endometriosis	
				OR (95% CI)	*P*	OR (95% CI)	*P*
No. patients	80	46	95				
	n (%)	n (%)	n (%)				
Parous							
No	22 (28.2)	14 (31.1)	15 (17.2)	Ref		Ref	
Yes	56 (71.8)	31 (68.9)	72 (82.8)	0.53 (0.25–1.12)	NS	0.46 (0.20–1.07)	NS
Parity							
0	22 (28.2)	14 (31.1)	15 (17.2)	Ref		Ref	
1	20 (25.6)	12 (26.7)	16 (18.4)	0.85 (0.34–2.16)	NS	0.80 (0.28–2.28)	NS
>1	36 (46.2)	19 (42.2)	56 (64.4)	0.44 (0.20–0.96)	0.06	0.36 (0.15–0.89)	**0.05**
Personal history of salpincgo-oophorectomy							
No	72 (90.0)	39 (84.8)	89 (93.7)	Ref		Ref	
Yes	8 (10.0)	7 (15.2)	6 (6.3)	1.6 (0.55–5.0)	NS	2.7 (0.84–8.4)	NS
History of hysterectomy						0.19	
No	72 (94.7)	41 (95.3)	82 (88.2)	Ref		Ref	
Yes	4 (6.3)	2 (4.7)	11 (11.8)	0.41 (0.13–1.36)	NS	0.36 (0.08–1.72)	NS
	Mean (SD)	Mean (SD)	Mean (SD)				
Age at menarche, y	13.3 (1.3)	12.9 (1.2)	13.7 (1.4)	0.25*		0.07*	
Age at menopause, y	50.2 (4.6)	49.2 (5.4)	48.8 (4.7)	0.14*		0.48*	

Ovarian endometriosis was defined at endometriosis in the ipsilateral or contralateral ovary at the time of diagnosis. Pelvic endometriosis was defined as endometriosis in the pelvis including ovarian endometriosis. Numbers may not add up to the total in all analyses because missing data.

**P* value, unadjusted independent-samples *t* test.

NS, not significant; Ref, reference.

$P < 0.001$). The stage distributions were comparable in all 3 groups.

In analysis restricted to patients who underwent primary debulking surgery and who were diagnosed in stages III to IV, ascites was more often present among patients with pelvic endometriosis as compared with patients without endometriosis. However, these observations did not reach a significant level. No significant difference according to macroradical surgery or carcinosis status assessed before surgery or rate of lymphadenectomy was observed, although it should be noted that the proportion of patients who had a lymphadenectomy performed were highest among patients with endometriosis (Table 4).

Overall survival tended to be poorer among CCC patients with concomitant pelvic and ovarian endometriosis (hazard ratios [HRs], 1.30 [95% CI, 0.79–2.14] and 2.56 [95% CI, 1.30–5.03], respectively). However, in a subanalysis of overall survival restricted to women with concomitant pelvic endometriosis other than ovarian (n = 35) as compared with CCC patients without concomitant endometrioses, no difference in overall survival was observed (HR, 0.93 [95% CI, 0.51–1.73]) in the multivariate analysis adjusting for stage (I–IV), residual tumor, age, and PS (I–V). Increasing stage and PS at the time of diagnosis as well as incomplete debulking at primary surgery were all associated with a poor prognosis among CCC patients (Table 5).

DISCUSSION

Tumors associated with endometriosis have previously been shown to have characteristics unique from most other subtypes of EOC in studies based on epidemiologic data and molecular studies. However, there are only limited data that directly compare the tumors associated with endometriosis with tumors not associated with endometriosis within specific subtypes. This nationwide study is, to our knowledge, the largest and most complete nationwide study based on prospectively collected data comparing the risk factor profile, histopathological data, prognostic factors, and survival data in CCC according to endometriosis status.

The current study has several strengths. The study is, to our knowledge, the only nationwide study investigating these

TABLE 3. Histologic characteristics and stage of ovarian CCCs according to endometriosis status: CCC with concomitant pelvic endometriosis (CCC + pelvic endometriosis) or CCC with concomitant ovarian endometriosis (CCC + ovarian endometriosis) as compared with CCC with no concomitant endometriosis (CCC no endometriosis)

	CCC + Pelvic Endometriosis	CCC + Ovarian Endometriosis	CCC No Endometriosis	Pelvic vs No Endometriosis, *P* value	Ovarian vs No Endometriosis, *P* value
No. patients	80	46	95		
	n (%)	n (%)	n (%)		
Histology of adenocarcinoma				**0.001**	**0.025**
Pure clear cell	78 (97.5)	45 (97.8)	78 (82.1)		
Clear cell/serous	0 (0)	0 (0)	10 (10.5)		
Clear cell/endometrioid	2 (2.5)	1 (2.2)	0 (0)		
Clear cell/mucinous	0 (0)	0 (0)	1 (1.1)		
Mixed	0 (0)	0 (0)	6 (6.3)		
Tumor stage				0.39	0.34
Stage I	48 (57.9)	31 (67.4)	55 (60.0)		
Stage II	10 (12.5)	5 (10.9)	7 (7.4)		
Stage III	17 (21.3)	8 (17.4)	21 (22.1)		
Stage IV	5 (6.3)	2 (4.3)	12 (12.6)		
Endometriosis location				—	—
Pelvic endometriosis*	80	46	0		
Pelvic other than ovarian	26	0	0		
Ovarian contralateral	13	13	0		
Ovarian ipsilateral	33	33	0		
Adenomyosis only	8	0	0		

Ovarian endometriosis was defined at endometriosis in the ipsilateral or contralateral ovary at the time of diagnosis. Pelvic endometriosis was defined as endometrisois in the pelvis including ovarian endometriosis.

*Including ovarian endometriosis and adenomyosis.

issues. The study is population based and includes an unselected representative group of CCC patients living in Denmark. Furthermore, all Danish citizens are provided with a personal identification number, which enables linkage between registers and ensures lifelong follow-up.

The main weakness of our study may be incomplete registration to the DGCD. However, because data are collected prospectively without knowledge of the hypothesis, this may decrease the power of the study but is unlikely to influence the direction of the estimates. We are aware of possible misclassification because reevaluation of pathological diagnosis and staging was not performed. However, skilled pathologist with special interest in gynecological cancers performed initial diagnosis and staging, and the Danish guideline on staging and diagnosing of gynecologic cancers follows the Gynecological Oncology Group and Federation of Gynecology and Obstetrics criteria. Furthermore, the incidence of concomitant pelvic and ovarian endometriosis in the present study is very similar to the incidences reported in the literature.[10–12]

Only 4 previous studies have examined the impact of endometriosis on clinical and prognostic factors among CCC patients.[10–13] Unfortunately, the inclusion criteria of CCC patients and definition of concomitant endometriosis in these studies have varied, which makes comparison between studies difficult. Thus, the study by Scarfone et al[11] included both primary pure CCC and mixed endometrioid CCC carcinomas and only included patients with concomitant endometriosis arising in the same ovary as the CCC. All other CCC patients with concomitant endometriosis were excluded. The histologic inclusion criteria of CCC were unclear in the studies by Komiyama et al,[14] Orezzoli et al,[10] and Ye et al.[12] However, these studies defined endometriosis as pelvic concomitant endometriosis using the same criteria as we have used in the present study. To be able to compare our data with previous observations, we have decided to include primary CCC cases only. Furthermore, both data on CCC with a concomitant diagnosis of pelvic endometriosis (defined as endometriosis anywhere in the pelvis including ovarian concomitant endometriosis) and data on CCC with ovarian concomitant endometriosis (defined as concomitant endometriosis in at least one of the ovaries) are presented.

In agreement with previous studies, CCC patients with coexisting endometriosis were significantly younger than CCC patients without endometriosis.[10–14] This difference may be due to diagnostic bias because patients with endometriosis are often followed up in a clinical setting and thus could be incidentally diagnosed earlier as compared with CCC patients without endometriosis who are frequently asymptomatic until advanced

TABLE 4. ORs of primary ovarian CCCs with a concomitant diagnosis of pelvic (CCC + endometriosis) or ovarian (CCC + ovarian endometriosis) endometriosis as compared with primary ovarian CCCs without a diagnosis of endometriosis (CCC no endometriosis) according to surgical variables (stages III and IV only)

	CCC + Pelvic Endometriosis	CCC + Ovarian Endometriosis	CCC No Endometriosis	Pelvic vs No Endometriosis		Ovarian vs No Endometriosis	
				OR (95% CI)	*P*	OR (95% CI)	*P*
No. patients	80	46	95				
	n (%)	n (%)	n (%)				
Complete cytoreduction							
No	13 (65.0)	5 (62.5)	15 (50.0)	Ref		Ref	
Yes	7 (35.0)	3 (37.5)	15 (50.0)	1.86 (0.58–5.95)	NS	1.67 (0.34–8.26)	NS
Ascites							
No	4 (22.2)	2 (25)	11 (37.9)	Ref		Ref	
Yes	14 (77.8)	6 (75)	18 (61.2)	2.14 (0.56–8.17)	NS	1.8 (0.31–10.7)	NS
Carcinosis before							
No	3 (30)	1 (20)	3 (17.6)	Ref			
Yes	7 (70)	4 (80.0)	14 (82.4)	0.5 (0.08–3.15)	NS	0.86 (0.07–10.7)	NS
Lymphadenectomy							
No	9 (45.9)	3 (37.5)	19 (63.3)	2.11 (0.67–6.68)	NS	2.87 (0.57–14.4)	NS
Yes	11 (55.0)	5 (62.2)	11 (36.7)				

Ovarian endometriosis was defined at endometriosis in the ipsilateral or contralateral ovary at the time of diagnosis. Pelvic endometriosis was defined as endometriosis in the pelvis including ovarian endometriosis. Numbers may not add up to the total in all analyses because missing data.

TABLE 5. Multivariate Cox regression analysis with overall survival of ovarian clear cell carcinomas as end point

	Analysis Included All CCC Patients (n = 175)			Analyses Included CCC With Ovarian Endometriosis or No Endometriosis* (n = 135)		
	HR	95% CI	*P*	HR*	95% CI*	*P**
Age per year	1.01	0.98–1.03	0.60	1.02	0.99–1.04	0.25
Performance score						
2 vs 1	2.12	1.23–4.30	0.009	2.18	1.18–4.01	0.01
3 vs 1	1.82	0.85–3.91	0.12	1.51	0.65–3.54	0.34
>4 vs 1	5.46	1.85–16.12	0.002	5.61	1.27–24.7	0.02
Residual tumor						
No vs yes	2.70	1.39–5.26	<0.003	2.29	1.05–5.0	<0.04
Stage						
II vs I	2.12	0.95–4.73	0.07	1.65	0.60–4.55	0.33
III vs I	3.26	1.69–6.28	<0.0001	5.0	2.35–10.6	<0.0001
IV vs I	5.44	2.39–12.4	<0.002	15.3	5.51–42.3	<0.0001
Endometriosis						
No vs yes	1.30	0.79–2.15	0.31	2.56	1.30–5.03	0.007

*Ovarian endometriosis is defined at endometriosis in the ipsilateral or contralateral ovary at the time of diagnosis; thus, patients with endometriosis in any other location were excluded from this analysis.

stages of the disease. If so, we would expect that CCC with concomitant endometriosis also presented at earlier stages. In our study, no significant differences between the 3 groups were found. However, an insignificantly higher proportion of CCC patients with concomitant ovarian endometriosis only were diagnosed in earlier stages (stage I or II) as compared with women with no endometriosis (78.3% vs 67.4%; P =0.34). The latter result is in line with the direction in most studies,[11,14] although not all reach a significant level.[10,12] Another explanation could be that endometriosis have burned out in the older age groups or that tumor spread may have veiled the endometriosis lesions in advanced CCC.

Alternatively, the presence of endometriosis, which causes inflammation and an immunological imbalance in the surrounding microenvironment, may enhance malignant transformation leading to ovarian cancer at an earlier age. Hence, it is still debated whether the observed differences in age and stage distribution at diagnosis are due to bias or developmental dissimilarities between patients with and without a concomitant endometriosis diagnosis.

The present study confirms that a larger proportion of CCC patients with concomitant ovarian and pelvic endometriosis are nulliparous compared with CCC patients with no endometriosis. Accordingly, we observed a significantly lower parity (>1 births vs no births) among patients with concomitant ovarian and pelvic endometriosis as compared with patients without endometriosis. These findings are consistent with the 2 former studies.[12,14] The higher incidence of nulliparity and a decrease in overall parity among CCC patients with concomitant endometriosis are most likely a result of the coexistence of endometriosis because endometriosis in several well-conducted studies have been strongly associated with infertility and thus nulliparity as compared with the control groups. Furthermore, recent research investigating the risk of ovarian cancer among endometriosis patients has consistently found evidence for nulliparity being an independent risk factor for malignant transformation of endometrioses lesions.[8,15] Thus, women with endometriosis who remained childless had an up to 4-fold increased risk for ovarian cancer as compared with parous women with an endometriosis diagnosis. Indeed, the latter group did only have a slightly, if any, increased risk for ovarian cancer despite the endometriosis diagnosis as compared with the general population.[16] The mechanism linking infertility in endometriosis patients with an increased risk for malignant transformation is unknown. However, it may be speculated that severe inflammation caused by endometriosis may result in both infertility and malignant transformation. Indeed, standard treatment of infertility among women with endometriosis is surgical removal of all visible endometriosis lesions combined with induction of a menopausal state, which down-regulates the inflammatory state. Likewise, the risk of developing CCC in women with known endometriosis seems to be reduced by extensive surgical treatment of endometriosis cases.[17]

Interestingly, a significantly higher proportion of CCC patients without endometriosis as compared with patients with endometriosis had a component of serous adenocarcinoma.To our knowledge, only one former study examined the histologic characteristics of CCC (that is proportion of pure clear cell carcinomas and proportion of mixed CCC [serous, mucionous, and endometrioid components]) according to coexistence of endometriosis. Although small in size, this study also found that 0 (0%) of 6 cases of endometriosis-associated CCC had serous features in addition to their CCC histology. The present findings do support the view that CCCs may develop through different pathogenic pathways according to their endometriosis status, although these observations need to be confirmed by future studies investigating the molecular profile of CCC with and without coexisting endometriosis.

No differences according to rates of complete cytoreduction at primary debulking surgery, carcinosis before surgery, or proportion of lymphadenectomy was observed in the present study. In contrast to 2 previous studies, ascites was observed in a higher proportion of CCC patients with concomitant pelvic endometriosis among patients diagnosed in stages III to IV. However, the former analyses were univariate and did not adjust for stage, which is known to be associated with ascites.

In line with most previous studies including a recent meta-analysis,[18] we did not find any difference in median survival times stratified by stage in the univariate analysis (Fig. 1). In the Cox regression analysis with overall survival as end point adjusted for age, residual tumor, stage (I–IV) and PS, and endometriosis status, no difference was observed when comparing CCC patients with concomitant pelvic endometriosis other than ovarian and no endometriosis (HR, 0.93 [95% CI, 0.51–1.73]), which is consistent with the previous literature. However, patients with ovarian CCC had a poorer prognosis compared with endometriosis-negative CCC patients. Furthermore, in analyses restricted to pure CCC, similar significant differences in overall survival were observed (data not shown). In addition, PS, stage at diagnosis, and no residual tumor did all have a significant impact on overall survival (Table 5), which is in line with results from several previous studies. As previously mentioned, it is difficult to compare data from previous studies with our data. However, our study is population based, minimizing the risk of bias. Furthermore, it is the only study adjusting for no residual tumor, which have a significant impact on overall survival.

The differences in overall survival between CCC patients with ovarian endometriosis and those with no endometriosis may be due to differences in chemosensitivity because more patients without endometriosis had a serous component and thus may be more sensitive to standard treatment with platine-based chemotherapy. Another explanation may be that indeed CCC associated with ovarian endometriosis is a more aggressive cancer type and thus progresses faster compared with CCC without endometriosis.

Only few studies have examined the molecular profile of CCC according to endometriosis status. A recent publication has shown that the epidemiologic association between endometriosis and endometriosis-associated cancers including CCC may be attributed to shared genetic susceptibility loci.[19]

Interestingly, a difference in expression of plasminogen activator inhibitor-1 was observed according to the presence of concomitant endometriosis.[20] Another study by Nishikimi et al[21] found a difference in expression patterns of ARID1A between CCC patients with the presence of adenofibroma and endometriosis. Finally, EGFR expression was significantly

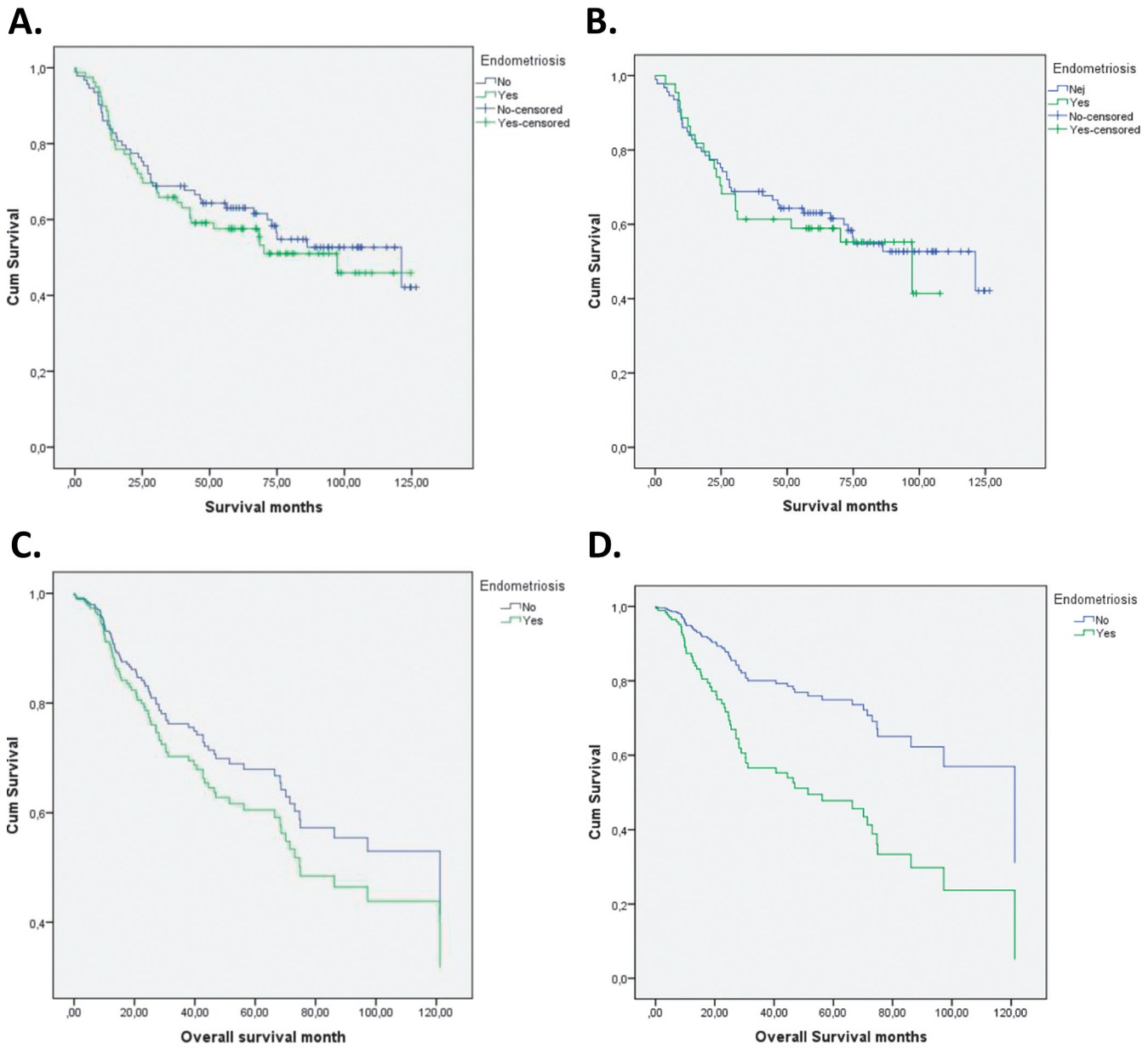

FIGURE 1. Survival curves for patients with primary clear cell carcinomas according to endometriosis status. A and B, Kaplan-Mayer plots for median survival in months according to endometriosis status: pelvic endometriosis vs no endometriosis (log-rank 0.55; A) and ovarian endometriosis vs no endometriosis (log-rank 0.72; B). C and D, Survival curves for multivariate Cox regression with overall survival as end point according to endometriosis status. C, Analysis adjusted for age, stage, performance scores at the time of diagnosis, residual tumor, and endometriosis status (pelvic endometriosis vs no endometriosis). Hazard ratio for patients with pelvic endometriosis vs no endometriosis (HR, 1.30 [95% CI, 0.79–2.15]). D, Analysis adjusted for age, stage, performance scores at the time of diagnosis, residual tumor, and endometriosis status (ovarian endometriosis vs no endometriosis). Hazard ratio for ovarian endometriosis vs no endometriosis (HR, 2.56 [95% CI, 1.30–5.03]).

higher among CCC patients with concomitant endometriosis as compared with those without endometriosis in one study.[22] None of these studies took histologic subtypes into account, and all studies need to be confirmed in larger studies. However, together with the results of the present studies, these results may suggest that CCC may be separated into 2 entities with distinct molecular, clinical, and pathological characteristics dependent on endometriosis status. If so, this may have implication for future research on handling and treatment of CCC. Indeed, the standard treatment of CCC today consists of primary surgery aiming to remove all visible tumor tissue followed by adjuvant chemotherapy based on carboplatin and

Taxol. Unfortunately, most CCCs are resistant to the adjuvant chemotherapy and new treatment modalities are urgently needed. Future studies should stratify their results according to endometriosis status in order not to miss important insights.

In conclusions, the present study confirms that age at CCC diagnosis and parity as well as histology differ between CCC patients with and without concomitant endometriosis. Furthermore, our findings show that CCC patients with concomitant ovarian endometriosis at diagnosis have a poorer prognosis compared with endometriosis-negative CCC patients. These differences warrant further research to determine to what extent CCCs with and without concomitant endometriosis develop through distinct pathogenic pathways and to elucidate individualized treatment for these women.

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