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# Serum CA19-9 as a Predictor of Malignancy in Primary Ovarian Mucinous Tumors: A Matched Case-Control Study

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**Background:** This study was designed to investigate the clinical characteristics correlated with serum CA19-9 elevation in primary mucinous ovarian tumors and to evaluate the role of serum CA19-9 in predicting borderline or malignant tumors.

**Material/Methods:** We retrospectively identified 27 women with pathologically-confirmed primary ovarian mucinous neoplasms (16 borderline and 11 malignant), who had been preoperatively checked for serum CA19-9 and CA125 levels. The control group was established by 1:2 matching for age among all women with pathologically-confirmed benign mucinous tumors over the same time period. The associations of the serum CA19-9 elevation and clinical characteristics, including tumor pathology, were evaluated.

**Results:** Serum CA19-9 was more frequently elevated in borderline or malignant than benign tumors (57.9% vs. 16.7%,  $P=0.001$ ), although the mean value of serum CA19-9 was not significantly different among histological subtypes. CA19-9 elevation was correlated with large tumor size (largest diameter  $\geq 15$  cm;  $p=0.028$ ), serum CA125 elevation ( $p=0.006$ ), and tumor pathology (borderline or malignant tumors;  $p=0.001$ ). Other clinical characteristics, including parity, menopause, bilateral tumor involvement, and torsion were not correlated with CA19-9 elevation. Multivariate analysis revealed that tumor pathology was the only independent factor for CA19-9 elevation in primary ovarian mucinous tumors (odds ratio 3.842, 95% CI 1.277–11.558,  $p=0.017$ ). Interestingly, subgroup analysis in women with normal serum CA 125 level revealed that CA19-9 was significantly correlated with borderline and malignant tumors but not with benign tumors (odds ratio 6.3, 95% CI 1.438–19.648,  $p=0.014$ ).

**Conclusions:** Serum CA19-9 can be a useful complementary marker in differentiating benign from borderline or malignant mucinous tumors in the ovaries, particularly when serum CA125 level is not elevated.

**MeSH Keywords:** **CA-19-9 Antigen • Cystadenoma, Mucinous • Ovary • Tumor Markers, Biological**

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## Background

CA19-9 is a monosialoganglioside, which is associated with various types of mucinous tumors in the gastrointestinal tract, such as in the pancreas and biliary tract [1–3]. Serum CA19-9 plays an important role in the diagnosis and prognostication of colorectal, pancreatic, and biliary tract cancers [4–6].

In the gastrointestinal tract and ovaries, primary tumors are associated with CA19-9 secretion. There have been a number of studies suggesting that serum CA19-9 level might be a useful marker in diagnosis of benign dermoid cyst [3,7]. In those studies, large tumor size, bilateral tumor involvement, and tumor torsion were correlated with serum CA19-9 elevation [3,7].

However, there have been limited reports of CA19-9 as a diagnostic marker in ovarian mucinous tumors [8]. Although many gynecologic oncologists are using serum CA19-9 level as a preoperative marker in the investigation of women with an ovarian mass, evidence is still insufficient. In addition, differentiation of malignant tumors from benign tumors will be more challenging if the role of CA125 as a screening tool is controversial in ovarian malignancy [9]. Serum CA125 is frequently elevated in benign conditions, including pregnancy, endometriosis, and pelvic inflammatory disease, as well as in malignant disorders. Moreover, a number of studies suggest that CA125 is not elevated in most primary ovarian mucinous neoplasms [10–13].

Therefore, we investigated the clinical characteristics correlated with serum CA19-9 elevation and evaluated the role of serum CA19-9 in differentiating benign from borderline or malignant mucinous tumors in the ovaries.

## Material and Methods

From 2001 to 2011 in Hallym Medical University Hospital, a total of 149 women with pathologically-confirmed primary ovarian mucinous tumors were preoperatively checked for serum CA19-9 and CA125 levels. Of those, 16 cases were borderline tumors and 11 cases were malignant tumors. All the patients with malignant mucinous tumors were in Stage 1 or 2. Among 122 women with pathologically-confirmed benign mucinous cystadenomas in the ovaries, the control group was established by 1:2 matching for age to complement the small sample size of borderline or malignant tumors compared to benign tumors. Our study was approved by the institutional review board of our hospital. Patients with benign disease in the gastrointestinal tract, such as in the pancreas and gall bladder, and patients with other co-existing malignant tumors, were excluded from the study group.

Patient characteristics (age at operation, parity, and menopause), ultrasonographic (US) findings of the lesion (the largest

diameter and site of the lesion), preoperative level of serum tumor markers (CA125 and CA19-9), and existence of torsion were retrieved from medical records and pathology reports. The serum level of CA 19-9 and CA 125 were determined by radioimmunoassay by using the Modular Analytics E 170 module (Roche Laboratory systems, Mannheim, Germany). The cut-off values for CA19-9 and CA 125 are 37 U/mL and 35 U/mL, respectively.

Statistical analyses were performed using SPSS for Windows (version 18.0, SPSS Inc.). Dichotomous variables were compared by Fisher's exact test or chi-square test. Continuous variables were compared by t-test. Multivariate analysis was performed using binary logistic regression. The hazard ratio (HR) and 95% confidence intervals (CI) were calculated. For all statistical tests, P value less than 0.05 was considered significant.

## Results

Serum CA19-9 was elevated in the ovaries in 16.7%, 56.3%, and 45.5% of benign, borderline, and malignant mucinous tumors, respectively (Table 1). In contrast, serum CA125 was elevated in only 27.3% of cases with malignant mucinous tumors in the ovaries. Although the mean value of serum CA19-9 was not significantly different among histological subtypes ( $P=0.774$ ), serum CA19-9 was more frequently elevated in borderline or malignant mucinous tumors than in benign tumors (57.9% vs. 16.7%,  $P=0.001$ ).

Clinical characteristics in association with serum CA19-9 elevation in women with primary ovarian mucinous tumors are described in Table 2. Specifically, the largest diameter of tumor ( $\geq 15$  cm in US finding), serum CA125 elevation, and tumor pathology (borderline or malignant) were correlated with elevated serum CA19-9 levels. However, torsion, bilateral involvement of tumor, and other patient characteristics, including parity and menopause, were not correlated with serum CA19-9 elevation. Multivariate analysis revealed that tumor pathology (borderline or malignant) was the only independent factor for serum CA19-9 elevation in primary ovarian mucinous tumors (odds ratio [OR] 3.842, 95% CI 1.277–11.558,  $p=0.017$ ) (Table 3).

Interestingly, subgroup analysis in women with normal serum CA 125 level revealed that serum CA19-9 elevation was significantly correlated with borderline or malignant tumors than benign (12.8% vs. 43.8%,  $p=0.014$ ) (Table 4). Odds ratio for serum CA19-9 elevation was 6.3 (95% CI 1.438–19.648). In other words, negative predictive value and positive predictive value of CA19-9 was 87.2% and 43.8%, respectively, for cancer discrimination in patients with normal CA125.

**Table 1.** Serum CA19-9 and CA125 levels in histological subtypes of primary ovarian mucinous tumor.

Tumor subtype	CA19-9		CA125	
	Elevated CA19-9 N (%)	Mean (range) (U/ml)	Elevated CA125 N (%)	Mean (range) (U/ml)
Benign (N=54)	9 (16.7)	127.8 (3.24~6000.00)	7 (13.0)	22.87 (4.51~234.61)
Borderline (N=16)	9 (56.3)	253.8 (4.95~1828.00)	8 (50.0)	52.8 (8.61~244.17)
Malignant (N=11)	5 (45.5)	107.5 (6.23~548.00)	3 (27.3)	45.8 (6.80~238.17)

**Table 2.** Clinical characteristics correlating with serum CA19-9 elevation in patients with mucinous tumors.

	CA19-9 normal (N=58)		CA19-9 elevated (N=23)		P value
<b>Patient characteristics</b>					
Age, years	42.3	(±2.27)	46.7	(±4.31)	0.329
Parity	2.8	(±0.34)	2.6	(±0.55)	0.759
Menopause					0.400
No	46	(79.3)	17	(73.9)	
Yes	12	(20.7)	6	(26.1)	
Serum CA125					0.006*
<35 U/ml	50	(86.2)	13	(56.5)	
≥35 U/ml	8	(13.8)	10	(43.5)	
<b>Tumor characteristics</b>					
Tumor size (largest diameter)					0.028*
<15 cm	38	(65.5)	9	(39.1)	
≥15 cm	20	(34.5)	14	(60.9)	
Bilateral involvement					0.610
No	48	(82.8)	19	(82.6)	
Yes	10	(17.2)	4	(17.4)	
Torsion					1.000
No	55	(94.8)	22	(95.7)	
Yes	3	(5.2)	1	(4.3)	
Pathology					0.001*
Benign	45	(77.6)	9	(39.1)	
Borderline or malignant	13	(22.4)	14	(60.9)	

Data are presented as mean ±SD or absolute numbers (%). \* P<0.05.

## Discussion

CA19-9 is a sialylated Lewis A antigen, which is associated with mucins in gastrointestinal adenocarcinomas and also is frequently expressed in mucinous tumors in the ovaries [14].

Although CA19-9 is recognized as a useful diagnostic marker in various types of mucinous tumors in the gastrointestinal tract (e.g., in the pancreas and biliary tree), there have been limited reports of CA19-9 as a diagnostic marker in ovarian mucinous tumors [3,7,8].

**Table 3.** Multivariate analysis for risk factors of serum CA19-9 elevation in patients with mucinous tumors.

Factors	Odds ratio (95% CI**)	P value
Pathology (borderline or malignant tumor)	3.842 (1.277–11.558)	0.017*
CA125 elevated	2.768 (0.807–9.494)	0.106
Tumor size (largest diameter ≥15 cm)	1.777 (0.579–5.451)	0.315

\* P<0.05; \*\* CI – confidence interval.

**Table 4.** Relationship between serum CA19-9 elevation and tumor pathology of women with primary ovarian mucinous tumors and normal serum CA 125 level.

	Benign (N=47)	Borderline or malignant (N=16)	P value	Odds ratio	95% CI**
CA19-9			0.014*	6.3	1.438–19.648
Normal	41 (87.2%)	9 (56.3%)			
Elevated	6 (12.8%)	7 (43.8%)			

\* P<0.05; \*\* CI – confidence interval.

Primary mucinous tumors, which account for approximately 12–15% of all ovarian tumors, can be subdivided into 2 distinct histogenetic types: the much more common intestinal (or non-specific) type and the less common Müllerian (or endocervical) type [15]. Therefore, CA125, which is secreted by mainly Müllerian origin tissue, cannot be a major tumor marker in mucinous tumors of the ovaries. Pathologically, primary ovarian mucinous tumors are classified as benign, borderline (mucinous tumor of low malignant potential), or malignant tumors [16]. Although 75% of primary mucinous tumors are benign, the other 10% and 15% are comprised of borderline and malignant tumors, respectively [16].

According to a recent model for ovarian carcinogenesis, ovarian neoplasms can be divided into type I and type II, and each should be considered as a different disease [17,18]. Type I tumors, including low-grade serous, mucinous, endometrioid, clear cell, and transitional cell carcinomas, are often confined to the ovary at the time of diagnosis, with a stable genome and without TP53 mutations [19,20]. In contrast, type II tumors, including high-grade serous carcinomas, undifferentiated carcinomas, and carcinosarcomas, are more aggressive and genetically highly unstable [19,21–23]. Actually, the behavior of mucinous ovarian carcinoma is different from that of serous ovarian carcinoma.

Despite a relatively good prognosis in early-stage disease, mucinous ovarian cancers are frequently associated with poorer response to platinum/taxane chemotherapies, and poorer survival, compared to serous ovarian cancers [24–26]. In addition, mucinous borderline ovarian tumors, which are generally

characterized as having low malignant potential without obvious stromal invasion, may present with peritoneal implants, lymph node metastases, and recurrence after the resection [16,27,28]. However, in contrast to serous tumors, differential diagnosis of benign from borderline or malignant tumors is more challenging in mucinous tumors because of their typical large size and the great variation in the degree of differentiation of individual tumors [29]. Although magnetic resonance imaging (MRI) has recently been suggested as a useful diagnostic tool for mucinous borderline or malignant tumors, considering its cost-effectiveness, the role of MRI is still questionable [30–33]. Moreover, serum CA 125 level, which is a typical tumor marker in serous-type ovarian cancer, is less frequently elevated in mucinous tumors than in non-mucinous tumors [10,11,34,35]. Therefore, verification of CA19-9 as an effective diagnostic marker is important.

In our results, serum CA19-9 was frequently elevated in primary ovarian mucinous tumors. Moreover, borderline and malignant mucinous tumors, but not benign mucinous tumors, were significantly associated with serum CA19-9 elevation. It might be natural that serum CA19-9, which is a sialylated Lewis A antigen associated with mucins, is frequently elevated in primary mucinous ovarian tumors. The principal mechanism of the elevation of CA19-9 in ovarian cysts is well-documented in a number of studies of mature cystic teratomas. For instance, Ito et al. demonstrated the presence of CA19-9 in the bronchial mucosa and glands of ovarian mature cystic teratoma by immunohistochemical staining [36]. They also revealed the secretion of CA19-9 into the cystic cavity of the lesion [36]. Considering to those findings, the leakage of CA19-9

from the cystic cavity into the blood stream might be a main mechanism of serum CA19-9 elevation [36].

We can predict that probable conditions of leakage into the blood stream, such as a larger size tumor, bilateral involvement of the tumor, and tumor torsion, may be correlated with serum CA19-9 elevation. Several studies have described the clinical characteristics correlated with serum CA19-9 elevation in women with primary ovarian mature cystic teratomas. Kyung et al. reported that CA19-9 elevation was correlated with larger tumor size and higher rate of ovarian torsion in ovarian mature cystic teratomas [7]. Similarly, Umin et al. demonstrated significant correlation between serum CA19-9 levels and larger tumor size, although they failed to show a positive relationship between bilateral tumor involvement and serum CA19-9 levels [37]. Likewise, Cho et al. reported that serum CA19-9 elevation was associated with larger tumor size and presence of a fat component in ovarian mature cystic teratomas [38]. Moreover, they suggested that simultaneous elevation of serum CA125 and CA19-9 was associated with a higher cancer risk ( $p < 0.001$ ; OR: 23.7; 95% CI: 8.863–63.576) than single elevation of serum CA 19-9 [38]. In our results, clinical characteristics associated with serum CA19-9 were not the bilateral tumor involvement or existence of torsion, but rather larger tumor size, serum CA125 elevation, and tumor pathology (borderline or malignant). In agreement with results of prior studies, we found that the elevation of serum CA19-9 in ovarian mucinous tumors was significantly correlated with larger tumor size, with leakage as a likely mechanism. But more importantly, we should focus on the fact that tumor pathology (borderline or malignant) was the only independent risk factor for serum CA19-9 elevation in primary ovarian mucinous tumors (OR 3.842, 95% CI 1.277–11.558,  $p = 0.017$ ). Subgroup analysis in women with normal serum CA 125 level showed that cancer risk ( $\geq$  borderline) in women with serum CA19-9 elevation is 6.3 times higher than in those with normal serum CA19-9 level (95% CI 1.438–19.648,  $p = 0.014$ ), which is comparable to results of Cho et al. [38].

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## Conclusions

Serum CA19-9, which is frequently elevated in primary ovarian mucinous tumors, can be a useful marker in predicting malignancy, particularly when serum CA125 level is not elevated. This is the first study suggesting a possible role of serum CA19-9 in diagnosis of borderline or malignant ovarian tumors, despite several weaknesses, including retrospective design and a small number of subjects. To clarify the diagnostic role of serum CA19-9 in discrimination of borderline and malignant tumors from benign mucinous ovarian tumors, more large-scale study will be required in the near future.



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