Expression of Trypsinogen-1, Trypsinogen-2, and Tumor-Associated Trypsin Inhibitor in Ovarian Cancer: Prognostic Study on Tissue and Serum

Annikka Paju,1 Juhani Vartiainen,2 Caj Haglund,3 Outi Itkonen,1 Kristina von Boguslawski,4 Arto Leminen,2 Torsten Wahlström,2 and Ulf-Håkan Stenman1

Departments of 1Clinical Chemistry, 2Obstetrics and Gynecology, and 3Surgery, Helsinki University Central Hospital, Helsinki, and 4Department of Pathology, University of Helsinki, Helsinki, Finland

ABSTRACT

Purpose: The purpose is to study the prognostic significance of tissue expression of trypsinogen-1, trypsinogen-2, and tumor-associated trypsin inhibitor (TATI) and serum concentration of trypsinogen-2, trypsin-2-API (complex of trypsin-2 with α-1-proteinase inhibitor), and TATI in epithelial ovarian cancer.

Experimental Design: Expression of trypsinogen-1, trypsinogen-2, and TATI was determined by immunohistochemistry with monoclonal antibodies in tissue sections of tumors from 119 patients with untreated primary epithelial ovarian cancer. Preoperative serum concentrations of trypsinogen-2, trypsin-2-API, and TATI were analyzed using specific immunoassays.

Results: Fifty-four percent of the tumors expressed trypsinogen-1, 45% expressed trypsinogen-2, and 30% expressed TATI. In patients with stage I and IV disease, TATI tissue expression (P = 0.002) and elevated TATI concentration in serum (P = 0.048) were associated with adverse cancer-specific and progression-free survival in univariate analysis. In multivariate analysis, TATI tissue expression (P = 0.005), tumor grade (P = 0.0001), histological type (P = 0.02), and stage (P = 0.0005) were independent prognostic factors for adverse cancer-specific survival and TATI tissue expression (P = 0.006) and grade (P = 0.0003) for progression-free survival. In multivariate analysis of all patients and those with advanced disease, serum trypsin-2-API concentration was an adverse prognostic factor for cancer-specific and progression-free survival, and it was independent of stage and histological type of the tumor (P ≤ 0.01).

Conclusions: Tissue expression of TATI and an elevated preoperative serum concentration of trypsin-2-API are strong independent prognostic factors in advanced epithelial ovarian cancer. These results suggest that trypsin expression plays a role in the progression of ovarian cancer. TATI and trypsin-2-API are of potential use as an aid for stratification of randomized studies and for selecting treatment strategies.

INTRODUCTION

Epithelial ovarian carcinoma is a leading cause of death from gynecological malignancies in most developed countries. The high mortality is largely because of advanced stage at presentation. Although stage, grade, and the presence of residual disease correlate with survival, the individual patient outcome is not entirely predictable on the basis of these. Other clinical and biological markers have therefore been studied in attempts to identify additional prognostic factors (1). Tumor markers, especially CA 125 in serum, play an important role in the diagnosis and follow-up of ovarian cancer (2). Some other serum markers, e.g., the β-subunit of human chorionic gonadotropin (3), inhibin (4), vascular endothelial growth factor (5), and human kallikrein-6 (6) and kallikrein-10 (7) have been shown to have prognostic value when measured before treatment.

Invasion and metastasis of solid tumors requires proteolytic enzymes that degrade the extracellular matrix and basement membranes (8). Therefore, factors affecting the proteolytic activity of cancer cells are potential predictors of survival, and tissue expression of matrix metalloproteinase (MMP)-2 (9), urokinase-type plasminogen activator (10), and plasminogen activator inhibitor 1 (11) have been shown to be prognostic factors in ovarian cancer.

Trypsinogen is a serine protease that may play a role in tumor invasion. It degrades a wide spectrum of extracellular matrix proteins (12) and activates proforms of other proteinases, including MMPs 1, 2, 8, 9, and 13 (13–16). Tumor-associated trypsinogen-1 and trypsinogen-2 are strongly expressed in most ovarian cancers (17–19) and in several other cancers, e.g., pancreatic (20), gastric (21, 22) and colorectal cancer (23, 24), cholangiocarcinoma (25), and in esophageal squamous cell carcinoma (26). In ovarian cancer, expression of trypsinogen is associated with tumor aggressiveness (17, 19), and in esophageal squamous cell carcinoma, it is strongly associated with recurrence and poor prognosis (26).

Tumor-associated trypsin inhibitor (TATI) is a 6-kDa inhibitor of trypsin originally purified from urine of an ovarian cancer patient and later found to be identical to pancreatic secretory trypsin inhibitor (27, 28). TATI is expressed together with trypsin in several tumors and cancer cell lines (29), and elevated serum concentrations are common in several malignant
diseases (29). TATI is a useful serum marker for diagnosis of mucinous ovarian cancer and a prognostic factor for ovarian (30, 31) and renal cell cancer (32).

We have studied tissue expression of trypsinogen-1, trypsinogen-2, and TATI by immunohistochemistry and analyzed the serum concentrations of trypsinogen-2, trypsin-2–α-1-proteinase inhibitor (trypsin-2-API) and TATI in patients with epithelial ovarian cancer and compared the prognostic value of these with other clinicopathological factors.

PATIENTS AND METHODS

Patients. The study population consisted of 119 patients treated for primary epithelial ovarian cancer at the Department of Obstetrics and Gynecology of Helsinki University Central Hospital between 1990 and 1995. The mean age was 56 years (range, 29–85 years). All tissue samples were obtained at primary surgery, and serum samples were drawn <4 weeks before surgery. Staging was done according to the 1988 International Federation of Gynecology and Obstetrics rules (33), with pelvic and para-aortic lymphadenectomy whenever feasible. All patients, except those with stage IaGI disease (n = 19), received cisplatinum-based combination chemotherapy as first-line treatment. Relapses were treated in casu. At the latest follow-up (January 12, 1999), 70 of 119 patients were alive with a median follow-up time 60 months (range, 6–98 months). Among 49 patients that had died, 46 died of ovarian cancer, 1 of another cancer, and 2 of other diseases. Patient and tumor characteristics are shown in Table 1. Ovarian cancer tissue obtained by surgery was frozen by immersion in liquid nitrogen and stored at −80°C until used for reverse transcriptase-PCR. The study has been performed in accordance with the principles of Declaration of Helsinki.

Antibodies and Immunoassays. A monoclonal antibody predominantly reacting with trypsinogen-1 (18), MAB 1482, was from Chemicon International (Temecula, CA). Monoclonal antibodies specific for trypsinogen-2 (8F7) (34) and TATI (6E8) (35) were prepared as described previously. TATI in serum was measured by radioimmunoassay using reagents from Orion Diagnostica (Oulunsalo, Finland) as described previously (27). A cutoff value of 22 μg/liter was used (36). Trypsinogen-2 (34) and trypsin-2-API (37) in serum were measured by time-resolved immunofluorometric assays as earlier described using cutoff values of 80 and 14 μg/liter, respectively.

Immunohistochemistry. Formalin-fixed, paraffin-embedded tissue sections (4-μm) were deparaffinized in xylene and rehydrated in graded concentrations of ethanol to water, pre-treated with 0.4% pepsin (pH 1.8) for 30 min at 37°C, and treated with 0.3% hydrogen peroxide in methanol for 30 min to quench endogenous peroxidase activity. Immunostaining was performed using the Elite ABC kit (Vectastain; Vector Laboratories, Burlingame, CA). Blocking serum was applied for 15 min. The antibody against trypsinogen-1 was used at a dilution of 1:1000 (ascites) and those against trypsinogen-2 and TATI at concentrations 1 and 0.2 μg/ml, respectively. Antibodies were incubated on the tissue sections overnight at room temperature. Both the biotinylated second layer antibody and the peroxidase-labeled avidin-biotin complex were incubated on the sections for 30 min. All dilutions were made in PBS (pH 7.0), and all incubations were carried out in moist chambers at room temperature. Between staining steps, the slides were rinsed in PBS. Peroxidase staining was visualized using 3-amino-9-ethyl-carbazole [Sigma, A 5754; 0.2 mg/ml in 0.05 M acetate buffer (pH 5.0)]. The sections were counterstained with Mayer’s hemalum (Merck) and mounted with Aquamount (BDH). As positive controls, paraffin sections of human pancreatic tissue were used. As negative controls, tissue sections were stained by replacing the monoclonal primary antibodies with nonimmune mouse IgG.

All sections were reviewed and scored for statistical analysis by an experienced gynecologic pathologist (T. Wahlström), who was blinded to clinical and outcome data. The antigen staining was categorized in four classes: negative (0), in which cases no staining of the neoplastic cells was seen; faintly positive (1), where a few neoplastic cells were faintly stained; unequivocally positive (2), where most but not all of the neoplastic cells were faintly to strongly stained; and strongly positive (3), designating that all neoplastic cells showed strong staining. In all cases, the nonneoplastic tissue in the sections was completely negative. These findings were reproducible in repeated experiments.

Reverse Transcriptase-PCR and Sequencing. Total RNA was extracted from frozen ovarian cancer tissue using RNeasy kit (Qiagen, Valencia, CA). The oligonucleotide primers were constructed on the basis of published sequences for trypsinogen-1 and trypsinogen-2 (38) and TATI (39): 5’-ATGTTCTGTTGGGGCTTC-3’ (trypsinogen sense) and 5’-TTG-

<table>
<thead>
<tr>
<th>Table 1 Clinical characteristics of 119 ovarian tumors</th>
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<tbody>
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<td>Age (years)</td>
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<td>58</td>
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<tr>
<td>Stage</td>
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<td>Unknown</td>
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<tr>
<td>Histologic type</td>
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<tr>
<td>Mucinous</td>
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<tr>
<td>Endometrioid</td>
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<tr>
<td>Anaplastic</td>
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<tr>
<td>Mesonephroides</td>
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<tr>
<td>Mixed</td>
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<tr>
<td>Tumor size (cm)</td>
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<td>&lt;2</td>
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<tr>
<td>2–10</td>
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<td>Residual tumor size (cm)</td>
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<tr>
<td>0</td>
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<td>&lt;0.5</td>
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<tr>
<td>0.5–1</td>
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<tr>
<td>1–2</td>
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<tr>
<td>&gt;2</td>
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<tr>
<td>Palliation</td>
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<td>Peritoneal carcinosis</td>
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TAGACCTTGGTGTAGACTC-3' (trypsinogen antisense); and 5'-TCAGCCATGAAAGTTAACAG-3' (TATI sense) and 5'-CAAGGCCCAAGATTTTTGA-3' (TATI antisense). The trypsinogen primers produced a fragment of 156 bp and those for TATI a fragment of 243 bp. Total RNA (1 μg) was transcribed into cDNA using SuperScript II-RT (Invitrogen-Life Technologies, Inc., Paisley, United Kingdom) according to the manufacturer’s instructions. Contamination of RNA samples with DNA was excluded with control reactions without reverse transcriptase. The reverse transcriptase product (1 μl) was amplified in a 40-μl reaction volume in 1× PCR buffer [10 mM Tris-HCl (pH 8.8), 1.5 mM MgCl2, 50 mM KCl, and 0.1% Triton X-100; Finnzymes, Espoo, Finland], 0.25 mM of each deoxynucleoside triphosphate, 20 pmol of both sense and antisense primers, and 1.6 units of Dynazyme DNA polymerase (Finnzymes). The amplification conditions were as follows: 35 cycles at 95°C for 1 min and 55°C for 1 min (trypsinogen) and 40 cycles at 95°C for 1 min and 53°C for 1 min (TATI). Water was used as a negative control and cDNA from COLO 205 colon adenocarcinoma cells as a positive control in all experiments. The agarose gel electrophoresis and sequencing of the PCR products were carried out as described previously (40).

**Statistical Analysis.** Differences between groups were analyzed by the Mann-Whitney U test. Survival curves were
constructed by the Kaplan-Meier method. Multivariate survival analyses were performed by Cox regression. Statistical end points were cancer-specific and progression-free survival measured from the date of operation to the date of death, relapse, or latest follow-up. Surviving patients were censored at the time of their last clinical control, and a case was censored if death resulted from unrelated disease. The relationship between tissue expression of TATI and concentration of trypsin-2-API in serum was analyzed by one-way ANOVA. All tests were two-sided, and the significance level was set to $P = 0.05$.

RESULTS

TATI in tissue was detected as diffuse cytoplasmic and partially membrane-associated staining in 30% (36 of 119) of all tumors (Fig. 1, A and B). Expression was more frequent in mucinous (95%, 20 of 21) than in endometrioid (35%, 6 of 17), mesonephroid (20%, 2 of 10), and serous (15%, 7 of 48) cystadenocarcinomas. There was an inverse correlation between TATI expression and stage ($P = 0.0048$) and grade ($P = 0.077$). The expression of TATI in tissue correlated positively with its serum concentrations ($P = 0.035$) and with tumor size ($P = 0.028$). Trypsinogen-1 was expressed in 54% (64 of 119) (Fig. 1, C and D) and trypsinogen-2 in 45% (54 of 119) (Fig. 1E) of all tumors. The trypsinogen staining was apical and perinuclear granular corresponding to Golgi and secretory vesicle staining. Trypsinogen-1 and trypsinogen-2 expression was most frequent in mucinous (57 and 62%, respectively), serous (54 and 43%, respectively), and endometrioid (53 and 41%, respectively) cystadenocarcinomas. There were no significant correlations between trypsinogen-1 or trypsinogen-2 expression and stage, grade, or size of the tumor. Expression of trypsinogen-1 and trypsinogen-2 and TATI in ovarian cancer tissue was confirmed by reverse transcriptase-PCR and sequencing of the PCR products (data not shown).

Serum TATI was elevated in 32 of 106 patients (30%). The median concentrations were significantly greater in patients with mucinous (25 μg/liter) than in those with serous tumors (15 μg/liter; $P = 0.004$) and in patients with grade 3 (19 μg/liter) than grade 1 (13 μg/liter) tumors ($P = 0.03$). Serum trypsinogen-2 was determined in 98 patients, and elevated levels occurred in 13 patients (13%). The median concentrations were significantly higher in patients with mucinous (49 μg/liter) than in those with serous (36 μg/liter) tumors ($P = 0.02$) and in patients with stage IV (63 μg/liter) than stage I (34 μg/liter) disease ($P = 0.03$). Preoperative trypsin-2-API concentration was determined in 53 patients, and elevated values were observed in 32 patients (60%). The concentrations were not related to histological type or stage, but they were significantly greater in patients with grade 3 (19 μg/liter) than in those with grade 1 (13 μg/liter) tumors ($P = 0.02$).

In univariate analysis of all patients, presence of ascites, high grade, high stage, residual tumor size $> 2$ cm, and lack of strong positive staining for trypsinogen-1 were all associated with short cancer-specific survival. An elevated preoperative serum trypsin-2-API concentration (Fig. 2) correlated with progression-free survival (Table 2). In serous tumors, lack of strong positive staining for trypsinogen-2 was also associated with poor prognosis ($P = 0.03$), whereas in mucinous tumors, only stage was of prognostic significance ($P < 0.0001$). In univariate analysis of patients with stage III and IV tumors, high grade, stage, elevated preoperative TATI concentration in serum, and positive tissue staining for TATI were associated with
short cancer-specific and progression-free survival (Tables 3 and 4, Fig. 2). Histological type was also of prognostic significance, patients with serous tumors having the best and those with mucinous tumors the worst prognosis.

In multivariate analysis of all patients, stage and grade were independent prognostic factors for cancer-specific survival ($P_{/H11005} = 0.007$ and $0.0001$, respectively), but only grade was significant for progression-free survival ($P_{/H11005} = 0.0001$). Because trypsin-2-API in serum was related to grade, we performed a multivariate analysis where only stage, histological type of the tumor, and trypsin-2-API were included. In this analysis, all factors were independent prognostic indicators for cancer-specific and progression-free survival ($P_{/H11005}$ values for trypsin-2-API are $0.004$ and $0.001$, respectively). In multivariate analysis of stage III and IV tumors, TATI tissue expression ($P_{/H11005} = 0.006$), grade ($P_{/H11021} = 0.0001$), stage ($P_{/H11005} = 0.01$), and histological type

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\begin{array}{lcccc}
\text{Table 2} & \text{Uni- and multivariate analysis of cancer-specific survival of patients with stage III or IV ovarian cancer: relative risk of death according to grade; histologic type; stage; TATI tissue expression; and preoperative serum TATI concentration} \\
\hline
\text{Grade} & n & \text{RR}^a & 95\% \text{ CI} & P & \text{RR} & 95\% \text{ CI} & P \\
1–2 & 28 & 1 & & & 12.4 & 4.02–38.5 & <0.0001 \\
3 & 27 & 5.64 & 2.52–12.66 & <0.0001 & 1 & & \\
\hline
\text{Histologic type} & & & & & & & \\
Serous & 44 & 1 & & 1.0001 & 1 & & \\
Mucinous & 4 & 3.54 & 1.51–8.28 & 0.004 & 1.20 & 0.31–4.70 & 0.79 \\
Endometrioid & 5 & 0.77 & 0.36–1.67 & 0.51 & 2.26 & 0.81–6.28 & 0.12 \\
\hline
\text{Stage} & & & & & & & \\
III & 47 & 1 & & & 1 & & \\
IV & 9 & 0.42 & 0.28–0.64 & <0.0001 & 3.70 & 1.30–10.6 & 0.01 \\
\hline
\text{TATI expression} & & & & & & & \\
Negative & 48 & 1 & & 1.0001 & 1 & & \\
Positive & 8 & 3.98 & 1.68–9.48 & 0.002 & 7.67 & 1.79–32.8 & 0.006 \\
\hline
\text{Serum TATI} & & & & & & & \\
\leq22 \mu g/liter & 14 & 1 & & 1 & & & \\
>22 \mu g/liter & 35 & 2.18 & 1.01–4.70 & 0.048 & 0.96 & 0.40–2.30 & 0.92 \\
\hline
\end{array}
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\begin{array}{lcccc}
\text{RR}, \text{relative risk; CI, confidence interval; TATI, tumor-associated trypsin inhibitor.}
\end{array}
\]
(\(P = 0.01\)) were independent prognostic factors for cancerspecific survival and TATI tissue expression (\(P = 0.01\)) and grade (\(P = 0.0001\)) for progression-free survival. Tissue expression of TATI was associated with a 6.1–7.7-fold increased risk of death (Tables 3 and 4). An elevated preoperative trypsin-2-API concentration in serum also predicted adverse cancer-specific and progression-free survival independently of stage and histological type of the tumor (\(P = 0.012\) and 0.013, respectively), and this was associated with an 8.1-fold increase in risk of death. Comparison of the tissue expression of TATI with serum concentrations of trypsin-2-API showed that these were not correlated (ANOVA, \(P = 0.9\); Fig. 3).

**DISCUSSION**

We have earlier shown that elevated preoperative serum TATI concentrations predict adverse prognosis in patients with stage III and IV epithelial ovarian cancer (3, 31). The results of the present study confirm these findings, and they additionally show that immunohistochemical expression of TATI also is a strong prognostic factor independent of tumor stage, grade, and histological type. Interestingly, the tissue expression of TATI was a much stronger prognostic factor than serum TATI, and its prognostic significance in advanced disease was actually comparable with that of grade and stage. Because trypsin is thought to mediate tumor invasion (12, 16) and TATI is a trypsin inhibitor, the correlation between high TATI concentrations in serum and tissue and poor prognosis may seem surprising. However, a poor prognosis has also found to be associated with high levels of another proteinase inhibitor, plasminogen activator inhibitor 1, in breast (41), lung (42), and colorectal cancer tissue (43).

The prognostic value of TATI has been explained by the association between TATI and trypsinogen expression. Thus, it was surprising to find that tissue expression of trypsinogen-1 and trypsinogen-2 was not associated with poor prognosis in any subset of patients. In contrast, univariate analysis showed that lack of trypsinogen-1 and trypsinogen-2 expression predicted impaired survival. Possibly the lack of trypsinogen immunoreactivity in tumor tissue reflects rapid secretion and activation of this protease. Activated trypsin is rapidly inactivated by \(\alpha\)-2-macroglobulin. Serine proteinases in complex with \(\alpha\)-2-macroglobulin are not detected by antibodies and they cannot be measured in serum (44). Trypsin reaching circulation can also be inactivated by API, and we were able to measure this complex by a specific immunoassay (37). Sixty percent of the patients had elevated serum concentrations of trypsin-2-API complex, and an elevated level was a strong prognostic factor

**Table 4** Uni- and multivariate analysis of progression free survival of patients with stage III or IV ovarian cancer: relative risk of death according to grade; histologic type; stage; TATI tissue expression; and preoperative serum TATI concentration

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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<tbody>
<tr>
<td></td>
<td>(n)</td>
<td>RR(^a)</td>
</tr>
<tr>
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<td></td>
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<tr>
<td>1–2</td>
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<td>1</td>
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<tr>
<td>3</td>
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<tr>
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<td>Endometrioid</td>
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<tr>
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<tr>
<td>Serum TATI</td>
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<tr>
<td>(\leq 22) μg/liter</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>&gt;22 μg/liter</td>
<td>35</td>
<td>2.54</td>
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\(^a\)RR, relative risk; CI, confidence interval; TATI, tumor-associated trypsin inhibitor.
for adverse outcome. Trypsin-2-API was related to grade, but it was independent of stage and histological type of the tumor, and it did not correlate with tissue expression of TATI.

The serum concentration of the inactive proenzyme trypsinogen-2 did not predict survival, although it was significantly greater in patients with high-stage than in those with low-stage disease. Elevated serum levels of trypsinogen-2 and trypsin-2-API have earlier been observed in a majority of patients with cholangiocarcinoma and pancreatic cancer (45). However, in these cancers, the elevation may be caused by release of pancreatic trypsin. This is not a likely cause in ovarian cancer. Thus, our findings indicate that ovarian cancer secretes trypsin and that this protease contributes to aggressive tumor growth.

Trypsin-1 and trypsin-2 are thought to be involved in the spread of ovarian cancer by degrading extracellular matrix (12) and by activating other proteases associated with cancer invasion, e.g., urokinase-type plasminogen activator and MMPs (13, 15, 46). Trypsinogen (17, 18) and TATI (27, 47) are often expressed in ovarian cancer, and immunohistochemical expression of trypsinogen-1 has been reported to be more frequent in malignant than in benign or borderline tumors (19). Trypsinogen-1, trypsinogen-2, and TATI occur at high concentrations in cyst fluid produced by ovarian tumors (15, 17). These, as well as complexes of API with trypsin-1 and trypsin-2, which reflect trypsin activation, occur at higher concentrations in cyst fluid from malignant than from benign ovarian tumors (15, 17), and this is associated with MMP-9 activation (15).

The strong prognostic value of TATI expression in ovarian cancer tissue appears to explain our earlier findings showing that serum TATI predicts adverse survival in epithelial ovarian cancer (3, 30, 31). Serum TATI correlated with prognosis in advanced ovarian cancer also in this study, but an elevated serum concentration of trypsinogen-2-API was a prognostic factor both among all patients and those with advanced disease. Thus, trypsin-2-API is a new prognostic serum marker, which together with TATI may be useful in the selection of therapy and stratification of patients for clinical studies.

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