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ORIGINAL ARTICLE

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# Stromelysin-3 expression in invasive ovarian carcinomas and tumours of low malignant potential

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**Abstract** Stromelysin (ST)-3 is considered to be a marker of invasion and preinvasive lesions to indicate the likelihood of subsequent invasion. The expression of ST-3 has not been systematically studied in ovarian neoplasms. We studied 47 ovarian carcinomas and 49 ovarian tumours of low malignant potential (LMP) to see whether the expression of ST-3 correlated with any histopathologic features and, in the LMP tumours, whether its expression might be a prognostic indicator. All of the primary tumours and available metastases or implants were studied using immunohistochemistry (IHC) for ST-3 and, in 52 selected lesions, in situ hybridisation (ISH) using a cDNA probe. Expression of ST-3 was seen in 42 of 47 (89%) of the carcinomas and in 16 of 49 (33%) of the LMP cases. A significantly higher percentage of carcinomas than LMP tumours ($P$<0.00001) expressed ST-3 in the stroma adjacent to the tumour, with a correlation to increasing FIGO (International Federation of Gynecology and Obstetrics) tumour stage. ST-3 was expressed in the surrounding stroma of 1 of 8 LMP implants and 46 of 55 (84%) of the carcinoma metastases. The single LMP patient who died of tumour recurrence had ST-3 expression, but a significant prognostic impact was not found. The infrequent expression of ST-3 in LMP compared with carcinoma metastases appears to be more consistent with a peritoneal "field effect" than spread from the ovarian LMP tumour.

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## Introduction

Stromelysin (ST)-3 is a member of the metalloproteinase family (MMP-11) of proteases and has been found to be expressed in a wide variety of carcinomas and in normal processes, such as wound healing and embryonic development. Although it was first described in 1990 [3], its substrate specificity, activation signals and potential role in the remodelling of the extracellular matrix (ECM) are not yet completely understood. ST-3 is unusual among proteases due to its pattern of expression, since it is not expressed by tumour cells, but rather in fibroblasts in discrete foci near areas of invasive carcinoma. Factors which have been found to induce ST-3 expression include basic fibroblast growth factor and platelet-derived growth factor (PDGF) in the lung [2] and PDGF and interleukin (IL)-6 in the endometrium platelet [28].

A majority of the invasive carcinomas of the breast [5, 15, 30], lung [2, 33], skin [16, 35], colon [17, 31], head and neck [18, 21] and pancreas [34], among others, have been found to express ST-3. The strength and extent of expression have been reported to be related to the degree [18] and pattern [17] of invasiveness. Recently, tissue levels of ST-3 determined using enzyme-linked immunosorbent assay (ELISA) have been found to be an independent predictor of survival in node-negative breast carcinoma [5]. Although other proteases, including the serine protease family of enzymes, have been studied in ovarian carcinoma and have been shown to have a prognostic impact [14], to date only one study has reported the expression of ST-3 in ovarian carcinoma, and this included only eight cases [22]. An additional area of interest with respect to ST-3 has been the fact that it has occasionally been found to be expressed in noninvasive premalignant neoplasms, including those of the breast, larynx, cervix and bladder; and that this expression shows a correlation with the histologic forms of these premalig-

nant lesions which are known to have a greater tendency to become invasive [10, 11, 19, 22]. This has led to the speculation that ST-3 may be involved in the very earliest phases of the process of invasion [21].

Carcinoma of the ovary usually has a very poor prognosis since it is nearly always detected at a late, advanced stage [4]. The majority of ovarian carcinomas appear to arise from the ovarian surface epithelium, but the steps of malignant transformation and progression that are responsible for the development of carcinoma are only poorly understood. A possible precursor neoplasm, which histologically appears to be an intermediate form between benign, epithelial-lined ovarian cysts and ovarian carcinoma, is the ovarian tumour of low malignant potential (LMP), also known as atypically proliferating neoplasm or borderline tumour. By definition, LMP tumours are architecturally and cytologically complex but lack definite areas of invasion. However, in about one-third of the cases, these tumours are associated with peritoneal lesions called implants [12]. The source of origin of the implants in LMP tumours is not known, and it is still debated whether these have spread from the primary ovarian tumour or whether they arise by a field effect on the peritoneal surface [26]. Although recent molecular biologic evidence tends to support the concept that LMP tumours might be the precursors of ovarian carcinoma [6, 7], their overall very good prognosis, especially when compared with ovarian carcinoma, has made this idea difficult to accept, particularly from the clinical point of view [32].

### Goal of the study

Despite the fact that most patients with LMP are cured of their disease, even when implants are present and the tumour is conservatively treated (i.e. surgery alone), occasional patients have disease progression and eventually die from their tumour [12]. To date, there is no marker which can reliably identify the small subgroup of LMP tumours which will progress. We carried out the present study of ST-3 expression in groups of ovarian LMP tumours and invasive carcinomas in order to determine whether it could be correlated with any known clinicopathologic variables (e.g. stage, degree of differentiation) in either group and to see whether any correlation could be found between ST-3 expression and the rate of tumour recurrence or patient survival in the LMP group.

## Material and methods

### Patients and tissue samples

The study group consisted of 49 patients with an LMP tumour of the ovary and 47 patients with an ovarian carcinoma (Table 1). Of the 49 LMP cases, a total of 56 ovarian tumours (7 cases with bilateral LMP tumours, 6 serous and 1 mucinous) and 8 implants (7 serous, 1 mucinous, none invasive) were studied for ST-3 expression. In the group of 47 carcinomas, a total of 52 ovarian tumours (5 cases with bilateral ovarian tumours) and 55 metastases were studied. In addition, four non-neoplastic lesions in specimens were studied for ST-3 expression, including one lymph node with granulomatous inflammation, one adenomyomatosis lesion from the wall of the uterus and two endometriotic ovarian cysts. The histologic types, tumour differentiation grades and FIGO (International Federation of Gynecology and Obstetrics) stages of the tumours of the two groups are shown in Table 1. The 7 FIGO III LMP cases included six serous and one mucinous tumour, and the eight implants (two from one case) were available from these cases.

**Table 1** Clinicopathologic characteristics of the ovarian tumours. LMP low malignant potential; FIGO International Federation of Gynecology and Obstetrics; – not applicable

| Characteristic | LMP tumours | Carcinomas | Total |
|---|---|---|---|
| Age (mean; range) | 57.7 (27–90) | 57.3 (26–81) | 57.5 (26–90) |
| Number | 49 | 47 | 96 |
| Histologic type | | | |
| Serous | 30 (61%) | 33 (70%) | 63 (66%) |
| Mucinous | 17 (35%) | 1(2%) | 18 (19%) |
| Endometrioid | 1 (2%) | 10 (21%) | 11 (12%) |
| Clear cell | 1 (2%) | 1 (2%) | 2 (2%) |
| Undifferentiated | 0 | 2 (4%) | 2 (2%) |
| Grade | | | |
| G1 | – | 4 (9%) | 53 (55%) |
| G2 | – | 15 (32%) | 15 (16%) |
| G3 | – | 26 (55%) | 26 (27%) |
| G4 | – | 2 (4%) | 2 (2%) |
| Stage (FIGO) | | | |
| I | 42 (86%) | 7 (15%) | 49 (51%) |
| II | 0 | 3 (6%) | 3 (3%) |
| III | 7 (14%) | 31 (66%) | 38 (40%) |
| IV | 0 | 6 (13%) | 6 (6%) |

Clinical follow-up data were available for 39 of the 49 patients with LMP tumours, including the clear cell and endometrioid cases, 11 of the 17 mucinous tumours and 26 of the 30 serous tumours. Clinical follow-up ranged from 3 to 97 months with a mean follow-up time of 53.4 months.

### Immunohistochemistry and in situ hybridisation

Immunohistochemistry (IHC) was carried out using the monoclonal antibody 5ST-4A9 (kindly provided by Prof. P. Chambon, Strasbourg, France) according to a previously described protocol [17]. The immunohistochemistry for ST-3 was followed with the avidin biotin method with diaminobenzidine (DAB) development.

In situ hybridisation (ISH) was performed using a 118 bp $^{35}$S cDNA-labelled probe on paraffin sections using a previously described method [17]. The probe was generated through two reactions (1) reverse transcription from an ST-3 insert in plasmid DNA (also provided by Prof. Chambon) and (2) a RNA polymerase reaction with T3 (sense orientation) or T7 (antisense orientation; Stratagene, Heidelberg, Germany). The sections were rehydrated in phosphate-buffered saline (PBS), digested by proteinase K [1 µg/ml proteinase K in 100 mM Tris (pH 8.0), 50 mM ethylene diamine tetraacetic acid (EDTA)] for 10 min at 37°C. Following digestion, the slides were incubated with 4% paraformaldehyde in PBS for 20 min at room temperature and then acetylated for 10 min (0.25% acetic anhydride and 100 mM triethanolamine (pH 8.0)). Hybridisation (12–16 h in a humidified chamber at 52°C) was with the $^{35}$S-labelled cDNA probe in a buffer [50% deionized formamide, 300 mM NaCl, 10 mM Tris HCl, 10 mM $NaP0_4$ (pH 6.8), 5 mM EDTA, 10% dextran sulfate, 1 µg/ml of tRNA, 10 mM dithiothreitol (DTT), ficoll 400, 0.02% polyvinylpyrolidone and 0.02% bovine serum albumin (BSA)]. A high stringency wash (three 2-h washes) at 52°C in the presence of 300 mM NaCl, 10 mM Tris HCl, 10 mM $NaP0_4$ (pH 6.8), 5 mM

EDTA, 50% deionized formamide, 10 mM DTT) was followed by dehydration in ethanol containing 300 mM ammonium acetate. The slides were coated with Kodak NTB2 film emulsion and exposed for an average of 10 days for autoradiography and then counterstained with haematoxylin after development.

### Semiquantitative evaluation of results

The results of ISH and IHC were evaluated according to the distribution and intensity of ST-3 positive areas according to a modification of a previously described method [23]. The intensity of the ST-3 signal or staining was graded from 1+ to 3+. The percentage of positive cells in the positive areas were estimated and scored as negative, 0; less than 30%, 1+; equal or greater to 30% but less than 70%, 2+ and more than 70%, 3+. Finally, the percentage of tumour–stroma interface areas on the slide were also scored using this method. For some of the tumours, tissue from implants or metastases was available, and the staining of ST-3 was compared in these areas with the primary tumours.

### Statistics

Comparisons of the rates of ST-3 expression between the groups (carcinoma, LMP tumours) and between primary tumours and metastases or implants and in comparison with histopathologic variables, including pT category, grade, FIGO stage and histologic type were performed using the $\chi^2$ test and, when appropriate, the Fisher exact test. A $P$ value of less than 0.05 was considered to be statistically significant. Comparison with survival in the LMP group was performed using Kaplan–Meyer survival analysis.

## Results

### General expression patterns

Using IHC, it was found that a total of 58 (60%) of the 96 cases of ovarian neoplasia had at least one tissue sample which was positive for ST-3. Of the 175 lesions studied, 111 (63%) were positive for ST-3 when analysed using IHC. When using both IHC and ISH, 52 lesions were found to be positive for ST-3 on serial sections of the same tissue area, and there was complete agreement of the results except for two small lesions (one metastasis and one implant) in which insufficient tissue remained in the block for the ISH. The pattern of expression using both ISH and IHC was typical for ST-3 in that it was only found in fibroblasts adjacent to areas of invasive tumour or epithelium. The extent of expression varied considerably in the positive lesions. In 58 (33%), 25 (14%) and 28 (16%) lesions, expression was focal (1+), moderate (2+) and widespread, respectively.

Using IHC, the four incidental non-neoplastic lesions were also stained with ST-3. One of these, an area of granulomatous inflammation in a lymph node, was negative for ST-3. The other three lesions (an area of adenomyomatosis and two endometriotic cysts) showed ST-3 expression which, in one endometriotic cyst, was moderately extensive (2+). The normal-appearing ovarian tissue adjacent to the lesions under study was consistently negative for ST-3.

**Table 2** Stromelysin-3 expression: results from the low malignant potential tumours. *ST* stromelysin; *LMP* low malignant potential; *FIGO* International Federation of Gynecology and Obstetrics

| Characteristic | ST-3 negative | ST-3 positive | Total |
|---|---|---|---|
| Cases (*n*) | 33 (67.3%) | 16 (32.7%) | 49 |
| Ovarian tumour | 38 (67.9%) | 18 (32.1%) | 56 |
| Implants | 7 (87.5%) (6 Serous, 1 mucinous) | 1 (12.5%) (Serous) | 8 |
| Histologic type (cases) | | | |
| Serous | 18 (60.0%) | 12 (40.0%) | 30 |
| Mucinous | 14 (82.4%) | 3 (17.6%) | 17 |
| Endometrioid | 0 | 1 | 1 |
| Clear cell | 1 | 0 | 1 |
| Stage (FIGO) | | | |
| I (IA:IB:IC) | 29 (27:1:1) | 13 (9:3:1) | 42 |
| III (IIIA:IIIC) | 4 (2:2) | 3 (2:1) | 7 |

### LMP tumours

Sixteen of the 49 LMP cases (33%) were positive for ST-3 in at least one of the specimens (Table 2). Of the seven cases with bilateral tumours, two had ST-3 expression in both tumours. Of the eight implants (all noninvasive), only one serous implant had ST-3 expression. The primary tumour of this case also showed expression. Except for one primary tumour (a FIGO Ia solitary tumour), which had moderately extensive expression, all of the rest of the positive lesions had only focal expression. In some of the tumours, the areas of ST-3 positivity were found in areas of marked cytologic atypia and architectural complexity (Fig. 1), but this was not always the case. As for histologic type, the single endometrioid LMP tumour was positive for ST-3. Mucinous (3 of 17; 17.6%) and serous (12 of 30; 40%) LMP tumours were positive for ST-3. There was no significant difference in ST-3 expression according to histologic type. When the clear cell and endometrioid tumours were excluded, ST-3 positivity in the mucinous versus serous LMP tumours showed no significant difference with respect to ST-3 expression ($P$=0.11). With respect to FIGO stage, 13 of the 29 (31%) FIGO I tumours and 3 of the 7 (43%) FIGO III tumours were positive for ST-3, which was also not a significant difference ($P$=0.67).

Three of the 39 LMP patients with clinical follow-up died during the observation period, but only one of these patients died from recurrence of the LMP tumour. This patient had had a serous FIGO Ia tumour which recurred 9 months after surgery, with death occurring 33 months post-operatively. This tumour was one of the 15 tumours that showed focal positivity for ST-3. None of the other patients with follow-up had tumour recurrence.

### Carcinomas

As shown in Table 3, 42 of the 47 ovarian carcinoma cases (89%) were positive for ST-3 in at least one lesion

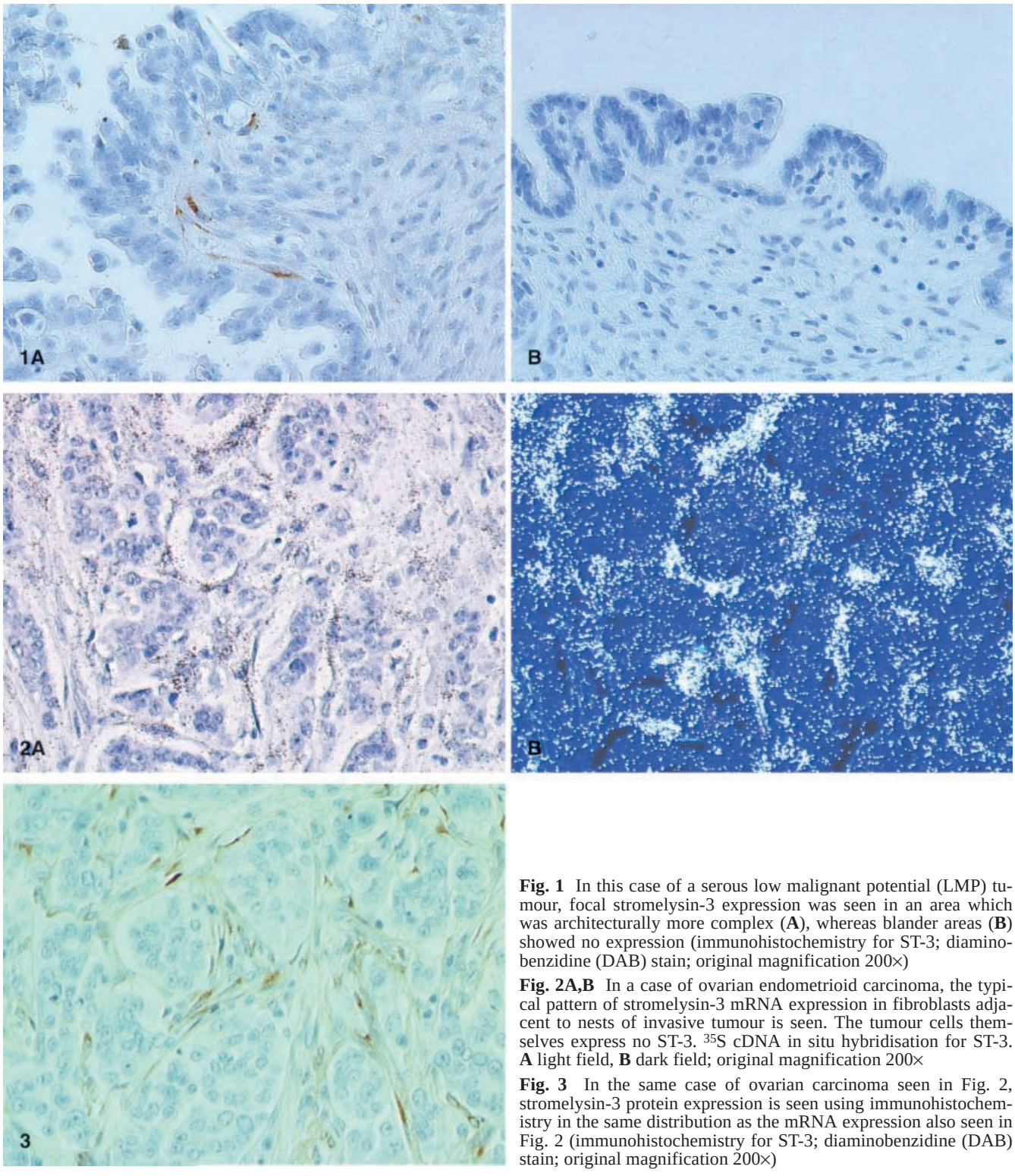


**Fig. 1** In this case of a serous low malignant potential (LMP) tumour, focal stromelysin-3 expression was seen in an area which was architecturally more complex (**A**), whereas blander areas (**B**) showed no expression (immunohistochemistry for ST-3; diaminobenzidine (DAB) stain; original magnification 200×)

**Fig. 2A,B** In a case of ovarian endometrioid carcinoma, the typical pattern of stromelysin-3 mRNA expression in fibroblasts adjacent to nests of invasive tumour is seen. The tumour cells themselves express no ST-3. $^{35}S$ cDNA in situ hybridisation for ST-3. **A** light field, **B** dark field; original magnification 200×

**Fig. 3** In the same case of ovarian carcinoma seen in Fig. 2, stromelysin-3 protein expression is seen using immunohistochemistry in the same distribution as the mRNA expression also seen in Fig. 2 (immunohistochemistry for ST-3; diaminobenzidine (DAB) stain; original magnification 200×)

when using IHC, which was a significantly higher proportion than in the LMP tumour group ($P<0.00001$). Of the 55 metastases, 46 (84%; including 8 of 12 regional lymph node metastases) showed at least focal expression of ST-3. Of the 53 primary tumours, 43 (83%) also showed at least focal expression of ST-3. In two cases, metastatic lesions were positive for ST-3, although no expression was seen in the primary tumour. Classification according to the extent of ST-3 expression showed that 21 (38%) and 10 (18%) of the 46 ST-3-positive metastases showed extensive (3+) and moderately extensive (2+) expression, compared with 7 (14%) and 13 (25%) of the primary lesions with 3+ and 2+ staining, respectively, which was a significantly greater extent of expres-

**Table 3** Stromelysin-3 expression: results from the carcinomas. *ST* stromelysin; *FIGO* International Federation of Gynecology and Obstetrics

| Characteristic | ST-3 negative | ST-3 positive | Total |
|---|---|---|---|
| Number (*n*) | 5 (10.6%) | 42 (89.4%) | 47 |
| Histologic type | | | |
| Serous | 2 (6.1%) | 31 (93.9%) | 33 |
| Mucinous | 1 | 0 | 1 |
| Endometrioid | 2 (20%) | 8 (80%) | 10 |
| Clear cell | 0 | 1 | 1 |
| Undifferentiated | 0 | 2 | 2 |
| Stage (FIGO) | | | |
| I (all IA) | 3 | 4 | 7 |
| II (IIA:IIC) | 0 | 3 (1:2) | 3 |
| III (IIIA:IIIB:IIIC) | 1 (1:0:0) | 30 (1:1:28) | 31 |
| IV | 1 | 5 | 6 |
| Ovarian tumour | 9 (17.3) | 43 (82.7) | 52 |
| (1+/2+/3+) | 0 | (23/13/7) | 52 |
| Metastases | 9 (16.4) | 46 (83.6) | 55 |
| (1+/2+/3+) | | (15/10/21) | 55 |

sion in the metastases than seen in the primary tumours ($P$=0.029). Examples of positivity for ST-3 using ISH and IHC in cases of ovarian carcinoma are shown in Fig. 2 and Fig. 3, respectively. With respect to histologic type, the single clear cell carcinoma and both undifferentiated tumours were positive for ST-3. Endometrioid (8 of 10) and serous tumours (31 of 33) were ST-3 positive and, the single mucinous tumour was negative for ST-3. With respect to FIGO stage, 4 of the 7 (57%) FIGO I tumours, all 3 FIGO II tumours, 30 of 31 (97%) FIGO III tumours and 5 of 6 (83%) FIGO IV tumours were positive for ST-3, which was a significant association of ST-3 positivity with increasing stage ($P$=0.0184), although not with UICC pT or pN categories. ST-3 expression showed no statistical correlation with degree of differentiation or histologic type in the carcinoma group.

## Discussion

This is the first detailed study of ST-3 expression in a group of ovarian neoplasms. The fact that most, but not all, ovarian carcinomas, a third of LMP tumours and all of the three endometriotic lesions that were studied expressed ST-3 is a reflection of the complex role that ST-3 plays in extracellular matrix turnover, not only in the process of tumour invasion, but also in nonneoplastic processes. The variation of the extent of ST-3 expression between tumours and among various areas within a given tumour or metastases is also evidence that ovarian tumours are quite heterogeneous with respect to ST-3 expression. In a study of ST-3 expression in a variety of tumour types, Rouyer, et al. found that eight of eight adenocarcinomas of the ovary expressed ST-3 [22], but this expression was not further described. A recent report based on a northern blot analysis has also found that ST-3 is expressed at a low level by the normal mouse ovary. However, unlike MMP-19 and tissue inhibitor of metalloproteinase-1 (TIMP-1), ST-3 expression does not appear to play any significant role in the process of ovulation [9]. We did not identify any expression of ST-3 by any normal ovarian tissue adjacent to the neoplasms which we studied using IHC or ISH, but the expression in the endometriotic lesions fits with the observation that ST-3 has been found to be active in the breakdown of the endometrium during the normal menstrual cycle, where its expression has been shown to be induced by PDGF and IL-6 [28].

One-third of the LMP tumour cases in our study expressed ST-3. Although one patient whose tumour expressed ST-3 eventually died from her tumour, no significant correlation of ST-3 expression with a poorer prognosis could be shown. It is possible that with a very large number of patients and a longer follow-up time, such an association could be found. This does not seem likely since the average follow-up time of our group of LMP tumours is already 4.5 years and one would not expect that any additional patients would develop a tumour recurrence after such a long period. However, late recurrences of LMP tumours have been described [27]. Perhaps the best correlation with our findings to date lies in the observation that a small percentage of routinely diagnosed LMP tumours have, in fact, areas of microinvasion when carefully examined, but this does not appear to have an adverse impact on prognosis [20, 29]. Therefore, although ST-3 expression might be a marker of invasion, it may not necessarily predict a poorer prognosis. A variety of other methods have been investigated for their usefulness in identifying LMP tumours which will later become progressive, including p53 overexpression, the expression of epithelial growth receptor (EGFR) and c-erbB2 [13], microsatellite analysis [8], interphase cytogenetics [7], S-phase fraction, aneuploidy and serine protease levels [25]. Although various abnormalities have been described, no reliable marker for LMP tumour progression has yet been found.

The finding that nearly 90% of the carcinomas in this study expressed ST-3 is not surprising based on the fact that Rouyer found ST-3 expression in all eight carcinomas that he studied [22]. Given the fact that all of these tumours had areas of frank invasion, it is not surprising that more carcinomas than LMP tumours expressed ST-3 and that it was much more extensive in the carcinomas. The correlation of ST-3 with increasing stage of the tumour is also in agreement with the concept that ST-3 is a marker for a more biologically aggressive and invasive neoplasm [1].

A particularly interesting finding was the fact that the metastases of the ovarian carcinomas expressed ST-3 with the same frequency as the primary tumours and that this expression was statistically even more extensive than that of the primary carcinomas. In fact, ST-3 was expressed in the metastases in two patients although the primary tumours were negative. The tendency for metastases to more strongly express proteases than the primary tumour has also been described for serine proteases [24]. In contrast, the implants of the LMP tumours were much

less active than the primary tumours with regard to ST-3 expression. These results indicate that the metastases of the carcinomas are more biologically aggressive than their primary tumour, but that the implants of the LMP tumours are less so. The origin of implants in LMP tumours is still not definitely proven. Some argue that these are true implants which have spread from the primary tumour [26], while others, citing the relative lack of prognostic impact of implants have, favour the idea that they are products of a "field effect", similar to endosalpingiosis or endometriosis [32]. Our findings, which fail to demonstrate progression with respect to ST-3 expression in the implants of LMP compared with the primary ovarian LMP tumour, are more consistent with the latter concept. However, it is certain that a large number of factors are responsible for the process of tumour cell spread in LMP tumours and will need to be investigated before the pivotal question concerning the origin of implants of LMP tumours can be answered.

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