

# Overexpression of tyrosine kinase receptor B promotes metastasis of ovarian serous adenocarcinoma by lymphangiogenesis

Weiping Zheng<sup>1</sup>, Qunyun Dai<sup>1</sup>, Pingping Tao<sup>1</sup>, Aijing Sun<sup>2</sup>, Yungen Wang<sup>1</sup>, Lei Bao<sup>3</sup>, and Guorong Zhang<sup>1</sup>

<sup>1</sup>Department of Gynecology and <sup>2</sup>Department of Pathology, Shaoxing People's Hospital and Shaoxing Hospital of Zhejiang University, Shaoxing; <sup>3</sup>Department of Pathology, Shaoxing Maternity and Child Health Hospital, Shaoxing, China

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## ABSTRACT

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**Aims and background.** The aim of this study was to detect the expression features of tyrosine kinase receptor B (TrkB) and analyze the possible correlation between TrkB expression and lymph vessel density (LVD) in metastasis of ovarian serous adenocarcinoma.

**Methods.** An immunohistochemical method was used to evaluate TrkB expression in 139 ovarian tumor sections (103 primary ovarian serous adenocarcinomas and 36 serous adenomas) and investigate the correlation between TrkB expression and LVD, which was estimated by means of VEGFR-3 assessment.

**Results.** TrkB was significantly upregulated in serous adenocarcinomas and absent in serous adenomas. There was no association between TrkB expression and the histological grade of cancer cells. The expression of TrkB was correlated with surgicopathological stage and metastasis in serous adenocarcinomas. The level of TrkB was higher in advanced-stage than in early-stage disease. TrkB was overexpressed in metastatic lesions compared with the corresponding primary lesions. Furthermore, a positive correlation between TrkB expression and LVD in serous adenocarcinomas was observed.

**Conclusions.** TrkB was overexpressed in ovarian serous adenocarcinomas and might be involved in cancer metastasis by associated lymphangiogenesis.

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## Introduction

Due to the difficulty in early detection and the lack of efficient therapeutic measures, ovarian cancer is still the leading cause of death among gynecological malignancies. Metastasis and chemotherapy resistance are responsible for treatment failure and death in patients with ovarian cancer. Nevertheless, the molecular mechanisms associated with metastasis and chemotherapy resistance remain elusive. An important feature of multicellularity is that cells only survive and differentiate in the normal tissue environment and eliminate themselves by apoptosis when not in that environment. Cells can sense their location through specific interactions with the extracellular matrix (ECM) and neighboring cells<sup>1</sup> and convert extracellular stimuli into chemical signals capable of modulating intracellular signal transduction. When detaching from the ECM and from neighboring cells, normal cells will be subject to anoikis, by which cells die in a programmed cell death process<sup>2</sup>. By contrast, malignant tumor cells can "leave home" and survive, and even thrive in a foreign tissue environment. It has been suggested that anoikis acts as a physiological barrier to metastasis. Resistance to anoikis may allow survival of cancer cells during systemic circulation and then facilitate secondary tumor formation in distant organs<sup>3-5</sup>. The important role of anoikis resistance in tumor metastasis has been attracting increasing attention<sup>6</sup>.

**Key words:** ovarian serous adenocarcinoma, tyrosine kinase receptor B, metastasis, lymph vessel density, immunohistochemistry.

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**Correspondence to:** Pingping Tao, Department of Gynecology, Shaoxing People's Hospital & Shaoxing Hospital of Zhejiang University, No. 568 Zhongxing Road, Shaoxing, 312000 China.

Tel +86-575-88229482;  
fax +86-575-88228587;  
e-mail tpp002@hotmail.com

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As a neurotrophic factor receptor encoded by the proto-oncogene *Trk* (tyrosine kinase), *TrkB* (tyrosine kinase receptor B) exists mostly in nervous cellular membranes and plays an essential role in the development and function of the neuronal system, including regulation of cell survival and differentiation<sup>7</sup>. *TrkB* works as a potent and specific suppressor of anoikis by activating the phosphoinositide-3 kinase (PI3K)/AKT pathway<sup>8</sup>. The kinases PI3K and AKT are involved in diverse survival signaling scenarios and have been implicated in anoikis as central regulators. For example, the activated *RAS* oncogene activates PKB/AKT and confers resistance to detachment-induced apoptosis<sup>9</sup>. PI3K/AKT signaling activated by *TrkB* contributes to anoikis resistance in rat intestinal epithelial cells, which are highly sensitive to anoikis. It has been reported that *TrkB* could specifically suppress anoikis of benign epithelial cells and induce tumor formation and metastasis of cancer cells<sup>8</sup>. *TrkB* is frequently overexpressed in a variety of human malignant tumors, ranging from neuroblastoma to pancreatic carcinoma. The signaling pathway mediated by *TrkB* is closely associated with more aggressive tumor behavior, resistance to chemotherapy, and poor prognosis<sup>10</sup>. Yu *et al.*<sup>10</sup> reported that *TrkB* was overexpressed in epithelial ovarian cancer and mediated anoikis suppression through the PI3K/AKT pathway, which was correlated with metastasis and chemotherapy resistance in ovarian cancer. In the present study, immunohistochemistry was used to assess the expression of *TrkB* in primary and metastatic lesions of ovarian serous adenocarcinomas and investigate the correlation between *TrkB* expression and LVD in metastasis of ovarian serous adenocarcinoma.

## Materials and methods

### Samples

One hundred thirty-nine routine formalin-fixed, paraffin-embedded samples of primary ovarian serous adenocarcinomas ( $n = 103$ ) and serous adenomas ( $n = 36$ ) were obtained from the archives of the Shaoxing People's Hospital and the Shaoxing Maternity & Child Health Hospital, with consent and ethical approval for the proposed research project. The average ages of both groups of patients at diagnosis were 48 years (range, 36-69 years) and 51 years (range, 36-75 years), respectively. Fifty-seven patients presented with peritoneal metastasis (including infiltration of the greater omentum and intestinal surface), 26 with pelvic cavity metastasis (including formation of a metastatic tubercle, infiltration of the uterine wall and/or contralateral ovaries), and 8 with lymph node metastasis. The paraffin-embedded tissue blocks from these patients dated back to the period from January 1999 to June 2008. All patients had primary tumors and none had received radiotherapy or

chemotherapy before surgery. Fifteen patients had low-grade tumors (grade 1), 25 had intermediate-grade tumors (grade 2), and 63 had high-grade tumors (grade 3); 33 had stage I disease, 13 had stage II disease, and 57 had stage III disease according to the International Federation of Gynecology and Obstetrics classification (FIGO 1988). The 36 women with serous adenomas were included in the study as normal controls. At least 2 pathologists independently made each diagnosis.

### Immunohistochemistry

For the detection of *TrkB* protein, immunohistochemistry was performed using the Envision™ Detection Kit (GK500705; Gene Company Ltd, Shanghai, China). The sections were dewaxed in xylene, rehydrated in graded alcohol, and rinsed in phosphate buffered solution (PBS; pH 7.2). Antigen retrieval was performed by heating the sections at 98 °C with 10 mM sodium citrate buffer (pH 6.0) for 5 minutes. The slides were cooled to room temperature, washed in PBS, and subjected to immunostaining. They were incubated with a primary polyclonal antibody for *TrkB* (sc-8316, diluted 1:500; Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA) and a primary polyclonal antibody for VEGFR-3 (sc-321, diluted 1:300; Santa Cruz Biotechnology, Inc.) in a humidified chamber at 4 °C overnight and then with EnVision™ Detection Kit at 37 °C for 30 minutes. Careful rinses were performed with 3 washes in PBS between each stage of the procedure. The sections were incubated with the ChemMate™ DAB+ Chromogen, lightly counterstained with hematoxylin (Dako, Glostrup, Denmark) for 40 seconds, exhaustively rewashed with tap water, air-dried, and mounted with mounting medium. Positive controls consisting of known prostate carcinoma sections and negative controls for every experiment were performed by replacing the primary antibodies with PBS. Immunohistochemical staining results were evaluated using a blind method.

### Staining assessment

The expression of *TrkB* was based on the presence of cytoplasmic and/or membranous staining. To evaluate *TrkB* immunostaining, we adopted a semiquantitative approach according to a previous report<sup>11</sup>, i.e., calculating the average percentage of positively stained cells out of all ovarian epithelial cells and the average staining intensity in multiple microscope fields. Positive staining was defined as immunostaining localized in the expected cellular compartments without background immunomechanical signals. The staining intensity was scored as follows: 0 (none of the cells stained positively); 1 (weak staining intensity); 2 (moderate); and 3 (strong or cytomembranous staining). The total staining was scored by multiplying the percentage of positive cells by the intensity score, resulting in a scale of 0-300. Evaluation of *TrkB* was performed according to a final staining

score, as follows: negative (0~20); weak (21~80); moderate (81~160); and strong (161~300). Staining assessment of lymph vessel density (LVD) was performed according to the procedure described by Weidner<sup>12</sup>. The 5 most vascularized areas detected by VEGFR-3 were first selected (so-called hot spots) in a 40× light microscopy field. The lymph vessels were counted in each of these areas under 400× light microscopy. Single endothelial cells or clusters of endothelial cells with a lumen were considered to be individual lymph vessels. The mean value of five 400× light microscopy fields (0.30 mm<sup>2</sup>) was recorded as the LVD of the section.

### Statistical analysis

All analyses were performed using SPSS (version 11.0; SPSS Inc., USA). The statistical significance of the relationship between the detection of TrkB and cell differentiation in ovarian serous adenocarcinoma was evaluated with a chi-square test. The correlation between TrkB expression and surgicopathological stage was analyzed with an independent-sample *t*-test and 1-way ANOVA. TrkB expression in primary and different metastatic lesions was compared using a paired-samples *t*-test. The correlation between the expression of TrkB and LVD was analyzed by linear correlation. *P* < 0.05 was considered statistically significant.

## Results

### Expression of TrkB in ovarian tumors

Using immunohistochemistry, we found the expression of TrkB to be localized to the cytoplasm and membrane of ovarian tumor cells. Cells with positive staining of TrkB were mostly arranged in foci or clusters (Figure 1A). In addition, evaluation of immunostaining in primary lesions gave the following results: 3 negative cases, 45 weak-positive cases, 40 moderate-positive cases, and 15 strong-positive cases. The total positive rate was 54.37% according to the standard that a final staining score exceeding 80 was considered positive. However, none of the serous adenomas displayed any TrkB expression (Figure 1B). TrkB was upregulated in serous adenocarcinomas compared with serous adenomas. There was no significant difference of TrkB expression in tumor cells of different histological grade (Table 1).

### Expression of TrkB in primary and metastatic lesions in ovarian serous adenocarcinomas at different stages

TrkB staining in the cytoplasm was extensively observed in serous adenocarcinomas, whereas membrane staining was more frequently present in cancers with moderate/poor differentiation, as well as in infiltrative and metastatic lesions. In addition, cancer cells with strong staining that presented in foci or clusters were mainly distributed around cancer nests, metastatic le-

sions in vessels, and other metastatic lesions (Figure 2A and B).

Figure 3 shows the expression of TrkB in primary and metastatic lesions at different surgicopathological stages. One-way ANOVA indicated that the level of TrkB expression in primary lesions of serous adenocarcinomas was associated with surgicopathological stage (*P* = 0.014). Moreover, the level of expression of TrkB in stage II and III disease was significantly higher than in stage I (*P* = 0.021 and *P* = 0.010, respectively). However, there was no significant difference in TrkB expression between stages II and III (*P* = 0.479). In stage III disease, TrkB expression levels in metastatic lesions of the pelvic and peritoneal cavity were clearly higher than in primary lesions (*P* = 0.039 and *P* = 0.006, respectively) (Figure 4A and B). Nevertheless, compared with primary lesions in stage II disease, expression of TrkB in metastatic lesions of the pelvic cavity was low (*P* = 0.513). In stage III, there were 8 cases with lymph node metastases and a high TrkB level was detected in the metastatic as well as the corresponding primary lesions (*P* = 0.005).

### Correlation between positive VEGFR-3, LVD and expression of TrkB

VEGFR-3 was often detected in endothelial cells of lymph vessels in the periphery of the tumor. The wall of the lymph vessels was thin, with an irregular lumen, and devoid of erythrocytes. Table 2 shows that LVD in primary ovarian serous adenocarcinomas with strong expression of TrkB was significantly higher than in those with weak or moderate expression. There was a significant correlation between TrkB expression and LVD (*r* = 0.767, *P* < 0.001).

## Discussion

Ovarian cancer is one of the tumors with the highest mortality among gynecological malignancies. The recovery rate has improved little and the 5-year survival rate has remained approximately 30% over the past decades<sup>13,14</sup>. Rapid metastasis and recurrence are important factors leading to treatment failure or death. Numerous complicated events are involved in tumor metastasis, including invasion of the surrounding tissue and penetration of the lymphatics or the vasculature by tumor cells, facilitating secondary tumor formation at distant sites<sup>15</sup>. Anoikis suppression is thought to be the prerequisite for metastatic tumor cells surviving in the vasculature<sup>16</sup>. TrkB is a neurotrophic factor receptor protein that can specifically suppress anoikis<sup>8</sup>. Overexpression of TrkB is frequently detected in human malignant tumors, particularly those with aggressive behavior and a poor prognosis including neuroblastomas<sup>17</sup>, pancreatic carcinomas<sup>18</sup>, lung cancer<sup>19</sup>, prostate carcinomas<sup>20</sup>, and multiple myelomas<sup>21</sup>.

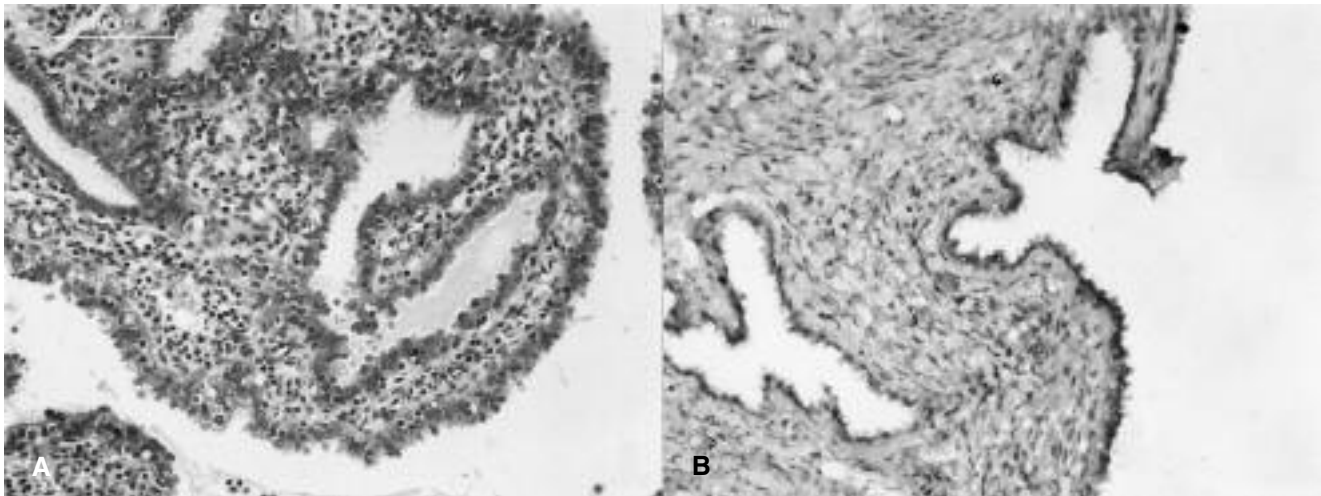


Figure 1 - Immunohistochemical staining for TrkB in ovarian tumors. A) Positive staining of TrkB in ovarian serous adenocarcinoma (x200). B) Negative staining of TrkB in ovarian serous adenoma (x200).

**Table 1 - Expression of TrkB in ovarian adenocarcinoma**

Category	Positive cases	Negative cases	$\chi^2$	P value
G1	5 (33.33%)	10 (66.67%)	4.017	0.134
G2	13 (48.15%)	14 (51.85%)		
G3	37 (60.66%)	24 (39.34%)		

Recently, Yu *et al.*<sup>10</sup> and Au *et al.*<sup>22</sup> confirmed that suppression of anoikis mediated by TrkB was associated with metastasis in ovarian cancer. Overexpression of TrkB was detected in invasive ovarian cancers, especially in metastatic lesions, high-grade serous papillary cystadenocarcinomas, and anoikis-surviving ovarian cancer cells. However, none of the benign epithelial ovarian

tumors and normal ovarian epithelial tissues displayed any TrkB immunostaining. Consistent with their reports, the current study revealed that TrkB expression was common in serous adenocarcinomas but absent in serous adenomas. Moreover, TrkB expression was stronger in higher stages of cancer than in lower stages. These findings suggest that overexpression of TrkB is associated with metastasis and dysregulated TrkB expression is important in early ovarian carcinogenesis.

It has been reported that escape from anoikis is the ultimate characteristic of tumor cells<sup>3,16,23,24</sup>. Anoikis suppression is directly correlated with tumor metastasis and it often occurs at the onset of metastasis. TrkB-induced anoikis resistance and tumorigenesis are consequences of TrkB kinase signaling activity<sup>25</sup>. Cancer cells with the ability of anoikis suppression have a more in-

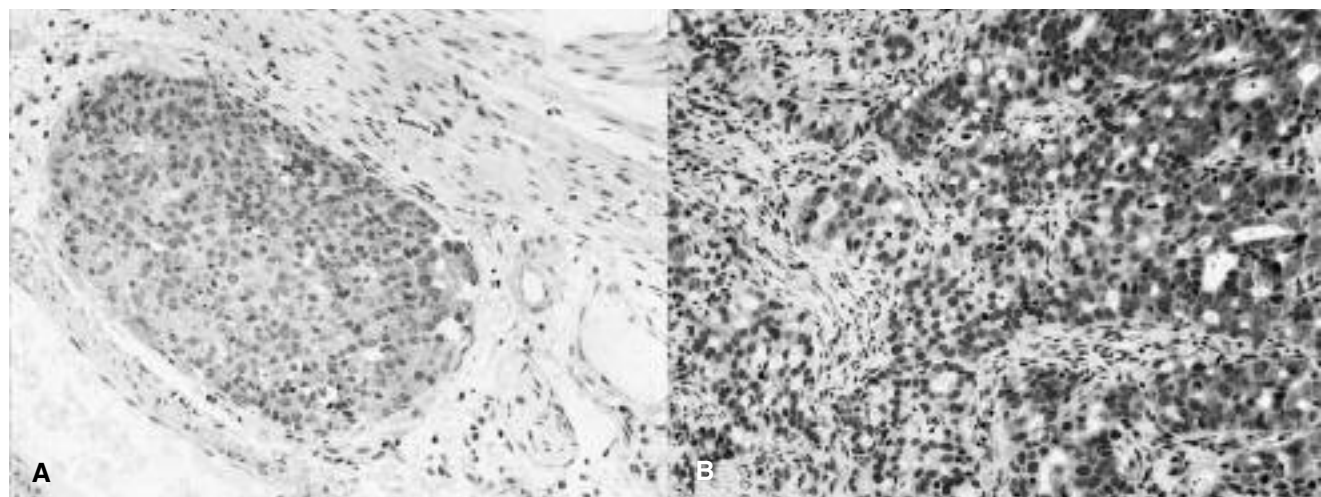


Figure 2 - Immunohistochemical staining for TrkB in metastatic lesion of ovarian serous adenocarcinoma. A) TrkB-positive staining in infiltrative lesion of the uterine wall (x200). B) Overexpression of TrkB in metastatic foci in peritoneal cavity (x200).

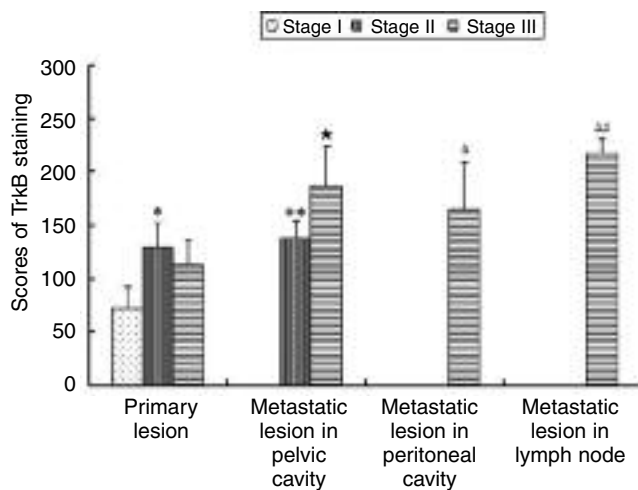


Figure 3 - Expression of TrkB in primary and metastatic lesions with different surgicopathological stages of ovarian serous adenocarcinoma. Data are expressed as mean  $\pm$  SD. \* $P < 0.05$  versus primary lesion in each stage; \*\* $P > 0.05$  versus primary and metastatic lesion in pelvic cavity;  $P < 0.05$  versus primary and metastatic lesion in pelvic cavity; # $P < 0.01$  versus primary and metastatic lesion in peritoneal cavity. ## $P < 0.01$  versus primary and metastatic lesion in lymph nodes.

vasive phenotype and metastasize easily. TrkB kinase activity was sufficient for tumorigenesis and an experimental model suggested that kinase-activating TrkB mutations could endow TrkB with oncogenic properties<sup>25</sup>. This study confirmed that foci or clusters of cancer cells with strong staining were distributed around cancer nests, metastatic lesions in vessels, and other metastatic lesions. TrkB expression was clearly higher in infiltrative metastatic lesions than in the corresponding primary lesions. Moreover, TrkB expression of primary lesions in cases with metastasis was significantly higher

than in primary lesions with no metastasis. This demonstrated that there was a TrkB-expressed cell clone in the process of cancer growth and proliferation. Cancer cells that acquire the ability of anoikis suppression present as highly invasive and metastatic, indicating that metastasis and infiltration of serous adenocarcinomas are associated with TrkB overexpression. Therefore, overexpression of TrkB possibly promotes the progression of serous adenocarcinoma.

Regional lymph node involvement is one of the early adverse events in ovarian cancer. In a mouse experiment *in vivo*, TrkB-expressing cancer cells could rapidly form growing tumors that infiltrated lymph vessels and regional lymph nodes to colonize distant organs<sup>8</sup>. A previous study showed that TrkB expression was correlated with lymphangiogenesis in colon cancer. Patients with higher TrkB expression had higher LVD and a significant metastatic phenotype<sup>26</sup>. In the present study, we found that overexpression of TrkB was closely associated with LVD. This suggests that TrkB probably facilitates metastasis of ovarian cancer by associated lymphangiogenesis.

Investigations in a series of carcinomas indicated that tumors with high expression of TrkB are usually associated with an unfavorable prognosis<sup>22,27</sup>. Due to the lack of follow-up data, we cannot perform a prognosis analysis. Meanwhile, the specificity of VEGFR-3 in labeling lymph vessels is not perfect, and this is a limitation of the present study. In addition, elucidation of the concrete mechanism of lymphangiogenesis associated with TrkB is pending. So we will further investigate the regulatory pathway of TrkB participation in invasion and metastasis, as well as the survival of patients with serous adenocarcinomas. Recently, tyrosine kinase receptor inhibitors have been applied in phase I clinical trials<sup>28,29</sup>.

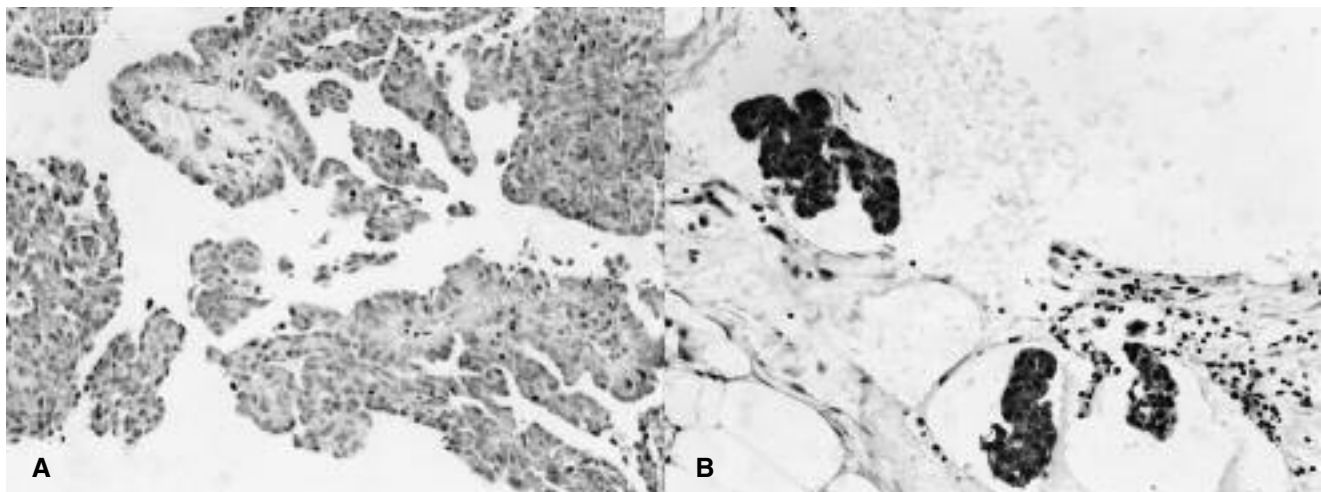


Figure 4 - Immunohistochemical staining for TrkB in primary lesion of ovarian serous adenocarcinoma and corresponding metastatic lesion in greater omentum. A) Weak expression of TrkB in primary lesion ( $\times 200$ ). B) Strong staining of TrkB in metastatic lesion in greater omentum ( $\times 200$ ).

**Table 2 - Correlation between expression of TrkB and LVD**

Expression of TrkB	LVD (mean $\pm$ SD)	<i>r</i>	<i>P</i> value
Weak positive	6.30 $\pm$ 0.99	0.767	<i>P</i> <0.001
Moderate positive	6.48 $\pm$ 0.78		
Strong positive	10.01 $\pm$ 1.57		

These trials appear to show a response in certain patients with tumors, although some problems need to be solved. Fortunately, phase II clinical trials are currently under way that may produce satisfactory results regarding the suitability of tyrosine kinase receptors as a therapeutic target in cancer. Patients with serous adenocarcinomas will greatly benefit from this approach.

## Conclusions

In conclusion, our study demonstrated overexpression of TrkB in serous adenocarcinoma, which suggested that TrkB might play a critical role in inducing serous adenocarcinoma tumorigenesis. We also found that increased expression of TrkB was correlated with higher metastatic ability, possibly by lymphangiogenesis. Taken together, TrkB could be a marker for predicting invasion and metastasis of serous adenocarcinoma and a new valuable target for anticancer therapy.

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