ONCOLOGY

Prostaglandins E in Primary Tumor, Metastases, and Ascitic Fluid of Patients with Ovarian Cancer

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The content of prostaglandins E (PGE) is compared in primary tumors, metastases, and ascitic fluid of patients with ovarian cancer, in benign tumors, and in neoplastic ovarian disorders. The PGE content in malignant tumors, neoplastic disorders, and benign tumors is higher than in normal tissues. A relationship between the PGE content, on the one hand, and the degree of differentiation and histological variant of malignant tumor, on the other, is revealed. The PGE content in the ascitic fluid of patients increases with the degree of tumor malignancy. The variants of ovarian cancer therapy with preparations modifying the arachidonic acid metabolism are considered.

Key Words: *ovarian cancer; prostaglandins*

Ovarian neoplasms are a widespread disorder of female reproductive system [6]. The pathogenesis of this disease has been extensively studied. The role of polypeptide growth factors, oncogenes, and steroid hormone receptors in the mechanisms underlying the growth and metastasizing of ovarian tumors and their significance for effective diagnostics and therapy of the disease have been evaluated [4,6]. Prostaglandins are known to participate in the initiation and promotion of carcinogenesis [1-3]. However, the mechanisms by which they are involved in the development of ovarian cancer remain obscure. The understanding of at least some components of these mechanisms may be helpful in the search and substantiation of new methods of pathogenic therapy and prevention of relapses and metastases of ovarian cancer.

Our goal was to analyze the content of prostaglandins E (PGE) in primary tumors, metastases, and ascitic fluid (AF) of patients with ovarian cancer in relation to the major clinical and morphological characteristics of the disease: age of the patient, stage of the disease development, degree of tumor malignancy and differentiation of tumor cells, and histological variant of the tumor.

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MATERIALS AND METHODS

One hundred and twenty-eight females aged 32-76 years were enrolled in the study; 89 of them had ovarian cancer. According to the FIGO classification, stage Ia tumor was diagnosed in 8 patients, stage Ic in 4 patients, stage IIc in 10 patients, stage III in 38 patients, and stage IV in 18 patients. Seventy-eight patients did not receive neoadjuvant therapy. All the patients were operated. Histological examination revealed the following variants of ovarian adenocarcinoma: serous in 58 patients, mucinous in 9 patients, endometrioid in 6 patients, and clear cell in five patients. Twenty-eight percent of the patients had highly differentiated, 28% patients had moderately differentiated, and 44% patients had poorly dif-

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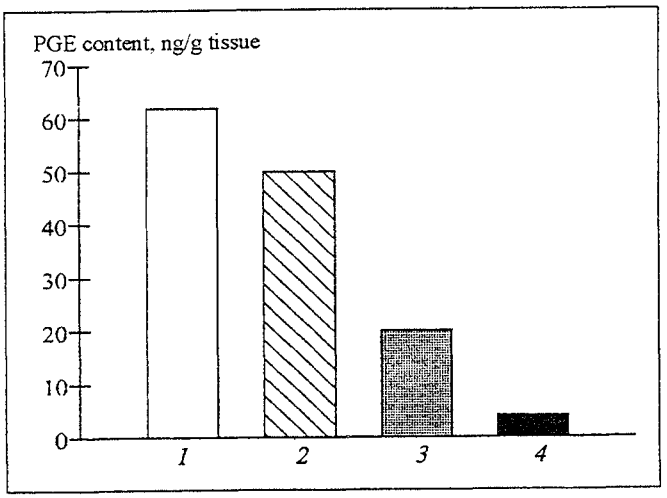

Fig. 1. Prostaglandin E content in malignant and benign ovarian neoplasms (*1*), neoplastic disorders (*2*), benign tumors (*3*), and uninvolved tissues (*4*).

ferentiated adenocarcinoma. The degree of malignancy was determined by the method [5] in modification for epithelial ovarian tumors [8]. The first degree malignancy was revealed in 5 patients, the second in 22 patients, the third in 33 patients, and the fourth in 16 patients. Eleven patients received neoadjuvant chemotherapy: two courses of platidiam in combination with cyclophosphane (4 patients) or two standard CMF courses (7 patients). The study also included 19 patients with neoplastic ovarian disorders: corpus luteum cyst (6 patients), simple cyst (4 patients), follicular cyst (4 patients), and endometrioid cyst (5 patients), 11 patients with benign ovarian tumors: mature teratoma (5 patients) and serous cystadenofibroma (6 patients), and 9 patients with uterine myoma after extirpation of the uterus and adnexa (PGE levels were determined in the ovaries).

The PGE content was measured by the radioimmunological assay (Clinical Assays kits) in AF and in homogenates of the primary tumor and metastases into the greater omentum. Prostaglandins were extracted with ethyl acetate in an acid medium [7].

The results obtained were analyzed with statistical software for medical research. The significance of differences was evaluated using the Student's *t* test.

RESULTS

The results of comparison of the PGE content in the primary tumor, neoplastic disorders, benign tumors, and normal ovaries are shown in Fig. 1. The mean PGE content in the primary tumor did not differ significantly from that in neoplastic disorders; however, it was significantly ($p<0.05$) higher compared with that in benign tumors and uninvolved ovarian tissue. The PGE content was he lowest in uninvolved ovarian tissue (between palpable follicles). Thus, PGE production increases in tumorigenesis.

The PGE content in the primary tumor was higher than in metastases and AF. There were no significant differences between PGE contents in primary tumor and metastases into the ovaries and greater omentum at stages III and IV of the disease. The differences in the PGE content of AF were statistically significant ($p<0.05$) only at stage Ic (1.7±

TABLE 1. Prostaglandin E (PGE) Content in Primary Tumor, Metastases, and Ascitic Fluid in Relation to the Degree of Tumor Malignancy

Degree of malignancy	Mean PGE content, ng/g (ml) tissue (fluid)		
	ovarian tumor	metastases in the greater omentum	ascitic fluid
I	43.9±4.9	31.0±3.4	1.6±0.7
II	70.6±8.6	40.6±4.6	1.8±0.9
III	61.6±3.6	34.7±3.9	2.0±0.3
IV	61.1±4.7	40.3±5.2	5.3±0.6

TABLE 2. Prostaglandin E (PGE) Content in Primary Tumor, Metastases, and Ascitic Fluid in Relation to the Degree of Tumor Differentiation

Degree of differentiation	Mean PGE content, ng/g (ml) tissue (fluid)		
	ovarian tumor	metastases in the greater omentum	ascitic fluid
High	56.8±4.6	42.9±5.3	1.8±0.3
Moderate	61.3±4.6	36.2±4.4	1.8±0.2
Poor	75.5±7.1	31.8±3.3	1.9±0.4

TABLE 3. Prostaglandin E (PGE) Content in Primary Tumor, Metastases, and Ascitic Fluid in Relation to Histological Variant of Tumor

Histological variant of ovarian adenocarcinoma	No. of patients	Mean PGE content, ng/g (ml) tissue (fluid)		
		ovarian tumor	metastases in the greater omentum	ascitic fluid
Clear cell	5	49.7±3.7	30.6±2.5	2.6±0.1
Serous	58	63.5±5.6*	38.0±4.6	1.7±0.4
Endometrioid	6	68.2±5.1*	38.3±4.2	1.8±0.3
Mucinous	9	76.7±3.8*	46.6±4.1*	2.3±0.4

Note. *$p<0.05$ compared with clear cell adenocarcinoma.

TABLE 4. Prostaglandin E (PGE) Content in Primary Tumor, Metastases, and Ascitic Fluid After Various Schemes of Neoadjuvant Therapy

Scheme of therapy	No. of patients	Mean PGE content, ng/g (ml) tissue (fluid)		
		ovarian tumor	metastases in the greater omentum	ascitic fluid
Platidiam+cyclophosphane	4	42.4±3.7	33.2±4.3	0.4±0.03
CMF	7	54.9±4.7	31.4±3.6	2.5±0.04*
Untreated	78	63.7±4.8*	37.9±4.6	2.0±0.40*

Note. *$p<0.05$ compared with platidiam+cyclophosphane.

0.4 ng/ml) and stage IV (3.7±0.3 ng/ml). As the disease progressed, PGE content increased in AF and decreased in primary tumor. A tendency toward a positive correlation ($r=0.08$, $p<0.05$, $n=9$) between PGE contents in primary tumor and the greater omentum metastases was observed at stage IV of the disease.

Table 1 shows PGE contents in primary tumor, metastases, and AF in relation to the degree of cancer malignancy.

In highly malignant tumors (I degree), the PGE content of primary tumor was 43.9±4.9 ng/g tissue, being significantly lower ($p<0.05$) compared with that in tumors of the II, III, and IV degree of malignancy. The PGE content in metastases into the greater omentum was the highest at II and IV degree of malignancy. A tendency toward an increase in the PGE content of AF was observed in highly malignant tumors. The PGE content in the IV degree tumors was significantly higher than in the I and III degree tumors. The highest PGE content was recorded in IV degree tumors. A positive correlation was established between the PGE levels in the primary tumor, AF, and metastases into the greater omentum at the I degree of tumor malignancy and analogous parameters at the IV degree of malignancy ($r=0.6$; $p<0.05$; $n=7$).

In 39 patients, the PGE content was analyzed in relation to the degree of tumor differentiation (Table 2). In highly differentiated tumors, this parameter varied in a wide range: from 12.9 to 121.4 ng/g tissue (56.8±4.6 ng/g tissue), being significantly lower ($p<0.05$) than in poorly differentiated tumors (75.5±7.1 ng/g tissue). The PGE content in moderately differentiated tumors did not differ significantly from that in highly and poorly differentiated tumors. A tendency toward a positive correlation was observed between the PGE content of the greater omentum metastases and the degree of tumor differentiation. There was no relationship between the PGE content in AF and the degree of tumor differentiation. A positive correlation was established between PGE contents of highly and poorly differentiated primary tumors, between the tumor and AF PGE contents and degree of differentiation, and PGE content in AF and the greater omentum metastases in highly differentiated primary tumor.

Clear cell adenocarcinoma had the lowest content of PGE (49.7±3.7 ng/g tissue). It was significantly different from that in serous, mucinous, and endometrioid tumors (Table 3). The PGE content was the highest in mucinous adenocarcinoma (76.7± 3.8 ng/g tissue) and reached the maximum in the mucinous adenocarcinoma metastases into the greater omentum, being significantly different only from that in the clear cell adenocarcinoma metastases. No relationship was revealed between histological variant of primary tumor and PGE content in AF. A positive correlation was observed between PGE contents in serous adenocarcinoma and in its metastases.

We have evaluated the effect of chemotherapy on the PGE content in primary tumor, metastases,

and AF of patients with ovarian cancer. Special attention should be paid to the PGE content in primary tumor and AF of patients treated with platidiam and cyclophosphane: it was lower than that in untreated patients. Neoadjuvant chemotherapy had no appreciable effect on the PGE levels in the ovarian cancer metastases. The PGE contents in primary tumor, AF, and metastases of patients after the CMF therapy did not differ significantly from those in untreated patients.

Thus, the PGE content in malignant tumors, neoplastic disorders, and benign tumors is higher than in uninvolved ovarian tissues.

The PGE content in malignant ovarian neoplasms does not depend on the stage of the disease.

The PGE content in the primary ovarian tumor correlates with the degree of differentiation and histological variant of the tumor.

The PGE concentration in the ascitic fluid is higher in patients with highly malignant tumors.

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