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MODELS OF OVARIAN TUMORS IN RATS

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Tumors of the ovary occupy a leading place among neoplasms in women. Because of the difficulty of early diagnosis, malignant ovarian tumors are found only in the late stage of development, and the results of treatment are still unsatisfactory. The solution of this problem may perhaps be linked to a certain extent with the elucidation of the pathogenesis of this neoplasm. The pathogenesis of ovarian tumors is a complex process which is under the influence of various neuroendocrine disturbances. The study of some of these aspects is possible only on experimental models. Various transplantable strains, corresponding to clinical cases only in their morphology, are widely used as models of malignant neoplasms in experimental oncology. Investigations on human tumors, transplanted into athymic animals, do not always help to shed light on whether disturbances of the endocrine system are the cause or effect of the development of ovarian neoplasms. The most suitable experimental model with which to study the role of neuroendocrine changes in the development of ovarian neoplasms is induced tumors. Various methods of obtaining ovarian tumors in rats have been described in the literature [3, 7].

The aim of this investigation was to compare experimental ovarian neoplasms induced in rats by different procedures.

EXPERIMENTAL METHOD

Experiments were carried out on 486 noninbred female rats reared at the All-Union Oncologic Scientific Center, Academy of Medical Sciences of the USSR. The distribution of the animals by groups is shown in Table 1. In group 1, a fragment of ovary was autografted beneath the capsule of the spleen in castrated rats aged 1.5 months. Rats of group 2 underwent subtotal castration at the age of 2 months, and rats of group 3 were irradiated with x-rays (200 R) in the lumbar region. The rats of group 4, aged 16-20 days, received a single intraperitoneal injection of nitrosoethylurea (NEU) in a dose of 30 mg/kg, whereas the rats of group 5 received NEU in a dose of 10 mg/kg by the transplacental route on the 21st day of embryogenesis. The animals of group 6, at the age of 2 months received a subcutaneous injection of 1,2-dimethylhydrazine (DMH) in a dose of 2 mg/kg. Rats of group 7 received testosterone propionate in a dose of 1 mg on the last 3 days of embryogenesis. Experimental groups 1, 6, and 7 had their own controls; common controls were provided for groups 2 and 3 and for groups 4 and 5. The animals were regularly inspected and rats in a poor condition were killed with ether. All the animals were autopsied, and the ovaries of the experimental and control

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TABLE 1. Ovarian Tumors Induced in Rats by Various Methods

Procedure	No. of rats	Frequency of tumor development		Histological structure of tumors									Time of appearance of first tumor, months
		Absolute	%	granuloso-theco-luteoma	granuloso-thecoma	theco luteoma	granulosa-cell	theco-cell	luteoma	androblastoma	fibrosarcoma	sarcoma	
Orthotransplantation of ovary beneath splenic capsule	132	101	76,5	26	—	6	45	2	22	—	—	—	6
Control	24	0											
Subtotal castration	25	5 (1)	20,0	—	2	—	2	—	—	—	—	—	11,5
X-ray irradiation	38	11 (2)	28,9	—	3	2	4	—	—	—	2	—	15,0
Control	18	0											
NEU	59	10 (2)	16,9*	—	1	—	1	—	2	4	—	2	14,0
Postnatally	29	0											
Transplacentally													
Control	31	1	3,2*				1						16,0
DMH	43	6	14,2	—	—	2	3	—	—	1	—	—	11,0
Control	21	0											
Testosterone propionate	36	7 (1)	16,8	—	1	1	1 (1)	3	—	1	—	—	12,5
Control	30	0											

Legend. Number of malignant ovarian tumors shown between parentheses. *) Compared with corresponding control.

groups of rats were treated by the usual histological methods and examined under the microscope. The frequency of tumors was calculated in rats which survived until the appearance of the first ovarian tumor. The experimental results were subjected to statistical analysis by Student's test.

EXPERIMENTAL RESULTS

The results of induction of ovarian tumors showed that only one of the 124 rats in the control groups developed a granulosa-cell tumor of the ovary (Table 1). This is in agreement with data in the literature showing that rats develop spontaneous ovarian tumors very rarely [7]. Their frequency in animals reared at the All-Union Oncologic Scientific Center, Academy of Medical Sciences of the USSR, does not exceed 1%, and these are mainly granulosa-cell tumors or tumors of mixed type [2]. If the hormonal balance was upset, by autografting of a fragment of ovary into castrated noninbred rats, the frequency of ovarian neoplasms was the highest observed (76.5%), and the time of appearance of the first tumor (6 months) was shorter than with all the other methods of induction (Table 1). In the case of primary depression of ovarian function (after subtotal castration for x-ray irradiation) tumors appeared in 20 and 28.9% of cases respectively. Under the influence of the androgen the frequency of ovarian neoplasms reached 16.8%, compared with 14.2 and 16.9%, respectively, after postnatal administration of carcinogens (DMH and NEU). After transplacental exposure to NEU no ovarian tumors developed in any of the animals. There were no special differences in the histological structure of tumors induced by different methods. They were mainly granulosa-cell and mixed types of tumors (granuloso-theco-luteomas, granuloso-thecomas, theco-luteomas). Androblastomas appeared after injection of carcinogens or androgens, whereas thecomas and luteomas developed after autografting of fragments of ovary beneath the capsule of the spleen, and in response to the androgen and NEU. One malignant granulosa-cell tumor developed in a rat which had received the androgen, three fibrosarcomas occurred in animals after x-ray irradiation and subtotal castration, and two ovarian sarcomas were induced by NEU administered postnatally.

When inducing ovarian tumors we attempted to create experimental conditions that would correspond to those pertaining during the development of this neoplasm in women. For this purpose we used methods aimed at depressing ovarian function, which is often observed in women. The possibility of development of ovarian tumors under the influence of carcinogens was investigated, as one external environmental factor, and although there are reports in the literature only of single cases of ovarian neoplasms appearing in rats under the influence of carcinogens [5, 7], we did observe that ovarian tumors developed in 14.2 and 16.8% of cases (after DMH and NEU respectively). The method of transplacental injection of testosterone

propionate corresponds to the clinical use of testosterone analogs, namely progestins, with a view to preventing threatened abortion. The results obtained in this group of experiments are in agreement with data in the literature [8] on the development of ovarian tumors in Long–Evans rats, treated with an oily solution of testosterone on the first day after birth. In our view, the most appropriate models of ovarian neoplasms are tumors arising in an ovarian transplant in castrated rats following hyperstimulation with gonadotropic hormones, the level of which rises as a result of failure of the feedback mechanism between sex and gonadotropic hormones [5, 6]. These data on a possible etiologic role of gonadotropins are in agreement with clinical observations [4]. The high frequency and relatively short period of development of tumors induced by these methods will be noted. A model of ovarian tumors arising as a result of disturbance of the hormonal balance is used in experimental oncology to study the role of various factors, including age [1], and there is every reason to suppose that this model is suitable for the study of the role of neuroendocrine disturbances in the etiology and pathogenesis of ovarian tumors, and also to reveal the molecular–endocrine mechanisms in the development of neoplastic changes in the ovaries.

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