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Contrasting Actions of Estradiol on the Growth of Human Gastric Cancer Xenografts in Nude Mice

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The effects of estradiol on the growth of six human gastric xenografts in nude mice were studied and diverse effects were found, including one case of stimulation, two of inhibition and three of unchanged condition. Neither the histological features of the original tumor nor the estrogen-binding capacity seemed to be related to the response to estradiol. It is concluded that the growth of human gastric cancer can be modulated by estradiol.

Key words: Estradiol — Gastric cancer — Growth

Increasing numbers of reports on gastric cancer showing positive binding activity for estradiol have been published.[1-3] Although gastric cancer has been shown to be estrogen receptor (ER)-positive in 20%–30% of cases, it is still open to question whether positive estradiol binding capacity in gastric cancer is metabolically active.

Clinical trials with the antiestrogen agent tamoxifen for the treatment of gastric cancer have recently been conducted by several researchers in Japan[4,5] as well as in the UK.[6] But the results obtained are controversial. Therefore, we designed an experiment to examine the effect of estrogen on the growth of human gastric cancer xenografts in nude mice.

Six human gastric cancer xenografts established in our laboratory were used for this experiment. Histologically, 3 xenografts were intestinal type and 3 were diffuse type of gastric cancer according to the classification of Laurén.[7] These phenotypes and growth rates of cancer have been stable for the past 4 years.[8] Eight nude mice each were implanted with the six gastric cancer xenografts into the flank and 4 nude mice were given estradiol in the treatment group or saline in the control group. Two micrograms of 17β-estradiol benzoate (Teikoku Hormone Mfg. Co. Ltd., Tokyo) suspension was injected sc into the treatment group twice a week after tumor inoculation. The implantation sites were carefully inspected and measured twice a week. Relative tumor volume (mm^3) was calculated as $1/2ab^2$ (a, long diameter; b, short diameter).

The tumor growth curves of one of the xenografts (NMS11) treated with estradiol are shown in Fig. 1a. The growth was significantly stimulated by estradiol in the third and fourth weeks after transplantation ($P<0.05$), showing estrogen-dependent growth. The growth curves of another xenograft in nude mice (NMS13) are shown in Fig. 1b, the growth being significantly inhibited by estradiol from 3 weeks after transplantation ($P<0.01$). Details of the xenografts and their hormone sensitivities are summarized in Table I. It was found that the tumor growth was stimulated in 1 of 6 xenografts, inhibited in 2 and not influenced in 3. There seemed to be no correlation between the estradiol-binding capacity of a tumor and its response to estradiol. These results indicate that the growth of human gastric cancer xenografts in nude mice can be modulated by estrogen.

The responses of tumor cells derived from a non-target organ to estrogen and antiestrogen remain controversial. Estrogen was reported to stimulate the growth of a tumor cell line derived from human medullary thyroid carcinoma,[9] whereas the antiestrogen agent tamoxifen produced inhibition. The growth of hamster melanoma cells showing specific binding for estrogen was inhibited not only by estrogen but also by tamoxifen.[10] Tumor remission was induced by administration of the sex steroid hormones, estradiol and progesterone, to nude mice with human colorectal cancer xenografts.[11] Experiments on gastric carcinogenesis in rats indicated that estradiol inhibited the growth of gastric cancer.[12] Variable effects of tamoxifen on the growth of gastric cancer cells *in vitro* have also been reported. The growth of the ER-positive human gastric cancer cell line established by Nohga was shown to be stimulated by estrogen and inhibited by tamoxifen.[13] Tamoxifen may thus have potent activity against this type of cancer cell. Recent studies have shown that the stimulation of gastric cancer cell growth by estrogen was not prevented by tamoxifen, and that a

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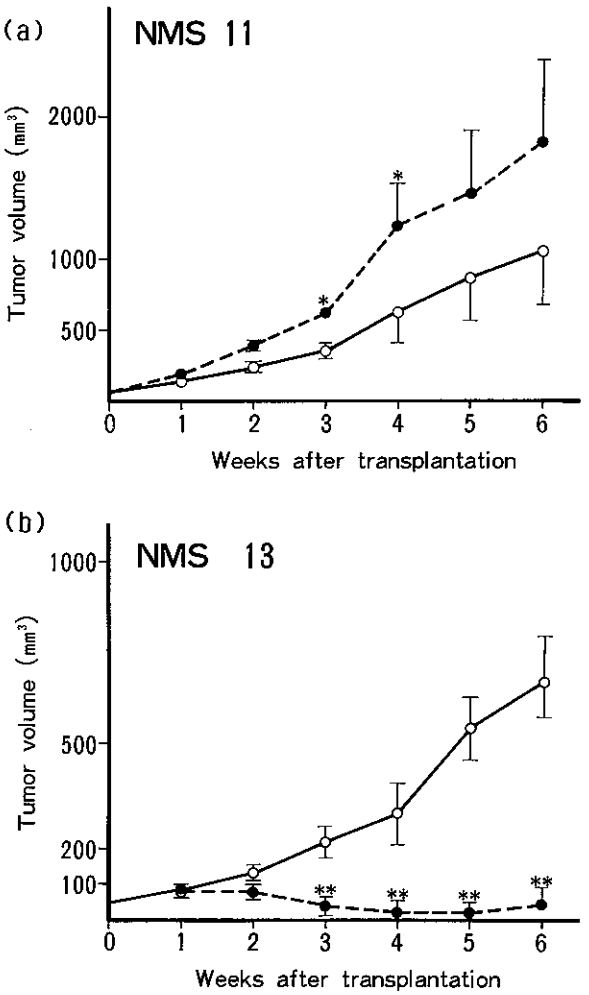

Fig. 1. Effect of estradiol on the growth of a human gastric cancer xenograft in nude mice. Estradiol was injected sc into male animals twice a week. (a) Significant increase of growth from the control (○) in the treatment group (●). Mean±SD (bar), n=4, * $P<0.05$ (b) Significant decrease from the control (○) in the treatment group (●). Mean±SD, n=4, ** $P<0.01$

Table I. Data on Six Human Gastric Cancer Xenografts in Nude Mice, Including Estrogen Status and Response to Estradiol

	Patient		Histological findings[a]	Xenograft	
	Age	Sex		ER[b]	Growth by estradiol[c]
NMS 2[d]	63	M	tub	+	Inhibition
6	68	M	tub	+	Unchanged
11	36	F	sig	−	Stimulation
12	61	F	por	−	Unchanged
13	71	M	por	−	Inhibition
24	73	M	tub	−	Unchanged

a) Microscopic classification according to "The General Rules for the Gastric Cancer Study in Surgery and Pathology."[15] tub, tubular adenocarcinoma; sig, signet-ring cell carcinoma; por, poorly differentiated adenocarcinoma.
b) ER, estrogen receptor, measured by the method of McGuire,[16] more than 5 fmol/mg protein is positive. +, positive; −, negative.
c) Growth of 4 estradiol-treated mice were compared with that of 4 control mice. Inhibition means significantly inhibited ($P<0.05$), stimulation means significantly stimulated ($P<0.05$) and unchanged means no significant difference between the 2 groups.
d) NMS; Serial number of transplantations of gastric cancer in our laboratory.

synergistic stimulatory effect was produced by a combination of estradiol and tamoxifen.[14] Tamoxifen may not be responsible for the cytocidal or cytostatic effect exerted on these gastric cancer cells. Thus, these conflicting reports indicate that estrogen can have either a stimulatory or inhibitory effect on gastric cancer cell growth.

The present findings emphasize the need for studies on hormonal modulation of gastric cancer growth. It is still open to question whether tamoxifen does, in fact, affect gastric cancer.

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