Effects of Sex Difference, Gonadectomy, and Estrogen on N-Methyl-N-nitrosourea Induced Rat Thyroid Tumors¹

Masahiro Mori, Masashi Naito, Hiromitsu Watanabe, Nobuo Takeichi, Kiyohiko Dohi, and Akihiro Ito²

Department of Cancer Research, Research Institute for Nuclear Medicine and Biology [M. M., M. N., H. W., A. I.] and the 2nd Department of Surgery at School of Medicine [N. T., K. D.], University of Hiroshima, Kasumi 1-2-3, Minami-ku, Hiroshima-734, Japan

ABSTRACT

The occurrence of thyroid tumors induced by N-methyl-N-nitrosourea (MNU) and low iodine diet in Long-Evans (LE) rats was studied with special reference to sex difference, effect of gonadectomy, and estradiol administration. Rats of experimental groups 1–6 were given i.v. injections of 40 mg of MNU/kg of body weight at 50 days of age and fed on low iodine diet from 28 days of age to the end of the experiment (30 weeks after MNU administration). They consisted of male, female, castrated male, ovariectomized female, and gonadectomized male and female rats given 2.5 mg estradiol pellets s.c. Rats of groups 7–10 served as the respective controls without MNU or low iodine diet. Levels of serum thyroid stimulating hormone and estrogen receptor of the thyroid lesions were also examined. It was noted that the incidence of thyroid carcinoma was higher in females than in males (P < 0.01) and did not change by castration in males but decreased in ovariectomized rats (P < 0.01). Administration of estradiol after gonadectomy significantly increased the incidence of thyroid carcinomas in castrated and ovariectomized rats. Increase of mean serum thyroid stimulating hormone levels and thyroid and pituitary weights was also predominant in females. Mean thyroid stimulating hormone levels of both sexes were decreased by gonadectomy. Mean thyroid and pituitary weights were inhibited from increasing not by castration but by ovariectomy. Estradiol supplemented after gonadectomy significantly increased all of these factors. Estrogen receptors were detected in transplanted thyroid tumors but not in euthyroid tissues.

The results suggest that estradiol promoted the thyroid tumorigenesis through activation of thyrotrophs in pituitary or direct interaction of estradiol and estrogen receptors in the thyroid.

INTRODUCTION

It has been well known that the incidence of thyroid cancer is higher in women than in men by ratios of 4:1 in Caucasians (1, 2) and 6:1 in Japanese (3). Nevertheless, thyroid cancers in young women are usually well differentiated and have a good prognosis. On the other hand, those in women over age 45 or in men sometimes transform to poorly differentiated or anaplastic types and take a poor and fatal prognosis (4–6). Concerning thyroid microcarcinomas such as latent or occult carcinomas, no significant difference has been reported in their occurrence between men and women (7, 8). In these studies, the incidence and biological activity of thyroid carcinomas appear to be related to both age and sex. These observations lead to the hypothesis that growth or progression of human thyroid carcinomas may be influenced by sex hormones.

In laboratory animals, there have been reports of sex differences on the occurrence of thyroid tumors induced mainly by irradiation or goitrogens (9–11). In these reports, male rats developed more thyroid tumors compared with female rats (9–12). Carcarnation markedly reduced radiation induced thyroid carcinomas (13), and testosterone treatment accelerated the occurrence of methyliothiouracil or radiation induced rat thyroid tumors (12–14). Napalkov (12), however, reported that thyroid adenomas induced by methyliothiouracil developed sooner in female rats and with greater frequency than in male rats. Doniach (15) described in his paper that female rats under intensive TSH stimulation were more susceptible to carcinogenesis by irradiation than male rats. Furthermore, female hamsters were more susceptible to goitrogens such as propylthiouracil or LID than male hamsters (16). Administration of estradiol to rats of either sex receiving thioucaril enhanced goiter size (17). Among the factors for thyroid tumorigenesis, the influence of sex hormone is considered to be crucial through thyroid functions and aging.

MNU has been known to be a broad spectrum carcinogen and MNU induced thyroid carcinomas were promoted by a low iodine diet (18, 19). In this study, a combined treatment of MNU and LID was used as a basic method for thyroid tumorigenesis. We have examined the effects of sex difference, gonadectomy, and estradiol supplement on the thyroid tumorigenesis in this model.

MATERIALS AND METHODS

Animals and Diets. One litter of inbred LE rats was kindly given to us by Dr. Yoshhide Yoshida (National Institute of Genetics, Mishima, Japan) in 1979, and they were maintained by brother-sister mating in our laboratory. All rats in this experiment were weaned 4 weeks after birth and were housed in plastic cages, 3–4 rats/cage, in a room air-conditioned at 24 ± 2°C (SE) and light (12-h light and 12-h dark cycle) controlled. LID and standard mouse feed diet were purchased from Oriental Yeast Co., Ltd., Tokyo, Japan. LID was prepared commercially as: corn meal, 78.0%; vital gluten 18.0%; yeast powder, 2.0%; calcium carbonate, 1.0%; and special grade sodium chloride, 1.0%. Iodine content was below 5 ppm. Rats fed on LID were given deionized water ad libitum.

Carcinogen. MNU, purchased from Sigma Chemical Co., St. Louis, MO, was stored in a refrigerator at 4°C packing in a desiccator, and immediately before use it was dissolved in physiological saline at a concentration of 8 mg/ml.

Estradiol. Pellets were made by melting 17β-estradiol (estradiol; Sigma) with cholesterol powder until fused. Each pellet was weighed and cut to make pellets containing 2.5 mg of estradiol.

Experimental Design. Animals of groups 1–8 were fed on LID from 28 days of age to the end of the experiment. Animals of groups 1–6 were given i.v. injections in the cervical veins of MNU (40 mg/kg of body weight) at 50 days of age. Groups 1 and 2 were intact males and females, respectively. Groups 3 and 4 were gonadectomized males and females, respectively. Animals of groups 5 and 6 were gonadectomized and given 2.5 mg estradiol pellet s.c. on the back. Gonadectomy was performed at 50 days and estradiol pellet was implanted at the same time. Animals of groups 7 and 8, males and females, respectively, received only LID. Rats of groups 9 and 10 received MNU and fed on standard mouse feed diet. All animals were sacrificed at week 30 after MNU injection. Animals that died before week 26 due to various
MNU INDUCED THYROID TUMORS

Table 1  Initial and final body weight, thyroid and pituitary weights, and TSH level in LE rats given MNU, LID, and estradiol

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex</th>
<th>Treatment</th>
<th>Effective no. of rats</th>
<th>Initial body wt (g)</th>
<th>Final body wt (g)</th>
<th>Thyroid wt (mg)</th>
<th>Pituitary wt (mg)</th>
<th>TSH level* at sacrifice (ng/0.1 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>LID MNU†</td>
<td>25</td>
<td>71 ± 10</td>
<td>287 ± 54</td>
<td>335 ± 177</td>
<td>11.7 ± 2.7</td>
<td>2.65 ± 0.92</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>LID MNU</td>
<td>20</td>
<td>71 ± 11</td>
<td>242 ± 48</td>
<td>485 ± 132</td>
<td>13.5 ± 3.5</td>
<td>3.64 ± 0.62</td>
</tr>
<tr>
<td>3</td>
<td>M (CAS)</td>
<td>LID MNU</td>
<td>20</td>
<td>66 ± 7</td>
<td>293 ± 53</td>
<td>330 ± 157</td>
<td>12.0 ± 2.0</td>
<td>2.23 ± 0.76</td>
</tr>
<tr>
<td>4</td>
<td>F (OVX)</td>
<td>LID MNU</td>
<td>22</td>
<td>68 ± 10</td>
<td>237 ± 45</td>
<td>343 ± 132</td>
<td>9.2 ± 1.8</td>
<td>2.88 ± 1.25</td>
</tr>
<tr>
<td>5</td>
<td>M (CAS)</td>
<td>LID MNU estradiol</td>
<td>21</td>
<td>69 ± 10</td>
<td>223 ± 60</td>
<td>988 ± 314</td>
<td>24.8 ± 5.7</td>
<td>9.92 ± 5.8</td>
</tr>
<tr>
<td>6</td>
<td>F (OVX)</td>
<td>LID MNU estradiol</td>
<td>19</td>
<td>72 ± 8</td>
<td>187 ± 41</td>
<td>914 ± 437</td>
<td>18.5 ± 5.1</td>
<td>6.36 ± 2.8</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>LID</td>
<td>18</td>
<td>68 ± 6</td>
<td>449 ± 65</td>
<td>197 ± 44</td>
<td>10.7 ± 1.6</td>
<td>3.63 ± 0.98</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>LID</td>
<td>25</td>
<td>69 ± 11</td>
<td>355 ± 21</td>
<td>228 ± 42</td>
<td>15.2 ± 1.7</td>
<td>4.74 ± 0.77</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>MNU</td>
<td>19</td>
<td>72 ± 11</td>
<td>537 ± 40</td>
<td>39 ± 5</td>
<td>9.2 ± 0.9</td>
<td>0.48 ± 0.29</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>MNU</td>
<td>25</td>
<td>69 ± 9</td>
<td>313 ± 49</td>
<td>32 ± 6</td>
<td>10.8 ± 1.5</td>
<td>0.40 ± 0.47</td>
</tr>
</tbody>
</table>

* Rats were observed for 30 weeks after MNU administration.
† Significant differences were noted for TSH levels; group 1 versus 2, group 7 versus 8, group 3 versus 5, groups 1-8 versus groups 9 and 10 by P < 0.01, group 2 versus 4 by P < 0.05.
‡ Each rat received LID from 28 days of age and 40 mg MNU/kg body weight at 50 days of age.
§ Mean ± SD.
* Significantly larger than group 1 by P < 0.01.
† Significantly larger than groups I and 4 by P < 0.01.
‡ Castration (CAS) and ovariectomy (OVX) were done at 50 days of age.
§ Cholesterol pellet containing 2.5 mg of estradiol was given every 3 months.

Pathology. At the time of necropsy, the body and pituitary and thyroid glands were carefully examined and weighed. Tissues were fixed in 10% buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Thyroid tumors were classified into focal hyperplasia, adenoma, and carcinoma using the histological classification of thyroid tumor reported by Napalkov (20). For the localization of the tumors and weight of organs or serum TSH level were evaluated by means of the x2 test with Yates’ correction or Fisher’s exact probability test and Student’s t test, respectively.

RESULTS

Weights in Body, Thyroid, and Pituitary. The mean body, thyroid, and pituitary weight were shown in Table 1. There were no significant differences among the final body weights in male, castrated male, female, and ovariectomized female rats treated with LID and MNU, respectively. Estradiol treatment disturbed the body weight gains in groups 5 and 6. The thyroid weights in LID groups from 1 to 8 were significantly greater than those in standard diet groups 9 and 10. In the LID groups, the mean thyroid weights in MNU treatment groups (groups 1–6) were significantly different from groups 1 and 4 by P < 0.01, group 4 by P < 0.05.

Table 2  Histological findings in thyroid lesions of LE rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex</th>
<th>Treatment</th>
<th>Effective no. of rats</th>
<th>Focal hyperplasia</th>
<th>Adenoma</th>
<th>Carcinoma</th>
<th>Total tumors</th>
<th>C-cell hyperplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>LID MNU</td>
<td>25</td>
<td>20 (80.0)</td>
<td>11 (44.0)</td>
<td>11 (44.0)</td>
<td>18 (72.0)</td>
<td>1 (4.0)</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>LID MNU</td>
<td>20</td>
<td>16 (80.0)</td>
<td>12 (60.0)</td>
<td>18 (90.0)</td>
<td>19 (95.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>3</td>
<td>M (CAS)</td>
<td>LID MNU</td>
<td>20</td>
<td>18 (90.0)</td>
<td>13 (65.0)</td>
<td>9 (45.0)</td>
<td>16 (80.0)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>F (OVX)</td>
<td>LID MNU</td>
<td>22</td>
<td>19 (86.4)</td>
<td>11 (50.0)</td>
<td>11 (50.0)</td>
<td>15 (68.2)</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>M (CAS)</td>
<td>LID MNU estradiol</td>
<td>21</td>
<td>17 (80.0)</td>
<td>19 (90.5)</td>
<td>19 (90.5)</td>
<td>21 (100)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>6</td>
<td>F (OVX)</td>
<td>LID MNU estradiol</td>
<td>19</td>
<td>13 (68.4)</td>
<td>14 (73.7)</td>
<td>18 (94.7)</td>
<td>19 (100)</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>LID</td>
<td>18</td>
<td>0</td>
<td>1 (5.6)</td>
<td>0</td>
<td>1 (5.6)</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>LID</td>
<td>25</td>
<td>0</td>
<td>1 (4.0)</td>
<td>0</td>
<td>1 (4.0)</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>MNU</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>MNU</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Diffuse hyperplasia was observed in almost all rats fed LID. Focal hyperplasia, adenoma, and carcinoma were observed among diffuse hyperplasias, and they were individually tabulated. Total tumors include the rats bearing either adenoma or carcinoma or both.
* Significantly different from groups 1 and 4 by P < 0.01.
‡ Significantly different from group 4 by P < 0.05.
§ Significantly different from group 3 by P < 0.01.
‡ Significantly different from group 4 by P < 0.01.
§ Significantly different from group 4 by P < 0.05.
MNU INDUCED THYROID TUMORS

Fig. 1. Thyroidal lesions in LE rats induced by the combined treatment of LID, MNU, and estradiol at 30 weeks after MNU administration. a, diffuse hyperplasia of a female rat fed on LID; b, focal hyperplasia among diffuse hyperplasia of a female rat treated with LID and MNU; c, follicular adenoma in diffuse hyperplasia of a female rat treated with LID and MNU; d, follicular carcinoma in a ovariectomized rat treated with LID, MNU, and estradiol. H & E, x 100.

significantly greater than those in non-MNU treatment groups (groups 7 and 8). In groups 1–6, the mean thyroid weight in female rats was greater than that in male rats. There was no significant difference between the thyroid weights in male and castrated male rats, whereas ovariectomy in female rats suppressed the increase of thyroid weights (group 2 versus group 4). Furthermore, estradiol supplemented to both gonadectomized male and female rats (groups 5 and 6) remarkably increased the thyroid weights compared with those in simply gonadectomized male and female rats (groups 3 and 4).

The pituitary weights were higher in females than in males among groups 1 and 2, 7 and 8, and 9 and 10, respectively. Castration did not influence the mean pituitary weight of male rats (groups 1 versus 3), but ovariectomy significantly decreased that of female rats (groups 2 versus 4). In groups 5 and 6 given estradiol after gonadectomy, the mean pituitary weights were significantly increased compared with other groups.

Thyroid Pathology. The histological classification of the thyroid lesions is summarized in Table 2. Diffuse hyperplasia was observed in almost all rats fed on LID. It was composed of follicles containing little or no colloid and lined by tall and cuboidal epithelial cells (Fig. 1a). In addition to diffuse follicular hyperplasia, focal hyperplasia, adenoma, or carcinoma were significantly increased in rats given both MNU and LID. The focal hyperplasia was characterized with dilated, cystic, or papillary irregular follicles, composed by hyperchromatic and basophilic cells. However, the continuity of histological changes from surrounding thyroid tissues was maintained (Fig. 1b). Adenomas were distinctly defined and showed an uniform cell growth; some had a thin, fibrous capsule (Fig. 1c). Carcinomas were usually large nodules and sometimes oppressed the trachea, but metastasis to cervical lymph nodes or distant organs were not observed. Carcinomas had capsules or scirrhous fibrosis and invaded into these capsules or adjacent thyroid tissues (Fig. 1d).

Incidence of Thyroid Tumors. In rats treated with MNU and LID, the incidence of carcinoma in females was significantly higher than that in male rats. Gonadectomy in female rats significantly decreased the occurrences of both carcinomas and total thyroid tumors compared with those of intact female rats.
were higher in male than in female rats ($P < 0.05$ at week 4). At week 12, there were no significant differences of serum TSH levels among each group. All data in groups 1–10 at the time of sacrifice are shown in Table 1. In groups 1–8 fed on LID, serum TSH levels were higher than those in rats of groups 9 and 10 fed on standard diet. In LID groups, serum TSH levels were higher in females than in males whether or not MNU was given. By gonadectomy, they did not increase more than those in intact male and female rats. Estradiol supplements given both sexes of gonadectomized rats significantly elevated the serum TSH levels compared with those of gonadectomized rats without estradiol ($P < 0.01$). Mean TSH levels and mean pituitary and thyroid weights in groups 1–10 were well correlated. Its correlation coefficient was $r = 0.93$ and $P < 0.01$ in pituitary weight and $r = 0.89$ and $P < 0.01$ in thyroid weight by correlation and simple regression analysis.

ER of the Thyroid Tissues. The ER levels of normal thyroids or thyroid tumors were all less than 1 fmol/mg protein. However, three transplanted thyroid tumors showed increases of ER levels more than 1 fmol/mg protein (Table 3).

Pathology of Other Tissues (Table 4). Except for thyroid tumors among both sexes of MNU treated rats, the incidence of mammary carcinoma was much higher in rats supplemented with estradiol (groups 5 and 6) than those in rats without estradiol (groups 1–4, 9, and 10). Mammary fibroadenoma had the highest incidence in group 5 (33%). Estradiol supplemented rats showed alveolar hyperplasia with milk secretion whether they have mammary tumors or not. Average diameters of those mammary tumors were less than 4 cm. Other developed tumors were mainly lymphomas and mandibular bone tumors. Two types of lymphoma were observed. One was the systemic type that spreads in liver, spleen, and systemic lymph nodes but not in thymus. The other was a thymic type localized in the thymus. Mandibular bone tumor was revealed to be enamel epithelioma. The total tumor incidence was highest in group 6 (71%), followed with groups 4 and 10. Compared to the rats who received MNU, rats without MNU (groups 7 and 8) showed less than 4% of the tumor incidence.

In pituitary glands of rats fed on LID, basophilic cell hyperplasias were found by the characteristic numerous appearance of round cells with ballooned cytoplasm. These cytoplasmas were weakly stained by anti-rat TSH-β but not stained heavily as with normal TSH cells. These cells were decreased by gonadectomy in both sexes. In rats supplemented with estradiol after gonadectomy, remarkably basophilic cell hyperplasias were also observed although these cells did not have swollen cytoplasms and were not stained by anti-TSH or anti-prolactin antiserum. However, small aggregates of prolactin positive cells were observed among these cells.

Except in neoplastic lesions, epidermal inclusion cysts were noted in the subcutaneous tissues of skin in group 1 (4%), group 3 (15%), and group 5 (5%).

DISCUSSION

In the present study, the effects of sex difference, gonadectomy, and estradiol as supplement after gonadectomy on thyroid tumorigenesis were studied under the basic method of a combined treatment of MNU and LID. In LE rats, females were more susceptible than males to thyroid tumorigenesis, particularly to the occurrence of thyroid carcinoma. Ovariec- tomy lowered the incidence of thyroid carcinoma in female rats, but castration did not influence it. Furthermore, administration
of estradiol significantly increased the incidence of thyroid carcinoma in castrated and ovariectomized rats. These results were contrary to the reports on the predominant occurrence of thyroid tumor in male rats mainly by irradiation (9–11) but were in agreement with other reports (12, 16, 17). In rats, basal TSH levels in serum and height of thyroid follicular cells were higher in males than those in females (15).

Castration reduced both basal and TRH-stimulated TSH and replacement of testosterone restored both of these TSH levels to the level of intact male rats (14). It has been considered that the sex-related difference in serum TSH level is mediated by androgen (22). Higher TSH levels in male rats may be the factor for their higher susceptibility on thyroid tumorigenesis by irradiation (15).

In this experiment, changes of serum TSH levels in each experimental group were well correlated to the occurrence of thyroid tumors. It is notable that although there was no significant difference between serum TSH levels in male and female rats fed standard diet, serum TSH levels in female rats fed LID, whether or not given MNU, increased more than those of corresponding male rats. It was also interesting to note that estradiol supplement after gonadectomy remarkably increased TSH levels. The effect of estrogen on pituitary gland has been well known to stimulate PRL cells (23–25). Other investigators reported the influence of estrogen on secretion of TSH, in which they observed a significant increase of the number of pituitary binding sites or the thyrotropin releasing hormone receptor (26, 27). Treatment with 17α-estradiol led to a remarkable increase in secretion of TSH and the effect was influenced by the amount of estradiol (28, 29). In addition to a direct effect of estrogen on pituitary gland, estrogen has been known to enhance extra-thyroidal conversion of thyroxine to triiodothyronine and to affect the pituitary-thyroid axis indirectly (27, 30). Moreover, production of TSH in pituitary gland may be affected by the interaction of thyroid hormones with estrogen. Recently, c-erbB oncoprotein was proved to code thyroid hormone receptors (31). Thyroid hormone receptor is a member of gene family of steroid receptors such as estrogen receptor (32). Actually, propylthiouracil treatment inhibited the proliferation stimulus by estrogen on the rat pituitary PRL cells (34). Thiouacil inhibited the growth of transplantable mammosomatotropin tumor in Fischer rats and also caused a decrease in the synthesis of PRL (34, 35). Nevertheless, the interaction of ER and thyroid hormone receptor at pituitary gland for the secretion of TSH is not clear. In the present experiment, the mean serum TSH level and pituitary weight in groups 1 to 10 were well correlated. These findings led to the concept that both estrogen and LID induced negative feedback functioned cooperatively to promote the growth of pituitary gland. The mean serum TSH level and mean thyroid weight in groups 1–10 were similarly correlated. It is also concluded that increased levels of TSH may act directly for the growth and development of thyroid tumors.

The role of estrogen for the thyroid tumorigenesis may be mediated directly through ER, since there were reports on the existence of ERs in the most neoplastic or nonneoplastic human thyroid tissues (36, 37). In the present experiment, a detectable amount of ER more than 1 fmol/mg protein was found only in the transplanted thyroid tumors. Estrogen has a broad spectrum of effects not only on the organs with ER but also on the cells without ER such as hematopoietic systems or immunosurveillance systems (38–40). However, the mechanism of estrogen in modifying carcinogenesis via these effects has yet to be elucidated.

The predominant occurrence of thyroid tumors in the female rats in the present study is the similar situation to the occurrence of human thyroid tumors. Incidence of incipient thyroid carcinomas in human was reported to be no sex difference (7, 8), but manifestation of these tumors was predominant in women (1–3). It is worthwhile to study the mechanisms of sex difference with our model so that the effects of sex hormones on human thyroid tumorigenesis and tumor progression can be better elucidated.

**REFERENCES**


---

**Table 4 Incidence of tumors except thyroid gland**

<table>
<thead>
<tr>
<th>Experimental groups</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective no. of rats</td>
<td>25</td>
<td>20</td>
<td>22</td>
<td>21</td>
<td>19</td>
<td>18</td>
<td>25</td>
<td>19</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

- Mammary tumors
  - Fibroadenoma: 0 1 (5%)
  - Carcinoma: 1 (4) 0 1 (4) 1 (4) 1 (4)
- Lymphoma
  - Systemic: 1 (4) 0 (10) 2 (9) 2 (9) 0 0 0 0 0 0
  - Localized: 0 0 1 (5) 1 (5) 0 0 0 0 0
- Mandibular bone tumor: 1 (4) 1 (5) 1 (5) 2 (9) 0 0 0 0 0 0
- Total: 3 (10) 3 (15) 3 (15) 9 (41) 15 (71) 5 (20) 0 (0) 1 (4) 2 (11) 8 (32)

* Numbers in parentheses, percentage of animals with tumors.
24. Furth, J., Ueda, G., and Clifton, K. H. The pathophysiology of pituitaries

25. Lloyd, R. V. Estrogen-induced hyperplasia and neoplasia in the rat anterior

pituitary gland: An immunohistochemical study. Am. J. Pathol., 113: 198-


of pituitary thyrotropin releasing hormone receptor levels by estrogen and


27. Chen, H. J., and Walfish, P. G. Effects of estradiol benzoate on thyroid-


thyroid system of the female rat: mechanism and loci of action. Endocrinol-


29. Miller, W. L., Knight, M. M., and Gorski, J. Estrogen action in vitro: 

regulation of thyroid stimulating and other pituitary hormones in cell cul-


30. Galton, V. A. Thryoxine metabolism and thyroid function in the pregnant 


31. Weinberg, C., Thompson, C., Ong, E., Lebo, R., Grul, J., and Evans, R. 

M. The c-erbA gene encodes a thyroid hormone receptor. Nature (Lond.), 


32. Evans, R. M. Steroid and thyroid hormone receptors as transcriptional regu-

lators of development and physiology. Science (Washington DC), 240: 889-


thyroid hormone receptor binds with opposite transcriptional effects to a 

common sequence motif in thyroid hormone and estrogen response elements.


34. Lloyd, R. V., and Mailloux, J. Effects of diethylstilbestrol and propylthiou-

acil on the rat pituitary. An immunohistochemical and ultrastructural study.


35. Potvliege, P. R. Effects of estrogen on pituitary morphology in goitrogen-

36. Molteni, A., Raymond, L. W., Molteni, L. B., and Forss, E. M. Estradiol 

receptor-binding protein in head and neck neoplastic and normal tissue.


G. Jr. Estrogen and thyroid-stimulating hormone (TSH) receptors in neo-


1985.


39. Cordingley, J. L. The mechanism of oestrogen stimulation of reticulo-


Effects of Sex Difference, Gonadectomy, and Estrogen on \(N\)-Methyl-\(N\)-nitrosoourea Induced Rat Thyroid Tumors

Masahiro Mori, Masashi Naito, Hiromitsu Watanabe, et al.


Updated version

Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/50/23/7662