

Spontaneous uterine adenocarcinomas in aged rats and their relation to endocrine imbalance *

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Summary. In addition to spontaneous uterine endometrial adenocarcinomas at a high incidence (35.1%), development of endometrial hyperplasia/adenoma was also frequently detected in rats of the Donryu strain. The total yield of all observed proliferative endometrial lesions was very high (60.6%). The tumors arose commonly in the uterine horn of aged rats. Histologically, most demonstrated glandular structures, consisting of cuboidal or columnar cells with weak eosinophilic or basophilic cytoplasm and large nuclei. In about half of the animals with adenocarcinomas, metastasis to remote organs such as the lung was observed. Histological examination of the ovary and vaginal epithelium revealed ovarian cysts, atrophy of the ovary and cornification of the vaginal epithelium more frequently in rats with endometrial carcinomas than in animals without tumors. These findings indicate that adenocarcinoma development in Donryu rats is associated with endocrine imbalance [increased serum estrogen: progesterone ($E_2:P$) ratios]. By comparative investigation of strain differences, it was confirmed that irregular estrous cycles began earlier with higher incidence in Donryu rats than in F344 rats, a low-incidence strain. Histological findings of the ovary and vaginal epithelium also suggested relatively increased estrogen levels in Donryu rats compared to F344 rats. Estimated plasma values of gonad steroids showed that the $E_2:P$ ratio in Donryu rats at 12 months of age was about five times that in F344 rats. These results therefore indicate that hormone imbalance, particularly an increased $E_2:P$ ratio, may play an important role in the spontaneous occurrence of endometrial adenocarcinoma in Donryu rats.

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Abbreviation: E_2/P , estrogen/progesterone ratio

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Introduction

Endometrial carcinoma is one of common malignant tumors found in women and a steady increase in its incidence has been observed during the last decade in Western industrial countries and also in Japan. An association between endocrine imbalance and endometrial carcinomas has been documented in the literature, and it has been pointed out that estrogen may play a most important role in the development of the tumors (Fox 1984; Hilliard and Norris 1979; Lingeman 1979; Zeil 1982). It is well known that estrogen-related endometrial lesions undergo progression from cystic to adenomatous hyperplasia to carcinoma (Gusberg and Kaplan 1963). While spontaneous uterine neoplasms are fairly common in rats, the most common type of spontaneous uterine tumor is the endometrial stromal polyp, and endometrial adenocarcinomas have been considered to be very rare in many rat strains such as Fischer and Sprague-Dawley (Goodman et al. 1979; Imai and Yoshimura 1988; Solleveld et al. 1984; Thompson et al. 1961). Previously we reported spontaneous tumor development in F344/DuCrj (Maekawa et al. 1983) and NRC:Donryu rats (Maekawa et al. 1986b). A high incidence (35%) of endometrial adenocarcinoma was observed in Donryu rats, while the incidence of this tumor was under 1% in F344 rats.

In the present report, we describe the histological and biological characteristics of Donryu spontaneous endometrial carcinomas and discuss their pathogenesis in relation to strain differences in hormonal environment. Their value as an animal model for human endometrial adenocarcinoma is briefly discussed.

Materials and methods

One hundred female inbred Japanese albino NRC:Donryu rats were purchased from Nippon Rat Co. Ltd. (Urawa). The rats examined were used as control group animals for a long-term carcinogenicity study (Maekawa et al. 1987b). A total of approximately 150 F344/DuCrj rats (Charles River Japan Inc., Atsugi), used as controls for three recent carcinogenicity studies (Maekawa et al. 1984, 1986a, 1987a), were also examined for comparative assessment of strain differences. Rats of both strains were housed 4 animals to a plastic cage, and kept in an air-conditioned barrier-system animal room at $24 \pm 1^\circ \text{C}$ with a relative humidity of $55 \pm 5\%$. F344 and Donryu rats were maintained with basal diets, CRF-1 (Oriental Yeast Co., Tokyo) and CE-2 (CLEA Japan Inc. Tokyo), respectively, and observed until about 120 weeks of age. The precise housing conditions of both rat strains and the occurrence of spontaneous tumors in the various organs of these rats have been described in our previous reports. All reproductive organs and related organs and/or tissues were fixed in buffered 10% formalin, processed and sectioned routinely, stained with hematoxylin and eosin, and examined microscopically.

About an additional 100 rats of both strains were also used for sequential examination of vaginal smears or plasma gonad steroid levels. For the latter, blood was collected periodically from the abdominal aorta and centrifuged at 3000 g for 10 min, and the plasma was stored at -80°C until assayed. The plasma values of estradiol- 17β and progesterone were estimated respectively with estradiol direct radioimmunoassay (Sorin Biomedica, Cis, France) and DPC progesterone (Diagnostic Product Corporation, Los Angeles) kits.

Results

Spontaneous endometrial adenocarcinoma incidence in rats

The incidences and types of spontaneous uterine tumors in Donryu rats were compared with those in F344 rats taken from our previous report (Maekawa et al. 1983). As summarized in Table 1, uterine tumors were relatively common in both rat strains, although the predominant histological types differed considerably. In Donryu rats, the endometrial adenocarcinoma was the most common type with incidences of 35.1%. In addition, endometrial hyperplasia/adenoma development was also detected with high incidence in Donryu rats, to give a very high total yield of 60.6% for all proliferating endometrial lesions. On the other hand, in F344 rats the most frequently observed uterine tumors were endometrial stromal polyps, the incidences of endometrial adenocarcinoma being under 1%.

Pathological findings regarding Donryu rat endometrial adenocarcinoma

Adenocarcinomas arose mainly in one or both of the uterine horns, about 75% of the tumors being restricted to this region (Fig. 1). In 10% of cases the tumors that developed in the corpus region seemed to invade the horns. In questionable cases it could not be determined whether the tumors originated from the corpus uteri or the uterine horns. Adenocarcinomas presented as solid nodules with or without projection into the uterine lumen. Sometimes hemorrhage and intra-nodular cyst formation were ob-

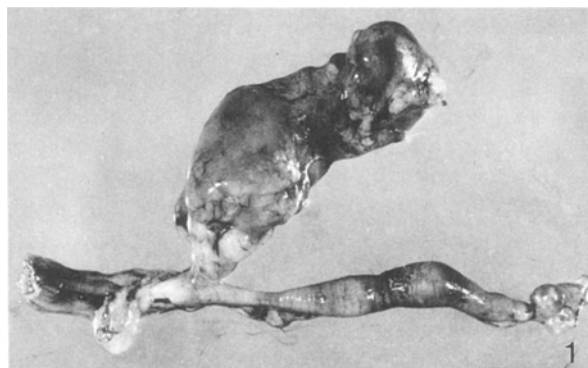


Fig. 1. Macroscopic appearance of an endometrial adenocarcinoma observed in a Donryu rat killed at the 114th week. The tumor originated from the right uterine horn.

Table 1. Incidences and types of spontaneous uterine tumors in Donryu and F344 rat strains

Sample size and uterine tumor type	Incidence (%)	
	NRC:Donryu ^a	F344/DuCrj ^b
No. of rats examined	94	297
Adenocarcinoma	35.1	1.0
Adenoma	2.1	1.3
Endometrial stromal polyp	1.1	21.2
Endometrial stromal sarcoma	2.1	2.4

^a Maekawa et al. (1986b)

^b Maekawa et al. (1983)

served and, in many cases, adhesion to the surrounding tissue/organs because of invasion into the serosa and widespread transcoelomic metastasis were evident.

Histologically, most of the tumors demonstrated glandular structures. An irregular proliferation of atypical glands and epithelia, consisting of one or more layers of cuboidal or columnar cells with weak basophilic or eosinophilic cytoplasm and large nuclei (Fig. 2), was characteristic, and tumor cells often infiltrated through the muscularis to the serosa (Fig. 3). In more anaplastic neoplasms, tumor cells were smaller and severe cellular and structural atypia and abundant mitotic figures were prominent. Glandular structures were not obvious in some of these cases (Fig. 4). Adenocarcinomas often invaded the adjacent abdominal organs and metastasis to remote organs such as the lung was frequently observed (Fig. 5). Thus, in 45% of animals with adenocarcinoma, distant metastasis was detected. Squamous metaplasia-like change was seen in uterine glands of about one-fifth of the animals. About two-thirds of the endometrial carcinomas were well-differentiated adenocarcinomas and the other one-third belonged to the poorly differentiated type. In addition to adenocarcinomas, atypical hyperplasias or adenomas of the endometrium were also observed frequently in the Donryu strain of rats. These lesions were glandular and lined by a single layer of cuboidal or columnar cells. Cystic dilatation of the glands was found in some cases of atypical hyperplasia. The lesions,

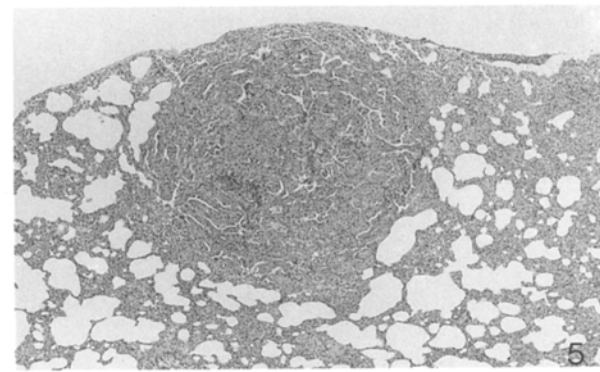
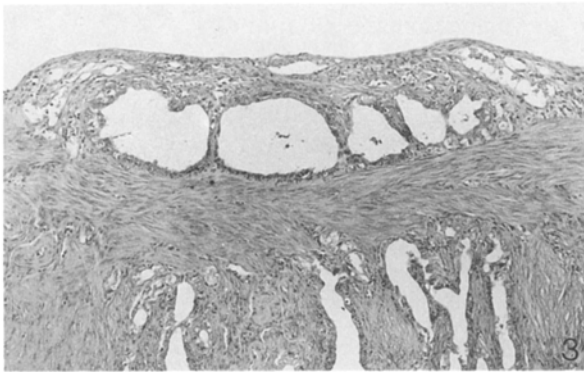
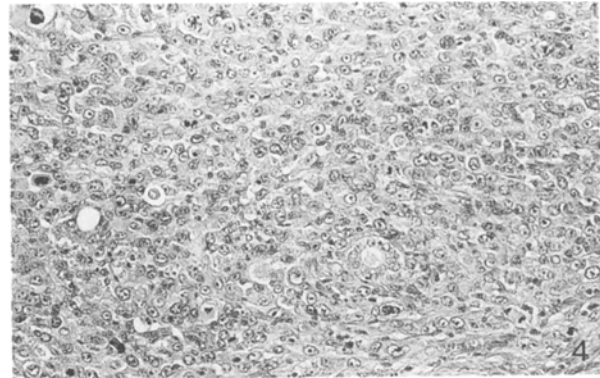
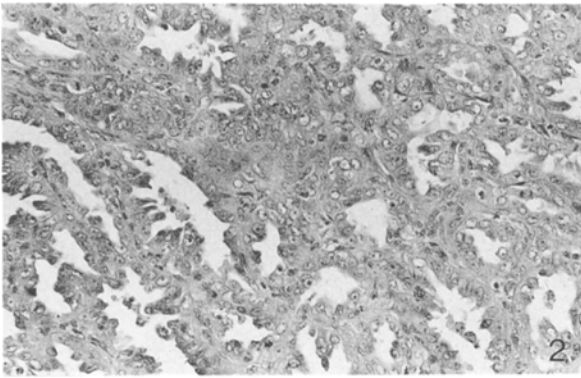


Fig. 2. Well-to-moderately differentiated endometrial adenocarcinoma detected in a Donryu rat killed at the 120th week. Irregular proliferation of atypical glands consisting of one or more layers of cuboidal or columnar cells with weak basophilic or eosinophilic cytoplasm. Large nuclei are prominent. H&E, $\times 150$

Fig. 3. Lower magnification of another adenocarcinoma found in a Donryu rat killed at the 120th week. Tumor cells are observed infiltrating through to the serosa. H&E, $\times 75$

Fig. 4. Anaplastic or poorly differentiated uterine carcinoma observed in a Donryu rat killed at the 114th week. Tumor cells are small and severe cellular and structural atypia and abundant mitotic figures are prominent. Glandular structures are not obvious. H&E $\times 150$

Fig. 5. Lung metastasis of an endometrial adenocarcinoma of a Donryu rat killed at the 114th week. H&E, $\times 30$

Table 2. Coincident occurrence of spontaneous uterine adenocarcinoma and other endocrine tumors in female Donryu rats

Tumor location	Incidence (%)	Coincidence (%)	
		Actual	Expected
Uterus (adenocarcinoma)	35.1	—	—
Pituitary	34.4	4.2	12.1
Thyroid	8.3	1.0	2.9
Adrenal	11.5	3.1	4.0
Mammary	41.7	8.3	14.6
Ovarian	2.1	0	0.7

however, were always restricted to the endometrium and characteristics of malignancy were absent.

Relation between endometrial carcinomas and endocrine tumors in Donryu rats

The coincidence between spontaneous endocrine tumors and endometrial carcinomas was examined, but in each

case values were under the expected levels, as shown in Table 2.

Histological findings in the ovary and vaginal epithelia of Donryu rats

The histological findings for the ovary and vaginal epithelia in Donryu rats with uterine adenocarcinoma were compared with those in rats without tumors.

As shown in Table 3, follicular cysts (Fig. 6) and atrophy were observed most frequently in the ovaries of rats with adenocarcinomas, to an intermediate extent in those demonstrating hyperplasia and most rarely in rats without any lesions. Absence of follicles was only detected in rats with adenocarcinoma. In the vagina, cornification of the epithelium (Fig. 7) was detected more frequently in rats with adenocarcinoma or adenoma/hyperplasia than in rats without proliferative lesions. In contrast, the incidence of columnar epithelium-like cells (Fig. 8) was lowest in rats with adenocarcinoma and highest in those without any endometrial proliferative lesions. Absence of the corpora lutea occurred with almost equal frequency in each group of rats.

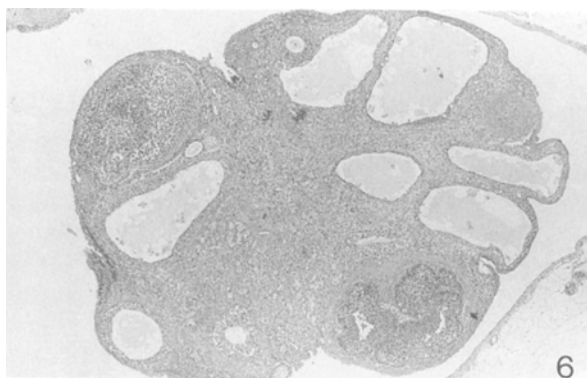


Fig. 6. Polyfollicular cysts and atrophy of the ovary in a Donryu rat with uterine adenocarcinoma killed at the 88th week. H&E, $\times 30$

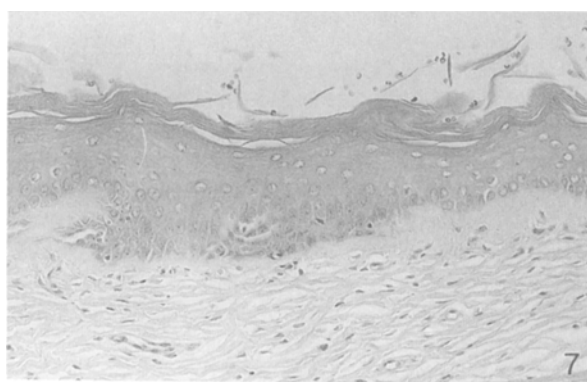


Fig. 7. Cornification of the vaginal epithelium found in a Donryu rat killed at the 70th week. H&E, $\times 75$

Strain differences in spontaneous endometrial carcinoma development and gonad steroid levels in the plasma

Histological changes in the ovary and vaginal epithelia in Donryu rats were compared with those in F344 rats for the purpose of estimating the hormonal environment in these two strains. In the present examination, the incidence of endometrial carcinomas in F344 rats was slightly higher than that in the rats reported previously (Table 1, Maekawa et al. 1983). As shown in Table 4, Donryu rats showed higher incidences of ovarian cysts, absence of corpora lutea and cornification of vaginal epithelium than did F344 rats. In contrast, F344 rats had a markedly higher incidence of columnar epithelium-like cells in the vagina than did Donryu rats.

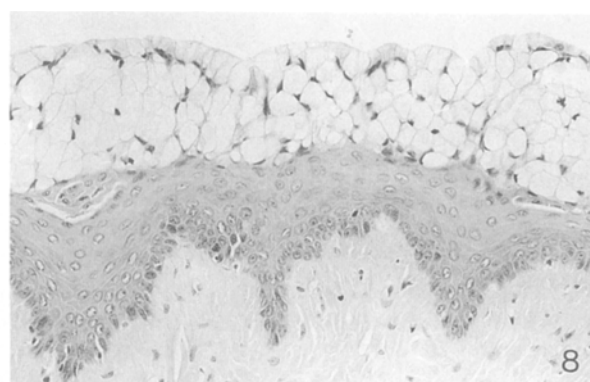


Fig. 8. Columnar epithelium-like cells of the vaginal epithelium in a F344 rat killed at the age of 110 weeks. H&E, $\times 75$

Table 3. Histological changes in the ovary and vaginal epithelium of Donryu rats with or without uterine lesions

Histological type of uterine endometrium	No. of rats	Incidence (%)					
		Ovary				Vagina	
		Cyst	Absence of corpus luteum	Absence of follicle	Atrophy	Cornification	Columnar epithelium
Adenocarcinoma	33	33.3	54.5	6.1	39.4*	27.3	18.2
Adenoma/hyperplasia	24	25.0	54.2	0	20.1	41.7	25.0
Normal	34	11.8	58.8	0	11.8	8.8	41.2

* Significantly different from normal ($P < 0.05$, χ^2 -test)

Table 4. Histological findings in the ovary and vaginal epithelium of Donryu or F344 rats

Strain	No. of rats examined	Incidence (%)						
		Adeno-carcinoma	Ovary				Vagina	
			Cyst	Absence of corpus luteum	Absence of follicle	Atrophy	Cornification	Columnar epithelium
Donryu	94	35.1	23.4*	57.4*	2.1	24.5	23.4*	27.7*
F344	146	4.1	8.2	7.5	8.2	15.8	7.5	79.5

* Significantly different from F344 rats ($P < 0.01$, χ^2 -test)

Table 5. Changes of mean plasma estrogen:progesterone (E_2/P) ratios in F344 and Donryu rats

Strain	No. of rats/months	$10^{-3} \times E_2/P$ for rats aged (months)				
		1.5	6	8	10	12
Donryu	5- 9	3.83	3.31	2.57	3.20	4.92
F344	4-11	2.52	3.99	1.54	2.10	0.96

To confirm strain differences in the reproductive pattern, sequential changes in vaginal epithelium were investigated by vaginal smear. In Donryu rats, irregular estrous cycles began at 5 months of age and about 90% animals showed persistent estrus at the age of 9 months. In contrast, in F344 rats, vaginal smears showed regular estrous cycles at 9 months of age and only few cases of persistent estrus at 12 months of age.

Plasma estrogen and progesterone levels were estimated for Donryu and F344 rats at 6 weeks, 6, 8, 10 and 12 months of age. In Donryu rats, plasma values of gonad steroids, estrogen and progesterone decreased with age. The decrease of progesterone was more severe than that of estrogen. In contrast, the decrease of estrogen was much less pronounced and the slight increase of progesterone continued until 12 months of age in F344 rats. As a result, estrogen/progesterone (E_2/P) ratios increased with age after 10 months in Donryu rats but decreased in the F344 strain, as shown in Table 5. The E_2/P ratio in 12-month-old Donryu rats was therefore about five times that of F344 rats at the same age.

Discussion

In rats, naturally occurring endometrial adenocarcinomas have been generally thought to be rare, as reviewed earlier by Baba and Haam (1976) and also by Goodman and Hildebrandt (1987). Recently, Han:Wistar or BDII/Han rats were also described to have a high incidence of spontaneous uterine adenocarcinomas (Deerberg et al. 1981; Deerberg and Kaspareit 1987). Although the presently observed incidence of this tumor in Donryu rats was a little lower, inclusion of other proliferative lesions in the endometrium presenting as hyperplasia or adenomas revealed an impressive total yield. In the present study, there was a difference in diets between Donryu and F344 rats. However, there was no important difference in the main nutritional components of those diets.

Histological findings for endometrial adenocarcinomas in Donryu rats were very similar to those described in women. The observation of endometrial hyperplasia at high incidence in this rat strain was of particular importance, because it has been considered that adenocarcinomas arising in the human situation are associated with adenomatous hyperplasia (Gusberg and Kaplan 1963). An additional similarity was that, as in man, the frequency of metastasis to remote organs in the Donryu rats was high, although metastases of spontaneous tumors in rats are generally very rare.

An association between endocrine imbalance and endometrial carcinomas has been documented in the literature, and it has been pointed out that estrogen may play a most important role in development of the tumors (Fox 1984; Hilliard and Norris 1979; Lingeman 1979; Zeil 1982). In experimental animals such as mice and rabbits, there is supportive evidence that endometrial adenocarcinomas can be induced by administration of estrogen (Gardner and Ferrigno 1956; Griffith et al. 1963; Meissner et al. 1957; Muñoz et al. 1979). In rats, however, it is well known that induction of this tumor is very difficult with estrogen alone (Baba and von Haam 1976; Goodman and Hildebrandt 1987).

A relationship between uterine adenocarcinomas and endocrine tumors, especially pituitary or ovarian tumors, has been documented in women (Barnes et al. 1981; Dockerty and Mussey 1951). These have been attributed to hormonal dysfunction. While pituitary gland adenoma is one of the most common spontaneous tumors in aging female rats, the coincidence of uterine adenocarcinoma with pituitary adenoma development in Donryu rats was under the statistically expected value in the present study. One granulosa cell tumor was also observed in the ovary of a Donryu rat without any uterine lesions. The results thus indicate that there is no correlation between uterine adenocarcinomas and endocrine tumors in rats, as also reported in the BDII/Han case (Deerberg and Kaspareit 1987).

Recently, Deerberg and Kaspareit (1987) did report that a constant estrous cycle appeared in the early stage of life in BDII/Han rats, which are known to have a high incidence of spontaneous uterine adenocarcinomas. The differences observed in the present study regarding estrus between high-incidence Donryu and low-incidence F344 rats are thus directly in line with the report.

It has been pointed out that follicular polycystic degeneration of the ovary results in an unopposed increase in serum estrogen levels in humans (Futterweit 1984). In experimental animals, polycystic ovaries were observed in BDII/Han rats with spontaneous endometrial adenocarcinoma (Deerberg and Kaspareit 1987) and also in rats with adenocarcinomas induced by *N*-methylnitrosourea (Verdeal et al. 1986). Cornification of the vaginal epithelium can be also used as the index of the serum estrogen level. In Donryu rats with adenocarcinoma in the present study, the incidences of follicular cysts, atrophy of the ovary and cornification of the vaginal epithelium were all elevated as compared to animals without endometrial lesions. Moreover, similar tendencies were observed in rats with precancerous lesions such as adenomas or hyperplasias. These results suggest that the estrogen level might increase relatively in rats with adenocarcinoma or adenoma/hyperplasia lesions. Furthermore, the columnar epithelium-like cells in the vagina, which are commonly observed in pregnant rats and are thought to be related to luteinization, were lowest in rats with endometrial carcinoma. This result indicates that serum progesterone levels may be higher in low-risk rats. Additional evidence for these conclusions was provided by the finding that ovarian cysts, absence of corpora lutea and cornification of vaginal epithelium are more

frequent in Donryu rats than in the F344 strain, while the latter were found to have the higher incidence of columnar epithelium-like cells in the vagina.

The hypothesis mentioned above was directly supported by the estimated plasma values of gonad steroids. The E_2/P ratio in Donryu rats was thus about five times that in F344 rats at 12 months of age. Morikawa et al. (1982) described how increased endogenous E_2/P ratios resulting from a hormonal imbalance, such as persistent estrus, constitute one high-risk factor for development of spontaneous endometrial carcinomas in androgen-sterilized rats. Gottardis et al. (1982) furthermore reported that polycystic disease of the ovaries and endometrial hyperplasia induced in rats by methylnitrosourea treatment were accompanied by reduced estrous serum progesterone levels with loss of the normal estrous peak, but normal estrogen concentrations. These results all indicate that an increased endogenous E_2/P ratio is a most important factor in the spontaneous occurrence of uterine endometrial carcinomas. The observed strain difference in the incidence of the adenocarcinomas can therefore be attributed to the different hormonal environment in Donryu and F344 rats.

The results of the present study suggest that Donryu rats may serve well for an appropriate animal model of human endometrial adenocarcinoma, because the histological findings, biological behavior and pathogenesis of the tumors appear essentially similar to those in man.

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