RAPID COMMUNICATION Jpn. J. Cancer Res. 85, 563–566, June 1994

Spontaneous Renal Cell Tumors in Long-Evans Cinnamon Rats

Keisuke Izumi,[1,4] Keisuke Kitaura,[1] Yoshifumi Chone,[1] Hideki Tate,[1] Tateo Nakagawa,[1] Yasuo Suzuki[2] and Kozo Matsumoto[3]

[1]Second Department of Pathology, [2]Department of Hygiene, and [3]Institute for Animal Experimentation, School of Medicine, The University of Tokushima, Kuramoto-cho 3-18-15, Tokushima 770

Neoplastic lesions of the kidneys in untreated Long-Evans Cinnamon (LEC) rats of 57–118 weeks old (85 males and 34 females) and male F344 rats of 64–93 weeks old (59 males) were examined histologically. The incidences of renal cell tumors in male and female LEC rats were 6/80 (8%) in weeks 57–65, 3/19 (16%) in weeks 66–75, 3/8 (38%) in weeks 76–105 and 7/12 (58%) in weeks 106–118. Of these tumors, 13 were microscopic adenomas and 7 were renal cell carcinomas. The copper content of the kidneys was about three times higher in LEC rats than in F344 rats ($P<0.001$), but the iron content of the kidneys was similar in the two strains.

Key words: LEC rat — Copper toxicity — Renal cell carcinoma

The LEC (Long-Evans with a cinnamon-like coat color) rat is a mutant strain displaying spontaneous liver cell injury with jaundice, so-called "hereditary hepatitis," and subsequently developing hepatocellular carcinoma at high incidence.[1-4] Copper toxicity due to congenital abnormal accumulation of the metal in the liver has been suggested to be responsible for hepatocarcinogenesis in this strain of rats.[5] The copper content in the kidney is two to three times that of control rats, although copper accumulation in the liver is over 40 times that of normal Long-Evans Agouti (LEA) rats.[5] There is no report of spontaneous tumors in LEC rats of 104 weeks or more or the development of neoplasms at high incidence in any organ of this strain except the liver. Kawano *et al.* did, however, observe renal cell tumors in 2 (8%) of 25 female LEC rats but not in 33 males of 85 weeks old.[6]

In this study, we examined the kidneys of untreated LEC rats of 57–118 weeks old (85 males and 34 females) and F344 rats of 64, 85 and 93 weeks old (8, 28 and 23 males, respectively). Both groups were the untreated controls of animals used for carcinogenesis studies in our laboratory in the last five years. The LEC rats were bred in our laboratory in specific pathogen-free conditions and the F344 rats were obtained from Charles River Japan, Inc., Kanagawa. Sections of both kidneys fixed in buffered formalin and embedded in paraffin were stained with hematoxylin and eosin for histological examination. In addition, some sections were stained with Prussian blue for examination of iron deposition. The copper and iron contents of the kidney of F344 and LEC rats of 64 weeks old and LEC rats of 91–118 weeks old were measured by the atomic absorption method.

[4] To whom correspondence should be addressed.

The incidences of renal cell tumors in male and female LEC rats are shown in Table I. The incidence increased with age to 7/12 (58%) in male and female LEC rats of 106–118 weeks old. Of the tumors, 13 were microscopic adenomas and 7 were renal cell carcinomas. Five of the 7 renal cell carcinomas were more than 6 mm in diameter, the others being microscopic in size. The gross appearance of a tumor in a 113-week-old male LEC rat and the histological appearance of renal neoplasms are shown in Fig. 1. No renal tumor was found in F344 rats. Renal neoplasms were not related to the presence of liver neoplasms. Malignant lymphomas developed in two of the LEC rats (a 62-week-old male and a 112-week-old male) and myelogenous leukemia developed in a 63-week-old male LEC rat. In other visceral organs, primary tumors were not observed. Fig. 2 shows the copper and iron contents of the kidneys of F344 and LEC rats. The copper content was higher in LEC rats than in F344 rats in week 64 ($P<0.001$), but the iron content was similar in the two strains. The decrease of the copper content in the kidney in weeks 91–118 may be related to the decrease in that in the liver (data not shown). Iron deposition in the kidney of LEC rats was not so marked as that in the liver and was similar to that in F344 rats except in some aged LEC rats (data not shown).

Spontaneous kidney tumors are rare in rodents. The incidence of spontaneous tumors (renal cell adenomas and carcinomas) is higher in male rats than in females, but was found to be only 0.3–0.6% in F344 rats,[7-10] 0.3% in Osborne-Mendel rats[11] and 0.1–1.2% in Sprague-Dawley rats[10,12] in two-year carcinogenicity studies. Eker rats, on the other hand, have been used as a hereditary renal cell carcinoma model, as they develop multicentric renal cell tumors spontaneously at high inci-

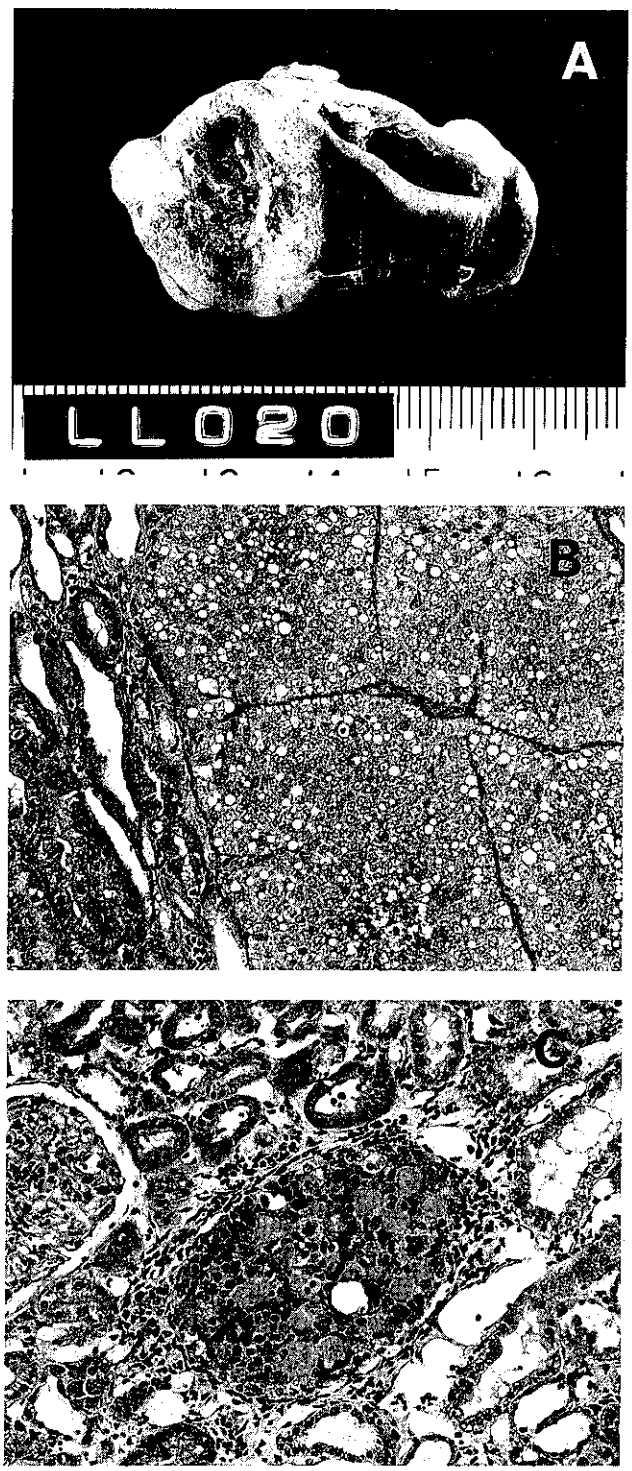

Fig. 1. Gross and histological appearances of kidney tumors in LEC rats. (A) Gross appearance of a kidney tumor (113-week-old male), (B) histological appearance of a renal cell carcinoma (112-week-old male, ×150), and (C) a renal cell adenoma (113-week-old male, ×150)

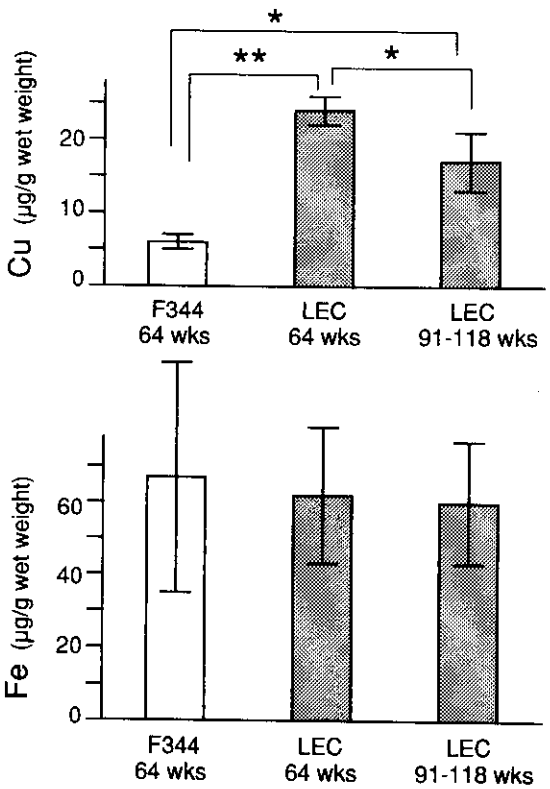

Fig. 2. Renal copper and iron contents in male F344 (n=3) and LEC (n=5) rats of 64 weeks old and male LEC rats (n=5) of 91–118 weeks old. *, $P<0.01$; **, $P<0.001$.

dence by one year of age.[13, 14] The incidence and multiplicity of renal tumors in LEC rats are lower than those in Eker rats and these tumors in LEC rats develop later in life. The incidence of renal tumors of LEC rats in this study was higher than that of Kawano *et al.*[6] We suppose that the difference may be due to the difference of the observation period, because they observed rats up to 85 weeks, but renal tumors mostly developed later than 90 weeks of age in our study.

In this study, we used F344 rats as controls. The LEA rat, one of the two inbred strains isolated from a closed colony of Long-Evans rats, has also been used as a control. There is no report of spontaneous liver or kidney neoplasms in LEA rats, and the copper contents of the kidneys were similar in LEA rats[5] and F344 rats in this study.

The present data suggest that 1) the LEC rat is a useful model of metal-induced renal carcinogenesis; and 2) copper toxicity is an important factor in renal carcinogenesis in LEC rats. The amount of 8-hydroxydeoxyguanosine in DNA, a marker of oxygen-derived DNA damage,[15] is increased in the liver and kidney of young

Table I. Incidence of Spontaneous Kidney Tumors in LEC Rats

Age (weeks)	Sex	No. of rats	No. of rats with liver tumors[a]	No. of rats with kidney tumors	Renal cell tumors	
					Adenomas	Carcinomas
57–65	M	56	27 (48%)	3 (5%)	1 (2%)	2 (4%)[c]
	F	24	9 (38%)	3 (13%)	3 (13%)	0
66–75	M	12	6 (50%)	2 (17%)	2 (17%)	0
	F	7	5 (71%)	1 (14%)	1 (14%)	0
76–105	M	7	7 (100%)	2 (29%)	1 (14%)	1 (14%)[d]
	F	1	1 (100%)	1 (100%)	0	1 (100%)
106–118	M	10	10 (100%)	5 (50%)[b]	3 (30%)	3 (30%)[e]
	F	2	2 (100%)	2 (100%)	2 (100%)	0

a) Hyperplastic nodule, hepatocellular carcinoma and cholangiocellular carcinoma.
b) One rat had an adenoma and a carcinoma.
Gross renal cell carcinomas were *c*) 35 mm (63 weeks), 6 mm (65 weeks), *d*) 10 mm (99 weeks), *e*) 15 mm (112 weeks) and 30 mm (113 weeks) in diameter. The other two were microscopic in size.

and old LEC rats[16] and the Cu, Zn-superoxide dismutase levels in LEC rats are lower than those in Wistar rats, especially in the liver and kidney.[17] These data suggest that oxygen radicals may have a carcinogenic effect in LEC rat kidney. Iron accumulation in the kidney was similar in LEC rats and F344 rats in our study, but further investigation is warranted because iron is a potent inducer of oxygen radicals and iron deposition was prominent in some aged LEC rats.

(Received January 20, 1994/Accepted March 2, 1994)

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