

## Feline Mammary Carcinoma: A Retrospective Evaluation of 17 Cases

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### SUMMARY

Seventeen biopsies of feline mammary carcinoma submitted to the Veterinary Pathology Laboratory, Nova Scotia Department of Agriculture and Marketing were reviewed. All 17 cases were female cats. Data on age, reproductive status (sexually intact vs. neutered), therapy, outcome of the cases and histological features were consistent with data on feline mammary carcinoma previously reported. Four of these 17 cats had a history of receiving exogenous progestin prior to tumor development. The possible role of progestins as initiators or promoters of feline mammary carcinoma was discussed. The use of feline mammary carcinoma as a model for carcinoma of the breast in women was reviewed.

**Key words:** Feline, mammary gland, neoplasia, carcinoma, animal model.

### RÉSUMÉ

#### Étude rétrospective de 17 épithéliomas mammaires félines

Cet article rapporte l'étude rétrospective de 17 épithéliomas mammaires de chattes, soumis sous la forme de biopsies chirurgicales au laboratoire de pathologie vétérinaire du ministère de l'agriculture de la Nouvelle-Écosse.

Les données relatives à l'âge et à l'intégrité sexuelle des chattes, au traitement et à l'issue des néoplasmes, ainsi qu'à leur aspect microscopique, ressemblaient à celles que contient déjà la littérature vétérinaire. Quatre des 17 chattes avaient reçu de la progestérogène avant le développement de leurs tumeurs mammaires. Les auteurs commentent le rôle possible de la progestérogène dans la genèse des épithéliomas mammaires de la chatte, ainsi que leur utilisation comme modèle pour l'étude du cancer du sein de la femme.

**Mots clés:** chatte, glande mammaire, néoplasie, épithélioma, modèle animal.

### INTRODUCTION

The epidemiology, clinical characteristics and prognostic factors of feline mammary tumors are well described (2,3,9,10,17,23). Most feline mammary tumors are malignant and occur in sexually intact females ten years old or older (10,17). Siamese cats are reported to have twice the risk of developing mammary carcinoma as all other breeds combined (10). Cats with mammary carcinoma which are treated only by surgical excision of the tumor(s) have a poor prognosis with a

postsurgical survival period averaging only 7.7 months (23). The etiology of these highly malignant tumors has not been determined. Virus-like particles have been identified morphologically and immunologically in feline mammary carcinomas, but their role as causative agents has not been established (22). For several reasons, considerable attention has been focused on reproductive hormones as a possible cause of feline mammary carcinoma. The overwhelming majority of cases of feline mammary carcinoma occur in females (10). Indeed, sexually intact female cats have been found to have a sevenfold higher risk of developing mammary carcinoma than neutered females (3). The feline mammary gland has been shown to respond to progesterone with abnormal hypertrophy (8) and there have been reports of mammary carcinoma developing in three female cats given progestins for 30 weeks, three years and 5.5 years (11,19). Progestins are also known to enhance the growth of mammary tumors in other nonhuman species including rats and dogs (12,15,18,25).

This report documents the occurrence of mammary carcinoma in 17 cats, four of which had previously received progestin therapy.

## MATERIALS AND METHODS

Case records of submissions to the Veterinary Pathology Laboratory, Nova Scotia Department of Agriculture and Marketing for the period January 1982 to January 1984, inclusive, were reviewed. Seventeen cases of feline mammary carcinoma, including both excisional and incisional biopsies, were found. All biopsies had been fixed in 10% neutral-buffered formalin, trimmed, processed in an automatic tissue processor, sectioned at 6  $\mu$  and stained with hematoxylin and eosin. All tissue sections from these cases were retrieved and reviewed. Additional sections were cut from the paraffin blocks and stained when necessary. After the diagnosis of mammary carcinoma was confirmed, the practitioners submitting the biopsies to the laboratory were surveyed to obtain additional data.

## RESULTS

### Anamnesis

Breed, age, sex, previous progestin treatment and method of tumor

Category	No. of Cats	Age (yrs) <sup>a</sup>		
		Range	Mean	$\pm$ S.D. <sup>b</sup>
All cats	17	4-17	10.5	3.3
All sexually intact cats	9	6-17	11.2	3.7
All neutered cats	8	4-13	9.6	2.7
Cats with prior progestin treatment	4	9-12	9.8	1.5
Cats without prior progestin treatment	11	4-17	10.7	3.8
Cats with unknown history of prior progestin treatment	2	10-15	12.5	3.54

<sup>a</sup> Calculations made using Hewlett-Packard 97 calculator and basic statistics program, HP-67/HP-97, Clinical Lab and Nuclear Medicine Pac, Hewlett-Packard Co., 1976.

<sup>b</sup>  $\pm$  Standard deviation.

treatment for these 17 cats are given in Table I. Eleven of these 17 cats were identified as domestic short-hair, one as domestic long-hair, two as Siamese, one as Himalayan and the breed was not given for two cats. The cats ranged in age from 4-17 years with an average age of 10.5 years (Table II). All 17 cats were female with eight being neutered and nine being sexually intact. Of five cats neutered before developing their

mammary tumors, four were neutered at less than and one at more than two years of age. Two cats were neutered after developing mammary carcinoma. The relationship between age when neutered and age when mammary carcinoma developed was not known for one cat. Four cats receiving progestin treatment prior to developing mammary carcinoma ranged from nine to 12 years of age with an average

TABLE I  
CLINICAL DATA ON 17 CATS WITH MAMMARY CARCINOMA

Case No.	Breed	Age (yrs)	Sex	Previous Progestin Treatment	Treatment	Outcome of Case	Follow-up (months)
1	DLH <sup>a</sup>	12	F(N) <sup>d</sup>	YES	S <sup>f</sup>	B <sup>i</sup>	1
2	DSH <sup>b</sup>	9	F(N)	YES	S	E <sup>l</sup>	4
3	DSH	15	F <sup>c</sup>	NO	S	A <sup>h</sup>	0
4	SIAMESE	10	F(N)	UKN	UKN	C <sup>j</sup>	2
5	DSH	9	F(N)	NO	COMB <sup>g</sup>	C	6
6	UKN <sup>c</sup>	12	F	NO	S	D <sup>k</sup>	10
7	HIMALAYAN	11	F(N)	NO	S	E	10
8	UKN	9	F	NO	S	A	0
9	DSH	8	F	NO	S	UKN	— <sup>m</sup>
10	DSH	4	F(N)	NO	S	D	7
11	DSH	6	F	NO	S	UKN	—
12	DSH	17	F	NO	S	UKN	—
13	SIAMESE	10	F	NO	S	D	7
14	DSH	9	F(N)	YES	S	D	6
15	DSH	15	F	UKN	S	UKN	—
16	DSH	13	F(N)	NO	S	D	2
17	DSH	9	F	YES	S	D	0

<sup>a</sup> Domestic long-hair

<sup>b</sup> Domestic short-hair

<sup>c</sup> Unknown

<sup>d</sup> Female, neutered

<sup>e</sup> Female, sexually intact

<sup>f</sup> Surgery only

<sup>g</sup> Combination surgical and medical

<sup>h</sup> Euthanasia

<sup>i</sup> Died, cause of death other than tumor

<sup>j</sup> Died, cause of death was tumor

<sup>k</sup> Survivor, no recurrence of tumor

<sup>l</sup> Survivor, recurrence of tumor

<sup>m</sup> Lost to follow-up

TABLE III  
SUMMARY OF CLINICAL DATA ON FOUR CATS RECEIVING PROGESTIN THERAPY PRIOR TO DEVELOPMENT OF MAMMARY CARCINOMA

Case No.	Drug	Dosage	Duration	Age Neutered	Time from neutering until Tumor Development
1	Megestrol acetate	5 mg SID x 5, then 5 mg q 7 days prn	Intermittently for several years	0.5 yr	11.5 yr
2	Megestrol acetate	5 mg SID x 5, then 5 mg q 7 days prn	2 months	0.5 yr	8.5 yr
14	Megestrol acetate	Unknown	Sporadic, not in last 3 years	2.0 yr	7.0 yr
17	Megestrol acetate	2.5 mg q 3-4 days prn	3.5 yrs	Not neutered	NA <sup>a</sup>

<sup>a</sup> Not applicable.

age of 9.8 years. Ages of 11 cats known to not have received progestins before mammary carcinoma developed were four to 17 years and averaged 10.7 years (Table II).

#### Clinical Findings

Fifteen of these 17 cats were treated only by surgical excision of the tumor and one received a combination of surgical and medical treatment. The nature of the medical treatment was not available (Table I). Data on tumor metastasis is incomplete as none of the cats had been necropsied, although physical examination and thoracic radiography revealed distant metastases in two cats. Two cats were euthanized after diagnosis and one cat died due to trauma one month after diagnosis of mammary carcinoma (Table I). Owners of two cats declined any treatment for their cats' tumors. These two cats died at home at two and six months after diagnosis. Six cats were alive without recurrence of tumor at one to ten months postsurgery. Two cats were alive but had tumor recurrence at four and ten months after the initial diagnosis and four cats were lost to follow-up (Table I).

All four cats known to have received progestin prior to developing mammary carcinoma had been given megestrol acetate.<sup>1</sup> Available information about dosage and duration of megestrol administration is given in Table III. Both owners and veterinarians varied the dosage and duration of megestrol administration based on the clinical

response of the condition for which the megestrol acetate had been initially prescribed. One cat had not received megestrol acetate within the three years immediately preceding development of its' tumor. One of these four cats was sexually intact and the remaining three developed their tumor 11.5, 8.5 and seven years after being neutered (Table III).

#### Histopathology

Using the classification scheme of Hampe and Misdorp (7), nine of these 17 mammary tumors were classified as

tubular adenocarcinomas, three as papillary cystic adenocarcinomas, four as solid carcinomas and one as mixed solid and tubular adenocarcinoma. There was variation in histological appearance between the different areas examined in most of the tumors (Figure 1).

#### DISCUSSION

The cases included in this report have features that are consistent with those previously reported for feline mammary tumors. All 17 cats in this study had malignant tumors, i.e. mammary

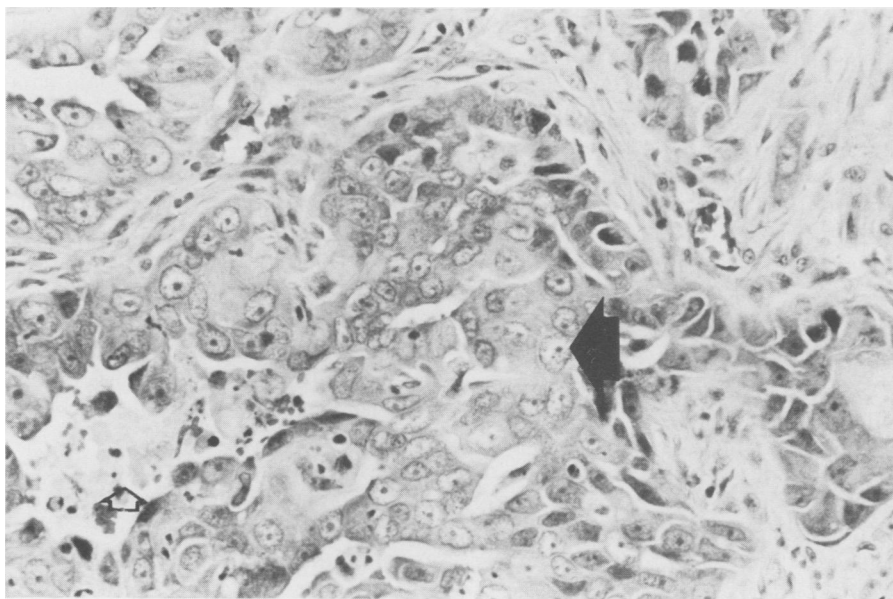


FIGURE 1. This example of a tubular adenocarcinoma from a feline mammary gland demonstrates a large duct almost filled with neoplastic epithelial cells (solid arrow). The small lumen (open arrow) contains debris from necrotic tumor cells. H & E. X160, original magnification.

<sup>1</sup>Ovaban Tablets, Schering Canada, Inc., Pointe Claire, Quebec.

carcinoma. Most cats with mammary carcinoma are ten years old or older (10,17). Nine of these 17 cats were ten years old or older and their average age was  $10.5 \pm 3.3$  years (Table I). The average age of sexually intact cats was similar to that of neutered cats ( $11.2 \pm 3.7$  years vs  $9.6 \pm 2.7$  years, Table II). The same was true when cats that received megestrol acetate prior to tumor development were compared to cats that did not ( $9.8 \pm 1.5$  years vs  $10.7 \pm 3.8$  years, Table II).

Sexually intact cats are reported to have a sevenfold higher risk of developing mammary carcinoma than are neutered cats (3). At the time of tumor diagnosis, eight of these 17 cats were indicated to be neutered. Three cats were neutered after their tumor developed, leaving five cats that had been neutered prior to tumor development. Three of these five cats had received megestrol acetate prior to tumor development. Thus only two of these 17 cats had been neutered and had not received megestrol acetate prior to tumor development. Even though this group of cats is small, this finding suggests a possible role for megestrol acetate in the etiology of feline mammary carcinoma.

The breed distribution of all feline submissions to the laboratory could not be determined. Thus, it was not possible to determine whether any breed was over or under-represented in this group of cats.

Hernandez *et al* (11) first reported the occurrence of mammary carcinoma in cats receiving a progestin for long periods. They reported the occurrence of mammary carcinoma in two of five cats receiving medroxyprogesterone acetate for periods of three and 5.5 years. Subsequently, Oen (19) reported the occurrence of mammary carcinoma in one of 397 cats given 2.5 mg megestrol acetate once weekly for at least 30 weeks. The present report documents the occurrence of mammary carcinoma in an additional four cats that had previously received megestrol acetate. Anecdotal reports such as these do not establish a cause and effect relationship between progestins and mammary carcinoma in cats. They do, however, clearly indicate the need for further study of the possible etiological role of progestins in feline mammary carcinoma. This is

important to veterinary clinicians because progestins are widely used to treat behavioral problems and skin conditions in cats. Endocrine therapy (both additive and ablative), based on tumor content of estrogen and progesterone receptors (ER, PR) is of value for the treatment of carcinoma of the breast in women (1,16). Further study of the role of progestins in feline mammary carcinoma might suggest a clinically useful hormone therapy for this devastating feline disease.

In species in which it has been studied, normal mammary gland development is dependent upon prolactin, estrogen and progesterone, as well as other factors (5,14). Although no studies detailing normal development of the feline mammary gland could be found in the literature, it seems unlikely that hormones would not play a role in feline mammary development. This view is supported by circumstantial evidence. Feline mammary hypertrophy (FMH), a benign proliferation of both epithelial and stromal elements of the mammary gland, has been shown to be a response to either exogenous or endogenous progestin in the intact female cat and to exogenous progestin in neutered males and females (8). It is also known that sexually intact female cats have a much greater risk of developing mammary carcinoma than do neutered females (3,10) and that mammary carcinoma is rare in male cats (3,9). In addition, there are the previously mentioned anecdotal reports of mammary carcinoma developing in female cats receiving exogenous progestin for the prevention of estrus (11,19). Finally, progestins are known to influence the occurrence of proliferative lesions in the mammary glands of other species including chemically induced carcinomas in rats (12) as well as hyperplastic and neoplastic lesions in dogs (15,18,25).

Steroid hormones normally exert their effects by binding to intracellular hormone receptors (16). In those mammalian systems studied, estrogen and ER are the inducers of PR in mammary gland (20). Among 53 feline mammary carcinomas evaluated for ER but not for PR, only two were found to contain ER (6,21). Only Johnston *et al* (13) have examined feline mammary carcinomas for both

ER and PR. In their series of seven cases, none had ER and all seven had PR. One tumor reported to contain PR was not evaluated for ER (4). Mammary tissue from two cases of FMH was reported to contain PR but not ER (8). This data indicates that feline mammary tissue contains the receptors necessary for it to respond to progestins. However, the role of estrogen and ER in the development of the normal feline mammary gland must be defined before the role of progesterone and PR in development of mammary carcinoma can be fully understood.

Feline mammary carcinoma has been proposed as a model for carcinoma of the breast in women based primarily on similarities in histological features, response to surgery and clinical behavior of these tumors in cats and women (17,24). There is a statistically significant correlation between ER and PR content and response to therapy in carcinoma of the breast in women (1). However, about 70% of cases of breast carcinoma in women contain ER while ER have been found in only two of 60 cases of feline mammary carcinoma (6,13,17,21). Perhaps feline mammary carcinomas thought to be ER- and PR+ do contain ER, as has been suggested in some ER- carcinomas of the breast in women where failure to detect ER may be due to methodological techniques employed (20). Thus, clarification of the role of estrogen, progesterone, ER and PR in feline mammary carcinoma is necessary to better define this tumor as a model for human mammary carcinoma.

The cases included in this report have features that are consistent with those previously reported for feline mammary carcinoma. The history of previous progestin therapy in four of these cats, three of which were neutered before two years of age, is further anecdotal evidence suggesting a role of progestins as either initiators or promoters of these highly malignant tumors. Further definition of the role of hormones and hormone receptors in the normal feline mammary gland and in feline mammary carcinomas may provide a sound basis for therapy of these devastating tumors.

#### ACKNOWLEDGMENTS

The authors sincerely appreciate the cooperation of all the practitioners in

gathering data for this paper and for their thought provoking questions.

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