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Association between Ovarihysterectomy and Feline Mammary Carcinoma

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The etiopathogenesis of feline mammary carcinoma is not well understood. Although putative, risk factors include breed, reproductive status, and regular exposure to progestins. An association between age at ovarihysterectomy (OHE) and mammary carcinoma development has not been established. Therefore, a case-control study was performed to determine the effects of OHE age, breed, progestin exposure, and parity on feline mammary carcinoma development. Cases were female cats diagnosed with mammary carcinoma by histological examination of mammary tissue. Controls were female cats not diagnosed with mammary tumors selected from the same biopsy service population. Controls were frequency matched to cases by age and year of diagnosis. Questionnaires were sent to veterinarians for 308 cases and 400 controls. The overall questionnaire response rate was 58%. Intact cats were significantly overrepresented (odds ratio [OR] 2.7, confidence interval [CI] = 1.4–5.3, $P < .001$) in the mammary carcinoma population. Cats spayed prior to 6 months of age had a 91% reduction in the risk of mammary carcinoma development compared with intact cats (OR 0.9, CI = 0.03–0.24). Those spayed prior to 1 year had an 86% reduction in risk (OR 0.14, CI = 0.06–0.34). Parity did not affect feline mammary carcinoma development, and too few cats had progestin exposure to determine association with mammary carcinoma. Results indicate that cats spayed before 1 year of age are at significantly decreased risk of feline mammary carcinoma development.

Key words: Cancer; Cat; Neoplasia; Spay.

Feline mammary tumors are the third most frequently diagnosed neoplasm in the cat, after skin tumors and hematopoietic tumors.[1,2] Mammary tumors occur primarily in middle-aged to older female cats, with an average age at diagnosis of 10–12 years.[3] Previous studies also suggest a breed-associated risk of mammary neoplasms in Siamese and domestic short-hair cats.[3,4] Eighty to 96% of feline mammary tumors are malignant, and most are carcinomas.[5–7] Feline mammary carcinomas locally infiltrate mammary and surrounding tissues. They metastasize frequently to regional lymph nodes and lungs and occasionally to other organs.[4,8] Median survival times are usually less than 1 year, and tumor size is considered the most significant prognostic feature.[3,9]

Feline mammary carcinoma primarily affects female cats, and it is assumed that estrogen and progesterone play an important role in feline mammary tumor development. However, the role hormones play in the etiopathogenesis of these tumors in cats is still not well understood. Previously published studies suggest that the endocrine environment is at least partly responsible for feline mammary carcinoma development. Specifically, these studies indicate that intact cats and cats exposed to regular progestin use have an increased risk of feline mammary carcinoma. Some studies also indicate that ovarihysterectomy (OHE) may be protective against mammary-gland tumor development in the cat.[2,4,10] In 1 study, cats ovariectomized at 6 months of age had an approximately 7-fold reduced risk of mammary tumor formation compared with intact cats.[2] None of these studies included age-matched controls for comparison and none specifically addressed the effects that differing ages at the time of OHE might have on the risk of feline mammary carcinoma development.

Studies in multiple species show that estrogen, progesterone, prolactin, and growth hormone affect growth of both normal and neoplastic mammary tissue.[11–16] Prolonged sex-steroid exposure induces proliferation of mammary epithelial cells and facilitates the accumulation of genetic errors that result in neoplasia in later life.[11,13,17,18] It is hypothesized that, under the influence of hormones, a mammary neoplasm starts as hyperproliferation of epithelial tissue and progresses to a preneoplastic state, which grows and eventually breaches the basement membrane, transforming into an invasive carcinoma.[12,13]

The risk of developing a mammary tumor is determined by the duration of hormonal exposure in other species, including the dog, mouse, and human.[19,20] In humans and mice, proliferative activity of the mammary epithelium varies with the degree of mammary-tissue differentiation and the number of hormone receptors present, with most cellular proliferation occurring in hormone-receptor rich, undifferentiated lobules of young, nulliparous females.[12] Studies performed in other species show that early OHE significantly protects against the risk of mammary tumor development.[12,13,19] In 1 study, dogs spayed prior to the first estrus cycle had only 0.5% the risk of mammary tumor development compared with the intact dog. Dogs spayed after 1 cycle had 8% of the risk. Dogs spayed after 2 or 3 cycles had 26% of the risk, and dogs spayed after 4 or more cycles or after 2.5 years of age had no protective effect.[19] These results indicate that overall risk of mammary tumor development is predetermined in the dog by 2.5 years of age. The goal of the current study was to evaluate the influence of age of OHE, parity, and progestin exposure on the risk of feline mammary carcinoma development.

Materials and Methods

We designed a case-control study to test for associations between selected factors and the development of feline mammary carcinoma to assess the contribution of these factors to carcinoma development.

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Table 1. Influence of spay age on the risk of feline mammary carcinoma development.

Factor	Cases		Controls		Odds Ratio	95% Confidence Interval	Risk Reduction
	N	%	N	%			
Intact[a]	41	27	17	13	—		—
<6 months	11	7	49	37	0.09	0.03–0.24	91%
7–12 months	16	11	46	35	0.14	0.06–0.34	86%
13–24 months	28	19	13	10	0.89	0.35–2.3	11%
>24 months	54	36.0	6	5	3.7	1.3–12.5	No benefit

[a] Reference group for odds ratio comparisons.

Specifically, we wanted to evaluate the effects of spay status, age of spay, breed, parity, and exogenous progestin use on the risk of mammary carcinoma development in the cat. The case population included female cats histopathologically diagnosed with feline mammary carcinoma by the outpatient biopsy service at the Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania from 2000 to 2001. All cases were reviewed and confirmed to have a histopathologic diagnosis of feline mammary carcinoma by a single pathologist (MHG). The control population included female cats diagnosed with a condition other than mammary carcinoma or other type of mammary lesion by the same biopsy service from 2000 to 2001. Controls were frequency matched by year of diagnosis to ensure similarities both in ascertainment of accessions and in veterinary practices. Controls were also frequency matched by age to avoid a younger control group, as feline mammary carcinoma is a disease of older cats (median age 10–12 years). The frequency matching was accomplished by stratifying cases into 5 strata for age (<4, 4–8, 9–12, 13–15, >15) and 2 strata for year of diagnosis (2000 and 2001) and choosing controls in the corresponding strata in the same proportion as cases in that strata.

Data about cases and controls were obtained through biopsy reports, mailed questionnaires, phone interviews, and review of medical records. Questionnaires, which requested information about the patient's sex, age, breed, exogenous progestin exposure, OHE status, age at OHE, parity, number of litters, and tumor type were initially sent to referring veterinarians. Further information was obtained through phone interviews with owners and by review of medical records as needed. When discrepancies arose in information obtained from medical records, veterinarians, and owners, veterinary records were assumed to be correct for medical data.

Because cats are seasonally polyestrous, counting estrous cycles is difficult, if not impossible. To evaluate the influence of the timing of OHE on feline mammary carcinoma development in this study, cats in the mammary carcinoma population were divided into groups according to age at spay, instead of the number of heat cycles, to evaluate the effect of OHE age on mammary carcinoma development. Most cats begin to cycle around 5–7 months of age, and it was assumed that most cats would have had, at most, one cycle at 6 months of age. Five groups were evaluated: cats spayed prior to 6 months, cats spayed between 6 months and 1 year, cats spayed from 13 to 24 months, cats spayed after 2 years of age, and intact cats. When evaluating the effects of spay age on feline mammary carcinoma development, cats were excluded from statistical analysis if the spay age could not be determined from the information provided.

To determine differences between cases and controls for categorical data, the chi-square test or Fisher's exact test was used. The Student's *t*-test or the Wilcoxon rank sum test was used for continuous data. When applicable, data were presented as odds ratios (OR) with 95% confidence intervals (CI). A $P < .05$ was considered statistically significant. Data were analyzed using SAS[a] statistical software.

Results

Review of biopsy service records showed that 308 cats diagnosed with feline mammary carcinoma were eligible for inclusion in the case population. Four hundred controls were randomly selected from the same biopsy service and frequency matched to cases as previously described. Of the 400 controls, 11 were excluded because they were dogs (N = 1), male (N = 2), previously diagnosed with a mammary tumor (N = 1), or duplicate biopsies from the same patient (N = 7). Sixty percent of controls were diagnosed with either benign or malignant tumors of organs other than the mammary gland, 20% were diagnosed with non-tumor–related dermatological disease, and the rest of the controls were diagnosed with a variety of other conditions. The mean age at biopsy date for cats in the study was 11.4 years and did not significantly differ ($P = .4$) between cases (median = 12, range = 1–20) and controls (median = 12, range = 1.5–21.5). Domestic short- and long-hair cats were equally represented in both populations (79% versus 76% and 8% versus 10%, for cases versus controls, respectively). Siamese cats were overrepresented in the mammary carcinoma population, but this difference was not statistically significant (OR 2.0; 95% CI = 0.9–4.3; $P = .06$). Siamese cats comprised 7% (N = 21) of cases and 3% (N = 14) of controls.

Questionnaire information was successfully obtained for 66% of cases (N = 204) and 51% of controls (N = 200). There was an overall questionnaire response rate of 58% (N = 404). There were 58 cats that were intact, and 346 were spayed. Of those that were spayed, the age of OHE was known for 64% (N = 223), of which 67% were cases (N = 109) and 62% were controls (N = 114). Intact females represented 27% (N = 41) of cases and 13% (N = 17) of controls. Intact cats were at increased risk of having mammary carcinoma (OR 2.7, 95% CI = 1.4–5.3, $P < .001$). Additionally, cats in the case population were significantly older at the time of OHE compared with controls. Median age of OHE in the case population was 48 months compared with 8 months in the control population ($P < .0001$).

Stratification by spay age revealed a significant protective effect for cats spayed prior to 1 year of age (Table 1). Data showed that cats had a 91% reduction in the risk of developing a feline mammary carcinoma if spayed prior to 6 months of age (OR = .09, 95% CI = 0.03–0.24) and an 86% reduction in risk if spayed prior to 1 year of age (OR = .14, 95% CI = 0.06–0.34) compared with intact cats. In other words, cats spayed prior to six months of age and cats spayed after six months but prior to one year of age had only 9% and 14%, respectively, of the risk of mammary carcinoma development compared with intact cats. Data also indicated a small and insignificant protective effect

Table 2. Summary of risk factors for feline mammary carcinoma.

Risk Factor	Cases		Controls		Odds Ratio	95% Confidence Interval	*P*-Value
	N	%	N	%			
Breed[a]							.02
Domestic long hair	25	8	37	9			
Domestic short hair	240	79	295	76			
Persian	8	3	10	3		0.9–0.43	
Siamese[b]	21	7	14	4	2.0		.06
Other purebred	10	3	33	8			
Intact females	41	20.1	17	8.5	2.7	1.4–5.3	<.0001
Number of litters[c]							.01
None	31	53	37	77			
1 litter	9	16	8	17			
2 liters	12	21	3	6			
>2 litters	6	10	0	0			
Ovarihysterectomy age (months)[d]	48		8				<.0001

[a] Based on data from biopsy reports for 697 cats.
[b] Siamese cats compared with all other breeds.
[c] Excludes cats spayed before 6 months of age.
[d] Presented as median with interquartile ranges.

(11%) if cats were spayed between 13 and 24 months of age (OR = .89, 95% CI = 0.35–2.3). OHE performed after two years of age increased the risk of feline mammary carcinoma development when compared with intact cats (OR = 3.7, 95% CI = 1.3–12.5).

Of all of the cats spayed after 6 months of age, cats diagnosed with feline mammary carcinoma were more likely to have had litters (N = 27; 37.5%) compared with controls (N = 11; 10.9%). However, when stratified by spay age, this effect disappeared. Only 6 cats (5 cases, 1 control) had reported exposure to exogenous progestins, so the numbers were too small to perform statistics on this risk factor. Results for the risk factors evaluated in this study are presented in Table 2.

Discussion

Oophorectomy in mice has a sparing effect on mammary tumor occurrence, and this effect decreases as age of oophorectomy increases.[11] Similarly, the risk of mammary tumor development in dogs increases with number of estrous cycles prior to OHE.[19] Dogs spayed prior to the 1st estrus, prior to the 2nd estrus, and after the 2nd estrus but before the 3rd had 0.5, 8, and 26% the risk of mammary tumor development, respectively, compared with intact dogs. The current study shows that, in cats, as in dogs, a gradated loss of protection occurs with increasing hormonal exposure prior to OHE.

The current study indicates that the duration of exposure to estrogen and progesterone is as important in the cat as it is in other species. It is still not shown, however, whether estrogen and progesterone act to promote mammary carcinoma development via the same molecular mechanisms in cats as in other species. Previous studies indicate that feline mammary tumors express fewer estrogen receptors than canine or human mammary tumors, and it is unclear whether estrogen, progesterone, or a combination of the two plays a more important role in the development of feline mammary carcinoma.[15,21–24]

Findings in the current study concur with an earlier study that showed that intact cats were 7 times overrepresented in a population of cats diagnosed with mammary tumors compared with a control population.[10] This study included benign and malignant mammary tumors, was performed in a different country, and used a control population that included healthy young cats. Several cats in the study received exogenous progestins on a regular basis, which increased risk of mammary tumor development.[10] In the current study, too few cats were exposed to exogenous progestins to permit statistical analysis.

One potentially surprising finding from this study was that data showed that cats spayed after 2 years of age had a statistically significant increased risk of feline mammary carcinoma development compared with intact cats. This result more likely reflects the fact that very few cats (5.3%) in the spayed control population were spayed after 2 years of age compared with 49.5% of spayed feline mammary carcinoma cases rather than a true increase in feline mammary carcinoma risk.

Parity was also evaluated as a risk factor for feline mammary carcinoma development. The human literature indicates that having children at a young age and/or having multiple births decreases the risk of mammary tumor development.[25] Parity has not been shown to be a risk factor for mammary tumor development in cats, and the influence of age at first pregnancy or of multiple litters has not been evaluated.[10] Canine studies have also not found parity or age at first pregnancy to be associated with a decreased tumor risk.[26,27] In the current study, more cats diagnosed with feline mammary carcinoma had litters than those that did not. However, the difference disappeared when cats were stratified by spay age. It must be assumed that more cats had litters in the case population because the cats had more time to have litters. Few cats in the control population

had 2 or more litters (N = 3), and the potential protective influence of multiple litters could not be determined.

Weaknesses of the study include its retrospective nature and the use of information from cases treated through private practitioners. The questionnaire response rate was 58%, and from those responses, adequate information to evaluate the effects of age at spay on the risk of feline mammary carcinoma was available for 70%. Known reasons for the 58% questionnaire response rate included noncompliance, confusion over why controls were questioned about mammary carcinoma, inability to contact owners, and inadequate record keeping. Reasons for incomplete information included the additional factor that many cats were adopted after spay and the age of spay could not be determined. Incomplete information can lead to bias. However, the current study included a large population of cats treated at over 30 hospitals, which makes it less likely that these factors significantly affected results.

Strengths of this study include the large number of cats and the use of a frequency-matched control population selected from the same biopsy service. Selection of controls from a population similar to that of the case population minimizes variation due to both geographical region and the behavior of owners in regard to veterinary treatment for their cats. Using a control population similar in age to the case population strengthened the results because it eliminated age as a confounding factor. Both populations were already at the age at which mammary carcinoma development would be expected to occur and controls were excluded if they had ever been diagnosed with a mammary tumor, which made it unlikely that a significant number of control cats would develop mammary carcinoma in the future.

Footnotes

[a] Version 8.2, SAS Institute, Cary, NC

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