MAMMARY CANCER IN CAPTIVE WILD FELIDS AND RISK FACTORS FOR ITS DEVELOPMENT: A RETROSPECTIVE STUDY OF THE CLINICAL BEHAVIOR OF 31 CASES


Abstract: This retrospective study was initiated because of the perceived high incidence of mammary gland cancer in zoo felids in which progestin contraception has been used. Our purpose was to describe the clinical behavior of these tumors and identify risk factors for their development. Clinical and historic records were reviewed from 31 captive wild felids with palpable and histologically confirmed mammary gland neoplasia. All mammary masses were classified histopathologically as carcinomas, with cribiform, solid, cyst-papillary, and adenocarcinoma patterns. Thoracic radiography was a sensitive antemortem procedure to detect metastases. Although other abnormalities (anorexia/lethargy, ventral mass or ulcer visible, anemia, neutrophilia, hypercalcemia, or azotemia) were noted, concurrent geriatric diseases often confounded clinical interpretation. Therefore, these findings were not specific for a diagnosis of cancer. Metastases were most common in lymph node, lung, and liver. Mammary cancer was most common in animals that had been implanted with melengestrol acetate (MGA)-impregnated silastic devices \( n = 29, 94\% \). This association was statistically significant \( P < 0.002 \). There was no significant difference in age at diagnosis of mammary cancer in MGA-treated felids \( \bar{x} \pm SD = 13.87 \pm 2.60 \) yr versus nontreated felids \( 16.33 \pm 9.49 \) yr. Mammary cancer behaves as aggressively in wild felids as in domestic cats, and long-term exogenous progestin exposure is a risk factor in its development. Zoos using MGA in felids should be cognizant of the strong association between progestin exposure and mammary cancer development and should employ alternative contraceptive methods whenever possible.

Key words: Felids, mammary cancer, melengestrol acetate, contraceptives.

INTRODUCTION

Mammary gland neoplasia in captive wild felids has been reported with increased frequency and concern in recent years, and most of these cases have been malignant.\(^1,3,4,8,18\) Disease surveillance by the Contraceptive Advisory Group of the American Zoo and Aquarium Association (AZA) has shown that exposure to exogenous progestins is a strong risk factor for development of severe endometrial hyperplasia and uterine carcinoma in captive wild felids\(^8,16\) and is a suspected risk factor for development of mammary cancer in domestic\(^9,7,12\) and captive wild\(^13,18\) felids.

Exogenous progestins have been used in
captive felids for contraception, dermatologic treatment, and behavior modification. Melengestrol acetate (MGA) is the most commonly used progesterin contraceptive in these felids, although megestrol acetate (MA, Ovaban®, Schering-Plough Animal Health, Union, New Jersey 07033, USA) and medroxyprogesterone acetate (MPA, Provera®, Pharmacia and Upjohn, Kalama-zoo, Michigan 49001, USA) have also been used. Silicone implants, impregnated with MGA and placed s.c. or i.m., have been the most common devices used for contraception in captive felids over the past 20 yr because of MGA's high potency and efficacy, ease of administration (implant placement once every 2–3 yr), reversible contraceptive effect (upon removal or depletion of the implant), minimal diabetogenic or adrenosuppressive effects, and minimal behavioral effects.\textsuperscript{11,21}

The purposes of this study are to describe the clinical behavior of mammary cancer in captive wild felids, to determine the relative values of diagnostic procedures and clinical findings in the confirmation of malignancy, and to determine whether MGA exposure, species, or nulliparity are significantly associated with occurrence of mammary cancer in captive wild felids.

**MATERIALS AND METHODS**

All U.S. facilities housing wild felids were solicited for historical information regarding occurrence of mammary neoplasia in their felid collections. Responses were collated with cases identified through the AZA Contraceptive Advisory Group's disease surveillance database. Fifty-three felids with mammary neoplasia were identified. Full clinical records were available for 31 of the animals, and these were the basis of subsequent analysis (Table 1).

Histopathologic examination of mammary tissue from all 31 animals was performed by one of us (L.M.) for tumor classification (adenoma vs. carcinoma). All of the mammary masses were carcinomas, and specific histologic patterns were seen in combination in these tumors. Further subclassification and correlation of pattern with clinical behavior was therefore not attempted.

The following factors were examined as potential risk factors for the development of mammary cancer: species (n = 31), parity history (n = 24), contraceptive history (n = 31), and duration of treatment and average dose of MGA (n = 29). Information was also collected regarding clinical signs

### Table 1. Captive wild felids affected by mammary cancer (n = 31).

<table>
<thead>
<tr>
<th>Species</th>
<th>Age at diagnosis (yr)</th>
<th>Average dosage of MGA (mg/kg)</th>
<th>Duration of MGA exposure (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiger (Panthera tigris)</td>
<td>10.0</td>
<td>5.58</td>
<td>115</td>
</tr>
<tr>
<td></td>
<td>12.5</td>
<td>6.19</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>16.2</td>
<td>8.33</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td>15.8</td>
<td>4.46</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>12.3</td>
<td>5.39</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>13.0</td>
<td>6.09</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>14.9</td>
<td>5.17</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>10.8</td>
<td>6.30</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>8.2</td>
<td>5.82</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>20.0</td>
<td>4.12</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>15.0</td>
<td>5.03</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>12.0</td>
<td>4.83</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>11.7</td>
<td>5.23</td>
<td>118</td>
</tr>
<tr>
<td></td>
<td>14.5</td>
<td>7.83</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>15.4</td>
<td>unk\textsuperscript{a}</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>11.6</td>
<td>6.54</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>12.7</td>
<td>5.94</td>
<td>70</td>
</tr>
<tr>
<td>Jaguar (Panthera onca)</td>
<td>15.7</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>16.4</td>
<td>12.49</td>
<td>115</td>
</tr>
<tr>
<td></td>
<td>11.9</td>
<td>12.37</td>
<td>108</td>
</tr>
<tr>
<td></td>
<td>18.1</td>
<td>6.03</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>13.4</td>
<td>10.47</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td>17.0</td>
<td>24.00</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>15.7</td>
<td>12.63</td>
<td>26</td>
</tr>
<tr>
<td>Lion (Panthera leo)</td>
<td>15.0</td>
<td>4.56</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>14.6</td>
<td>6.22</td>
<td>149</td>
</tr>
<tr>
<td>Cougar (Felis concolor)</td>
<td>15.4</td>
<td>9.42</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>17.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Leopard (Panthera pardus)</td>
<td>14.3</td>
<td>11.56</td>
<td>128</td>
</tr>
<tr>
<td>Jungle cat (Felis chaus)</td>
<td>10.0</td>
<td>17.92</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>14.2</td>
<td>30.32</td>
<td>26</td>
</tr>
</tbody>
</table>

\textsuperscript{a} MGA = melengestrol acetate.

\textsuperscript{b} unk = unknown.
Table 2. Species distribution of captive wild felids affected by mammary cancer.

<table>
<thead>
<tr>
<th>Species</th>
<th>No. (%) affected felids in database</th>
<th>No. (%) MGA-treated felids in database</th>
<th>No. felids with confirmed mammary carcinoma (% by species)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiger (Panthera tigris)</td>
<td>48 (28%)</td>
<td>32 (36%)</td>
<td>17 (35%)</td>
</tr>
<tr>
<td>Lion (Panthera leo)</td>
<td>21 (12%)</td>
<td>18 (20%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Jaguar (Panthera onca)</td>
<td>16 (9%)</td>
<td>13 (15%)</td>
<td>7 (44%)</td>
</tr>
<tr>
<td>Leopard (Panthera pardus)</td>
<td>17 (10%)</td>
<td>9 (10%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Cougar (Felis concolor)</td>
<td>9 (5%)</td>
<td>4 (5%)</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>Jungle cat (Felis chaus)</td>
<td>3 (2%)</td>
<td>2 (2%)</td>
<td>2 (67%)</td>
</tr>
</tbody>
</table>

* Age-matched felids from the American Zoo and Aquarium Association Contraceptive Advisory Group's disease surveillance database. Percentage is of total felids in the database (n = 170).
* MGA = megestrol acetate. Percentage is of all contracepted felids in database (n = 89).

P < 0.05.

RESULTS

Comparisons between mammary cancer group and age-matched cohort

The species distribution of felids affected by mammary cancer (n = 31) is similar to that of all nonaffected felids in the disease surveillance database (n = 139), with the exception of tigers and jaguars, which have a higher occurrence of mammary cancer (P < 0.001 and P < 0.01, respectively) (Table 2). In this database, MGA implant usage has tended to be more common in jaguars (P < 0.05) and lions (P < 0.005) than in all other felids for which contraceptive history is known (n = 164).

Comparisons between mammary cancer group and age/species-matched cohort

Mammary cancer occurred more frequently in animals that had been exposed to MGA than in those that had not been exposed (P < 0.002). Twenty-nine (94%) of the 31 cancer-affected animals in this study had been given MGA (Table 1),
Table 3. Sensitivity and specificity of antemortem diagnostic procedures in 31 captive wild felids with mammary gland cancer. Diagnostic procedures were performed 0–14 days before necropsy. For this study, the standard for detection of masses was defined as necropsy results for corresponding anatomical sites.

<table>
<thead>
<tr>
<th>Diagnostic procedure</th>
<th>No. felids tested</th>
<th>No. true positives/ no. false positives</th>
<th>No. true negatives/ no. false negatives</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Test accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracic radiography</td>
<td>10</td>
<td>6/0</td>
<td>3/1</td>
<td>86%</td>
<td>100%</td>
<td>90%</td>
</tr>
<tr>
<td>Thoracic ultrasonography</td>
<td>1</td>
<td>1/0</td>
<td>0/0</td>
<td>100%</td>
<td>—</td>
<td>100%</td>
</tr>
<tr>
<td>Abdominal radiography</td>
<td>3</td>
<td>0/0</td>
<td>0/3</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Abdominal ultrasonography</td>
<td>4</td>
<td>2/0</td>
<td>0/2</td>
<td>50%</td>
<td>—</td>
<td>50%</td>
</tr>
</tbody>
</table>

whereas 48 (63%) of the 76 felids in the nonaffected cohort had been given MGA. MGA exposure was not significantly longer in cancer-affected felids (t ± SD = 74.24 ± 33.85 mo, n = 29) than in those felids without mammary cancer (58.56 ± 37.2 mo, n = 48) (P < 0.08). Mean dosages of MGA for cancer-affected felids (7.53 ± 3.34 mg/kg, n = 27) and nonaffected felids (8.39 ± 4.58 mg/kg, n = 38) also did not differ significantly (P = 0.41).

Comparisons within mammary cancer group

For those felids with mammary cancer, age at time of diagnosis did not differ significantly between MGA-treated and non-treated felids (Table 1). Overall, the mean age at time of diagnosis for nulliparous animals (13.05 ± 1.87 yr, n = 9) did not differ significantly from that for parous animals (14.07 ± 2.29 yr, n = 15) (P = 0.27). Specifically, the mean age at time of diagnosis did not differ significantly between those felids that had experienced pregnancy only before their first MGA exposure (14.38 ± 2.36 yr, n = 8) and those felids that had been pregnant only after MGA exposure (11.17 ± 0.59 yr, n = 2) (P = 0.10), although those felids that were pregnant before MGA treatment tended to be older when cancer was first detected.

Antemortem clinical presentation

Zookeepers and veterinarians noted non-specific clinical signs in the felids of this study. Signs of disease included anorexia/lethargy, vomiting, weight loss, diarrhea, and abdominal distension (58%, 23%, 19%, 6%, and 6% of animals respectively). The more specific signs of mammary skin ulceration, respiratory difficulty due to pulmonary metastasis, or rear leg swelling due to lymphatic obstruction were only seen in a small proportion of the cases (29%, 12%, and 6% of animals, respectively).

Data regarding specific sites and sizes of mammary masses were not available for this study.

Procedures to diagnose and detect metastasis of mammary cancer were initiated at a mean (±SD) of 9.28 (±14.26) days (n = 29) after onset of signs. Antemortem diagnostic techniques included physical examination, thoracic and abdominal radiography and ultrasonography, abdominal magnetic resonance imaging, and hemotologic testing. Definitive diagnosis was accomplished by biopsy or aspiration of a palpable mammary mass or a suspected site of metastasis or by necropsy of those animals that had no premonitory signs.

Thoracic radiography was a sensitive tool for detection of pulmonary metastasis, and all radiographic lesions that were suggestive of cancer were confirmed at necropsy (high specificity) (Table 3). Thoracic radiographs were obtained for 10 animals, and radiographic abnormalities (bronchiolar or nodular patterns) were noted in six of these felids. Thoracic ultrasonography was performed in one animal, and two metastatic nodules were identified in the pulmonary parenchyma. Abdominal radiography was an insensitive test for detection of visceral...
metastasis; abdominal metastases in three animals were not detected by this method (Table 3). Abdominal ultrasonography was more sensitive than radiography for detecting metastasis to liver, kidney, or spleen. However, two other animals had metastasis to several abdominal organs (liver, adrenal gland, ovary, and lymph node) that was not detected by ultrasonography but was confirmed by necropsy.

Seventeen (68%) of the 25 animals in which blood work was performed had one or more hematologic abnormalities. Hypercalcemia was noted in seven (26%) animals, including two with concurrent renal lesions, one with metastasis-related renal lesions, and three without apparent renal lesions (Table 4). Anemia was noted in seven (26%) animals (Table 5); four of these anemias were normocytic in nature, one was microcytic, and one was macrocytic. Neutrophilia was diagnosed in four animals that did not have evidence of inflammatory disease other than mammary cancer; the neutrophil count in these animals was 30,695 (±4,575) neutrophils/µl, and the range of immature neutrophils was 0–4,788 bands/µl.

Renal values (blood urea nitrogen or creatinine) were elevated in two animals because of histologically confirmed renal diseases common in aged felids (cortical atrophy, glomerulonephritis, interstitial nephritis with ischemic necrosis, or pyelonephritis). In two animals, peritoneal carcinomatosis was so severe as to cause ureteral stenosis, hydrourereter, hydronephrosis, and resultant azotemia. One animal with renal metastasis and no other histologically confirmed renal lesions had a creatinine concentration of 4.9 mg/dl.

Hepatic metastases were also associated infrequently with abnormal hepatic values (aspartate aminotransferase, alanine aminotransferase, bilirubin, or bile acids). Nine animals showed hepatic metastasis (without other hepatic lesions) at necropsy, but only two of these animals (out of four from which blood was collected) showed eleva-
Table 5. Selected clinicopathologic findings in seven anemic felids with mammary gland cancer. Reference intervals for each species are noted in parentheses.  

<table>
<thead>
<tr>
<th></th>
<th>Jaguar</th>
<th>Jaguar</th>
<th>Jaguar</th>
<th>Leopard</th>
<th>Tiger</th>
<th>Cougar</th>
<th>Jungle cat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>11.9</td>
<td>15.7</td>
<td>13.4</td>
<td>14.3</td>
<td>15.8</td>
<td>15.4</td>
<td>10.0</td>
</tr>
<tr>
<td>Feline leukemia virus antigen test result</td>
<td>neg</td>
<td>unk*</td>
<td>unk</td>
<td>neg</td>
<td>neg</td>
<td>unk</td>
<td>unk</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>23 (28.3–37.5)</td>
<td>24.3</td>
<td>24.7</td>
<td>24.3 (26.8–49.6)</td>
<td>26 (29.3–48.5)</td>
<td>23 (25.9–47.9)</td>
<td>28.5 (24.5–46.1)</td>
</tr>
<tr>
<td>Hemoglobin (mg/dl)</td>
<td>8 (9.2–14.0)</td>
<td>7.7</td>
<td>7.7</td>
<td>8.1 (9.2–16.8)</td>
<td>9.2 (10–16.4)</td>
<td>unk</td>
<td>8.9 (8.7–14.7)</td>
</tr>
<tr>
<td>Mean corpuscular volume (fl)</td>
<td>45.6 (32.5–52.5)</td>
<td>59</td>
<td>44</td>
<td>47 (39.6–58.4)</td>
<td>unk</td>
<td>32.9 (41.6–53.2)</td>
<td>56.3 (41.8–55.8)</td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td>9.2 (6.8–7.2)</td>
<td>6.7</td>
<td>8.3</td>
<td>7.6 (6.4–8.4)</td>
<td>7.5 (6.2–7.8)</td>
<td>8.5 (6.6–8.2)</td>
<td>6.5 (5.9)</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>unk (12–28)</td>
<td>60</td>
<td>79</td>
<td>42 (19–43)</td>
<td>20 (14–38)</td>
<td>29 (11–55)</td>
<td>29 (18)</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>unk (1.2–2.8)</td>
<td>2.7</td>
<td>4.9</td>
<td>4.5 (1.2–4.0)</td>
<td>2.1 (1.5–3.9)</td>
<td>2.8 (1.6–2.8)</td>
<td>1.8 (1.2)</td>
</tr>
<tr>
<td>Metastasis to kidney</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>unk</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Other renal lesion(s) at necropsy*</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>unk</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>White blood cell count (×10⁶ cells/µL)</td>
<td>10</td>
<td>39.9</td>
<td>27.7</td>
<td>19.5</td>
<td>12.1</td>
<td>7.8</td>
<td>14</td>
</tr>
</tbody>
</table>

*Mean ± 2 SD, International Species Inventory System Clinical Pathology database (J. Andrew Teare, D.V.M., pers. comm.).

unk = unknown.

*Renal lesions included glomerulosclerosis, pyelonephritis, metastatic calcification, and cortical infarcts.

DISCUSSION

Exposure of captive wild felids to MGA greatly increases their risk of developing mammary cancer. Regular (continuous) treatment of domestic cats with MPA or MA has been associated with increased prevalence of mammary carcinoma, but in this study the relationship could not be found. In our study, no relationship could be found between duration of MGA treatment and incidence of mammary cancer. However, given the long (≥3 yr) duration of contraception afforded by MGA in its currently available form, it is likely that many captive wild felids have been subject to progestin exposure and exhibited mammary gland tumors even without the influence of MGA exposure. Further work is needed to determine whether continuous exposure to progestins, particularly MGA, is associated with a higher prevalence of mammary carcinoma in wild felids.

Table 6. The distribution of metastases in 12 animals with limited necropsies (n = 11) was similar to that of animals with comprehensive necropsies.

Necropsy examination

All mammary gland tumors evaluated for this study were classified as carcinomas. Further histopathologic characterization of these tumors included combinations of cystic, microcystic, solid, papillary, and adenocarcinoma patterns. Twenty-eight (96%) of the 29 cases had evidence of metastasis at necropsy. The distribution of metastases in the 12 animals is listed in Table 6. The distribution of metastases in the 12 animals with comprehensive necropsies was similar to that of animals with limited necropsies (n = 11).

Annual mammography was not increased in any felid that received MGA. Alkaline phosphatase was not increased in any felid with mammary cancer. However, exposure of captive wild felids to MGA greatly increases their risk of developing mammary cancer.

Of eight animals with abnormal hepatic values, four had hepatic lesions or hepatic metastases confirmed by necropsy. Alkaline phosphatase was not increased in any felid with mammary cancer.
Table 6. Sites of metastasis noted in comprehensive necropsies of 12 captive wild felids with mammary cancer.

<table>
<thead>
<tr>
<th>Site</th>
<th>No. cases</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node(s)</td>
<td>9</td>
<td>75%</td>
</tr>
<tr>
<td>Lung/pleura</td>
<td>8</td>
<td>67%</td>
</tr>
<tr>
<td>Liver</td>
<td>7</td>
<td>58%</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>4</td>
<td>33%</td>
</tr>
<tr>
<td>Spleen</td>
<td>3</td>
<td>25%</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>2</td>
<td>17%</td>
</tr>
<tr>
<td>Heart</td>
<td>2</td>
<td>17%</td>
</tr>
<tr>
<td>Uterus</td>
<td>2</td>
<td>17%</td>
</tr>
<tr>
<td>Ovary</td>
<td>2</td>
<td>17%</td>
</tr>
<tr>
<td>Kidney</td>
<td>1</td>
<td>8%</td>
</tr>
<tr>
<td>Bone</td>
<td>1</td>
<td>8%</td>
</tr>
<tr>
<td>Intestine</td>
<td>1</td>
<td>8%</td>
</tr>
<tr>
<td>Vagina</td>
<td>1</td>
<td>8%</td>
</tr>
<tr>
<td>Eyelid</td>
<td>1</td>
<td>8%</td>
</tr>
<tr>
<td>No metastasis</td>
<td>1</td>
<td>8%</td>
</tr>
</tbody>
</table>

exposure for a period that should be considered continuous and long term, and thus our findings would be consistent with those of domestic cat studies.

No association was found in this study between MGA dosage and occurrence of mammary cancer, possibly because of the broad dosage range of MGA in both cancer-affected and unaffected captive wild felids. Studies have shown that concurrent progestin and estrogen exposure increases the risk of mammary cancer in women, endogenous estrogens enhance mammary tumorigenesis in dogs and cats, and suppression of ovarian activity confers a protective effect in dogs. In captive wild felids, follicular activity is often not suppressed by currently used dosages of MGA (unpubl. data), thus a concurrent estrogen/progestin hormonal environment is common in MGA-exposed felids and could be an important mechanism for mammary carcinogenesis in these animals.

The increased occurrence of mammary cancer in tigers and jaguars may be due predominantly to the increased exposure of these species to MGA. Jaguars also appear to have a high prevalence of ovarian and uterine cancer. It is unclear why lions (with their significantly higher prevalence of MGA exposure) do not have a high occurrence of mammary cancer.

Neither pre-MGA nor post-MGA pregnancy(ies) were associated with a delay in onset of mammary cancer. This finding contrasts with those in human studies, in which pregnancy early in life has been found to confer a protective benefit against mammary cancer because of early differentiation of stem cells that would otherwise be susceptible to neoplastic transformation. Only two cancer-affected felids had been pregnant after MGA exposure; this low number is believed to reflect general reproductive management practices in zoos and should not be interpreted as supporting theories regarding possible protective benefits of pregnancy after MGA exposure.

The clinical signs of disease in this study were not specific for cancer. All cancer-affected felids had palpable mammary nodules, but it is unknown how many felids with nodules from mammary hyperplasia or other nonneoplastic causes were excluded from this study. The most accurate ante-mortem procedures for diagnosis of mammary cancer were thoracic radiography and evaluation of fine-needle aspirates or biopsy samples. Other procedures that were helpful in increasing the index of suspicion for cancer, although they were less commonly associated with positive findings, were thoracic ultrasonography, abdominal ultrasonography, serum chemistry analysis (to detect hypercalcemia), and hematologic analysis (to detect anemia or neutrophilia).

Hypercalcemia has been associated with mammary cancer in a variety of species, but this association has never been documented in felids. Moderate hypercalcemia may be secondary to primary renal disease, but the marked hypercalcemia (without hyperphosphatemia) seen in five felids of this study is suspected to be due to other mechanisms such as secretion of tumor-related humoral factors (e.g., parathyroid hormone-related protein [PTHrP]) or metastasis-induced bone resorption. Bone metastasis was confirmed in one felid of this study; the lack
of routine necropsy examination of bone precludes discussion of bone involvement in the other cases. In immunohistochemical studies (now in progress), we are trying to demonstrate higher levels of PTHrP in mammary carcinoma tissues of hypercalcemic felids of this study.

Anemia was noted in seven mammary cancer-affected captive wild felids. Anemia is the most common hematologic disorder of human cancer patients and may have several causes, including chronic inflammatory disease (a normocytic anemia), blood loss (microcytic), hematopoietic dysplasia (macrocytic), and (in cats) concurrent feline leukemia virus infection (normocytic or macrocytic). Any of these factors could have played a role in development of anemia in the felids of our study, although none of our cases were known to be leukemia test positive. One leopard in this study had undergone chemotherapy (adriamycin and cyclophosphamide) and was presumed to be in renal failure, thus the chemotherapy or decreased renal production of erythropoietin could have contributed to her anemia.

Neutrophilia has been associated with several types of widely metastatic cancer, especially those with pulmonary metastases. This association may be due to tumor-induced release of cytokines (e.g., colony stimulating factors) or to a nonspecific host response to tumor growth. All four of the neutrophilic felids of this study had widespread metastases (including to the lung) evident at necropsy.

It is difficult to draw specific prognostic conclusions from the diagnosis-to-death time intervals of this study. Zoo staff members have become aware of the aggressive nature of mammary cancer in domestic cats and captive wild felids (which has been confirmed by this study) and therefore often choose euthanasia soon after a diagnosis of mammary cancer is made to minimize duration of animal suffering. The cancer cases in this study demonstrated widespread metastasis at necropsy. Once clinical signs of disease were noted, mammary cancer had likely already metastasized and would have been difficult or impossible to eradicate. Histopathologic examination of mammary nodules is necessary for confirmation of malignancy (vs. hyperplasia, which is commonly reported, or adenoma development, which is rare in felids) so that appropriate medical management decisions can be made.

CONCLUSIONS

All 31 mammary neoplasms evaluated in this study were malignant, 94% of these cancer-affected felids had been contracepted with MGA. In the felids of this study, thoracic radiography was the most useful antemortem procedure to detect metastasis. Mammary cancer should be considered as a differential diagnosis in hypercalcemic or anemic captive wild felids. Short duration of clinical signs and widespread metastasis of mammary cancer in these animals are indicative of the aggressive nature of mammary carcinoma in zoo felids.

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LITERATURE CITED


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