

# Prevalence of malignancy in masses from the mammary gland region of dogs with single or multiple masses

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## OBJECTIVE

To determine the prevalence of malignancy in masses from the mammary gland region of dogs with single or multiple masses.

## ANIMALS

95 female dogs from which mammary gland masses had been excised.

## PROCEDURES

Medical records of all female dogs from which mammary gland tissue was submitted to the Angell Animal Medical Center Pathology Department from 2009 through 2014 were reviewed. For each dog, data were obtained on breed, body weight, age, reproductive status, and number, location, and histologic classification of masses. The prevalence of malignancy was compared between dogs with single versus multiple masses and among the 5 pairs of mammary glands. Dogs with single versus multiple masses were also compared with respect to age and reproductive status.

## RESULTS

Among 161 evaluated masses, 137 (85%) were classified as benign or non-neoplastic and 24 (15%) as malignant. Five of 95 (5%) dogs had masses that were not of mammary gland origin. Age, reproductive status, and quantity of masses (single vs multiple) were not significantly associated with the prevalence of malignancy. The prevalence of malignancy in masses from the fourth (caudal abdominal) mammary gland was significantly lower than that in the other 4 mammary glands combined.

## CONCLUSIONS AND CLINICAL RELEVANCE

Dogs with multiple masses in the mammary gland region were not significantly more likely than dogs with single masses to have a malignancy, suggesting that these 2 groups could be managed similarly. Further studies are needed to evaluate the clinical relevance of the lower prevalence of malignancy in masses from the fourth mammary gland. (*J Am Vet Med Assoc* 2019;255:817–820)

Mammary gland tumors are the most common type of neoplasia in sexually intact female dogs, representing up to 70% of tumors in this group.<sup>1–4</sup> Previous studies<sup>3–5</sup> of dogs have shown that benign MGTs are 2 to 5 times as common as malignant ones, whereas another study<sup>6</sup> revealed that the incidence of malignant MGTs among female dogs in Norway was 53.3%. Mammary gland tumors are most commonly identified in middle-aged to older dogs, with the peak prevalence observed in dogs between 7 and 11 years of age.<sup>7–12</sup> Dogs with malignant MGTs have a higher mean age than dogs with benign tumors (9.5 and 8.5 years, respectively).<sup>13</sup> Several breeds, including Poodle (Toy and Miniature), English Springer Spaniel, Brittany, Cocker Spaniel, English Setter, Pointer, Maltese, Yorkshire Terrier, and Dachshund, are reported to have a higher prevalence of MGTs than other breeds.<sup>14</sup> Certain mammary gland regions appear more predisposed to tumors than others, with

approximately 65% to 70% of identified tumors located in the fourth (caudal abdominal) and fifth (inguinal) glands.<sup>4,15</sup>

Female dogs neutered prior to the first estrous cycle have a lower risk of malignant MGTs than females that have never been neutered (relative risk, 0.005); those neutered between the first and second estrous cycles or after the second estrous cycle also have a lower risk (relative risk, 0.08 and 0.26, respectively).<sup>16</sup> This reduction in risk is thought to be attributable to hormonal influence because both benign and malignant MGTs express estrogen receptors,<sup>17</sup> and dogs exposed to progestin have an increased risk of developing mammary tumors.<sup>18</sup> Additionally, the use of exogenous estrogen and progestin to prevent estrus in dogs is thought to contribute to an increased risk of malignant MGTs in dogs in many European countries.<sup>6,14</sup>

Benign MGTs include simple and complex adenomas, mixed tumors, ductal adenomas, fibroadenomas, and ductal papillomas. Additionally, nonneoplastic conditions such as ductal ectasia, cysts of the

## ABBREVIATIONS

MGT Mammary gland tumor

hair follicles, and tumors that occur in tissue overlying the mammary glands (ie, not of mammary gland origin) may resemble MGTs on physical examination. Malignant MGTs include various forms of carcinoma, fibro- and osteosarcoma, and carcinosarcoma.<sup>7,13,19</sup> No differences in the gross characteristics among malignant or benign MGTs or nonneoplastic conditions of the mammary gland region have been reported, with the exception of inflammatory mammary carcinoma, an especially aggressive form of carcinoma, which is rapidly progressive with a high metastatic rate.<sup>20,21</sup> Clinical signs of inflammatory mammary carcinoma indicate the presence of intense inflammation (eg, erythema, edema, pain, and warmth of the mammary glands). Cytologic or, more often, histologic examination is required for definitive diagnosis of masses in the mammary gland region; a diagnosis is often followed by treatment with lumpectomy, mastectomy, or radical chain mastectomy.<sup>4</sup>

Studies<sup>7,11</sup> show that > 60% of dogs with MGTs have multiple tumors that often represent different histologic types, suggesting individual tumor formation rather than metastasis. If multiple MGTs arise independently, the presence of multiple tumors at the time of diagnosis should not increase the likelihood that an individual tumor is malignant but may increase a patient's overall risk of having a malignant tumor. To the authors' knowledge, a comparison of the prevalence of malignancy between dogs with a single mass and those with multiple masses in the mammary gland region has not been previously reported. In the study reported here, the prevalence of malignancy (determined by histologic examination of masses after surgical removal) was compared between dogs with single versus multiple masses in the mammary gland region. Our hypothesis was that dogs with multiple masses in the mammary gland region would not have a higher prevalence of malignancy than would dogs with single masses.

## Materials and Methods

### Dogs

The medical records of all female dogs for which masses excised from the mammary gland region had been submitted to the Angell Animal Medical Center Pathology Department from January 1, 2009, through December 31, 2014, were identified and reviewed. For each dog, data were obtained on breed, body weight, age at the time of initial examination, age at the time of ovariectomy (if applicable and available), and reproductive status at the time of mass removal; data on the number, location, and histologic classification of removed masses were obtained from the physical examination records and the histologic and surgical reports. Only dogs that had complete medical records with respect to all variables except age at ovariectomy were included.

All submitted masses from the mammary gland region were evaluated by a single pathologist (PJM)

and classified as benign, nonneoplastic, or malignant on the basis of a previously described classification scheme.<sup>19</sup> For dogs with multiple submitted masses, if at least one of the masses was classified as malignant, then the dog was considered to have a malignancy; if no malignancy was identified in any of the masses, the dog was considered to have no malignancy.

### Statistical analysis

Statistical analyses were performed with a commercial software package.<sup>a</sup> Descriptive statistics were generated, and the  $\chi^2$  test was used to compare characteristics (ie, quantity of masses [single vs multiple] and reproductive status) between dogs by malignancy status (ie, malignancy vs no malignancy [benign or nonneoplastic masses]). The Student *t* test was used to compare the mean age between dogs with single masses and those with multiple masses. For dogs with masses that were classified as being of mammary gland origin, the prevalence of malignancy was compared by reproductive status. The prevalence of malignancy was determined for masses in each pair of mammary glands; these prevalence measures were compared by use of the  $\chi^2$  test. Univariate logistic regression was performed to determine whether age (as a continuous variable) or reproductive status was associated with malignancy status or with quantity of masses. Given the variation in dog breed sizes and the lack of available information regarding body condition score, no attempt was made to evaluate the association between body weight and malignancy status or quantity of masses. Values of  $P < 0.05$  were considered significant.

## Results

Ninety-five dogs had masses from the mammary gland region submitted for histologic examination during the study period; all identified dogs had complete medical records with respect to the required study variables (ie, none were excluded). Among the 95 included dogs were Chihuahuas ( $n = 9$ ); Dachshunds (6); Yorkshire Terriers, Shih Tzus, and German Shepherd Dogs (5 each); mixed-breed dogs (4); Labrador Retrievers, Golden Retrievers, Shetland Sheepdogs, and Miniature Pinschers (3 each); and breeds represented by  $\leq 2$  dogs each (49). Fifty-five dogs were sexually intact, and 40 had previously undergone ovariectomy. Mean age and body weight were 8.9 years (range, 4 to 16 years) and 15.0 kg (33.0 lb; range, 1.8 to 47.6 kg [4.0 to 104.7 lb]), respectively. Age at the time of ovariectomy, which was available for 33 of 40 (83%) ovariectomized dogs, ranged from 10 weeks to 10 years (mean, 4.8 years).

A total of 161 masses were removed from the mammary gland region and histologically classified. Fifty-nine of 95 (62%) dogs had a single mass in the mammary gland region, and 36 (38%) had multiple masses; dogs with multiple masses had a mean of 2.8 masses/dog (range, 2 to 10 masses/dog). One hundred thirty-seven (85%) masses were classified as benign or nonneoplastic and 24 (15%) as malignant. Benign

masses were further classified as mixed tumor (n = 42), simple adenoma (38), complex adenoma (26), fibroadenoma (5), infundibular keratinizing acanthoma (3), ductal adenoma (2), lipoma (2), intraductal papilloma (2), and plasmacytoma (1). Nonneoplastic masses were classified as lobular hyperplasia (n = 8), ductal ectasia (4), lymphoid hyperplasia (2), and follicular cyst (2). Malignant masses were classified as simple carcinoma (n = 13), carcinoma arising from a benign mixed tumor (4), complex carcinoma (2), carcinosarcoma (1), carcinoma in situ (1), ductal carcinoma (1), comedocarcinoma (1), and carcinoma and malignant myoepithelioma (1). Masses from 5 of 95 (5%) dogs were deemed to have an origin other than the mammary glands; 4 dogs had a single mass, and 1 dog had 2 masses (ie, 6/161 [4%] masses were not of mammary gland origin). All masses that were not of mammary gland origin were classified as benign.

Masses were classified as malignant in 17 of 59 (29%) dogs with single masses. Among 36 dogs with multiple masses submitted for histologic examination, malignancy was identified in at least 1 mass from 6 (17%) dogs. Specifically, at least 1 mass was classified as malignant in 3 of 21 dogs with 2 masses, 2 of 10 dogs with 3 masses, 1 of 4 dogs with 5 masses, and 0 of 1 dog with 10 masses. Histologic classification of masses as benign or nonneoplastic was approximately 2 times as likely for dogs with multiple masses as for dogs with single masses (OR, 2.02; 95% confidence interval, 0.71 to 5.74); however, this association was not significant ( $P = 0.18$ ).

The mean age of dogs with a malignancy was 9.4 years (range, 4 to 14 years) and of dogs with no malignancy was 8.3 years (range, 4 to 16 years). Age was not significantly ( $P = 0.28$ ) associated with the likelihood of having a malignancy. The mean age of dogs with a single mass (mean  $\pm$  SD, 8.9  $\pm$  2.9 years) did not differ significantly ( $P = 0.70$ ) from that of dogs with multiple masses (8.7  $\pm$  2.8 years).

Among the 23 dogs with malignant masses, 11 (48%) were sexually intact at the time of mass removal and 12 (52%) had previously undergone ovariectomy. Among the 55 dogs that were sexually intact at the time of mass removal, 29 (53%) had a single mass and 26 (47%) had multiple masses. Among the 40 dogs that had previously undergone ovariectomy, 28 (70%) had a single mass and 12 (30%) had multiple masses. Reproductive status was not significantly ( $P = 0.14$ ) associated with the quantity of masses (ie, single vs multiple).

Among dogs with masses that were of mammary gland origin (n = 90), the masses in 67 (74%) were classified as benign or nonneoplastic and the masses in 23 (26%) were classified as malignant. Of dogs with benign or nonneoplastic masses, 45 (67%) were sexually intact at the time of mass removal and 22 (33%) had previously undergone ovariectomy; of dogs with malignant masses, 11 (48%) were sexually intact at the time of mass removal and 12 (52%) had previously undergone ovariectomy. Reproductive status was not

**Table 1**—Anatomic distribution of 161 masses removed from the mammary gland region of 95 female dogs by malignancy status (benign or nonneoplastic vs malignant).

Mammary gland	Benign or nonneoplastic (n = 137)	Malignant (n = 24)
First (cranial thoracic)	11 (79)	3 (21)
Second (caudal thoracic)	19 (79)	5 (21)
Third (cranial abdominal)	22 (79)	6 (21)
Fourth (caudal abdominal)	45 (94)	3 (6)
Fifth (inguinal)	40 (85)	7 (15)

Values represent the number (%) of all masses in the indicated gland.

significantly ( $P = 0.10$ ) associated with the likelihood of having a malignancy.

Masses were identified in all 5 pairs of mammary glands (**Table 1**). The prevalence of masses in the fourth (caudal abdominal) and fifth (inguinal) mammary glands combined (95/161 [59%]) was significantly ( $P < 0.01$ ) higher than that in the first (cranial thoracic), second (caudal thoracic), and third (cranial abdominal) mammary glands combined (66/161 [41%]). The prevalence of malignancy did not differ significantly ( $P = 0.58$ ) among individual pairs of mammary glands. However, the prevalence of malignancy was significantly ( $P = 0.04$ ) lower in masses from the fourth mammary gland (3/48 [6%]) than in masses from the other 4 glands combined (21/113 [19%]).

## Discussion

Previous studies<sup>22-24</sup> indicate a high mortality rate and a high rate of recurrence<sup>24</sup> for dogs following local resection of malignant MGTs. Thus, it is important to know the risk of malignancy when multiple masses are present to determine the prognosis and optimal treatment options and to guide owner expectations. In the dogs of the present study, the presence of multiple masses did not increase the likelihood of a malignancy; therefore, the presence of multiple masses did not appear to be a negative prognostic indicator.

The effects of age, breed, and body condition on the risk of MGT development have been previously investigated.<sup>6-12,14,21,25-27</sup> In the present study, dogs with a malignancy (ie, at least one of the excised masses was histologically classified as malignant) had a higher mean age (9.4 years) than did those with only benign or nonneoplastic masses (8.3 years). Forty-six dog breeds were represented in the present study; small breeds (eg, Chihuahua, Dachshund, Yorkshire Terrier, and Shih Tzu) were common, suggesting that small-breed dogs may be more at risk than other breeds, although further studies are needed to evaluate the role of breed size in MGT development. In addition, a previous study<sup>26</sup> shows that the risk of malignant MGTs among spayed dogs that had been thin at 9 to 12 months of age was lower than that for other dogs. However, an evaluation of the association between breed or body weight and risk of malignancy was beyond the scope of the present study.



A reduction in the risk of MGT development is often cited as a reason for ovariectomy at an early age. Although age at the time of ovariectomy was not available for all neutered dogs in the present study, 58% of included dogs were sexually intact at the time of mass removal; the prevalence of malignancy did not differ significantly between dogs that had previously undergone ovariectomy and those that were sexually intact. The mean age at the time of ovariectomy was 4.8 years among the 33 dogs for which the age at the time of ovariectomy was known. Therefore, it was likely that these 33 dogs had already undergone multiple estrous cycles prior to ovariectomy, with a resultant loss of the protective effect of early ovariectomy.

In the present study, the fourth and fifth mammary glands were the most commonly affected (59% of masses identified in these glands), which is consistent with what has been previously reported.<sup>4,15</sup> This distribution pattern may have been attributable to the presence of a relatively higher amount of glandular tissue in the fourth and fifth glands.<sup>4</sup> No significant difference in the prevalence of malignancy was noted among individual pairs of mammary glands; however, masses from the fourth mammary gland had a significantly lower prevalence of malignancy than those from the other 4 glands combined. The clinical relevance of this finding is unknown, and further studies are indicated to determine the reasons for this difference.

To the authors' knowledge, no previous study has compared the prevalence of malignancy between dogs with single and multiple masses in the mammary gland region. One study<sup>28</sup> showed a more favorable prognosis for dogs with multiple versus single tumors in the mammary gland region; however, the prevalence of malignancy was not examined. In the present study, no significant difference was noted in the prevalence of malignancy between dogs with a single mass and those with multiple masses; the prevalence of malignancy in all dogs, those with a single mass, and those with multiple masses was 24%, 29%, and 17%, respectively.

In the present study, age and reproductive status were not associated with the quantity of masses (ie, single vs multiple) in the mammary gland region. Additionally, the prevalence of malignancy did not differ significantly by age, reproductive status, or quantity of masses. The finding that dogs with multiple masses had no higher prevalence of malignancy than those with single masses suggested that similar protocols for diagnosis and treatment could be used for these groups.

## Footnotes

- a. SAS, version 9.4, SAS Institute Inc, Cary, NC.

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