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The odds of neoplasia in dogs with and without diabetes mellitus

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Abstract

Background: Increased risk of neoplasia in humans with diabetes mellitus (DM) is well documented. It is unknown if dogs with DM have increased risk of neoplasia.

Objective: Determine if dogs with DM have an overall increased risk of neoplasia and risk for specific forms of neoplasia compared to dogs without DM.

Animals: Seven hundred dogs with DM and 700 breed, age, and sex-matched dogs without DM, examined during the same years.

Methods: Retrospective case-control study. Odds ratios (OR), corresponding 95% confidence intervals (CI), and *P*-values were calculated using conditional logistic regression to determine if dogs with DM had increased odds of developing neoplasia compared to dogs without DM.

Results: The overall odds of developing neoplasia were not significantly different in dogs with and without DM. However, dogs with DM had significantly higher odds of developing an adrenal mass (OR, 4; 95% CI, 1.1-14.2; $P = .03$) compared to dogs without DM. The odds of developing a splenic mass in dogs with DM (OR, 1.2; 95% CI, 0.99-1.39) were increased compared to dogs without DM, but this difference was not significant ($P = .07$).

Conclusions and Clinical Importance: Dogs with DM may be at increased risk for adrenal neoplasia. Awareness of this risk can facilitate early diagnosis of this life-threatening comorbidity. Larger studies are needed to confirm these findings.

KEYWORDS
adrenal, cancer, canine, diabetic, hyperadrenocorticism, tumor

1 | INTRODUCTION

The increased risk of cancer in humans with diabetes mellitus (DM) has been recognized for decades.[1] However, it is still unknown if the increased risk of cancer in humans with DM is directly related to blood glucose concentrations, hyperinsulinemia, inflammation, changes in insulin-like growth factor expression, obesity, or exogenous insulin administration.[1-9] It is also possible that the etiology of diabetes-related neoplasia is different in various types of cancer.[1]

The type of cancer observed more commonly in humans with DM varies according to the type of DM, sex, and the population studied. A study in Sweden reported that there was an overall 20% increase in cancer incidence in type 1 DM patients with specific increased risk of gastric, cervical, and endometrial cancer.[10] Another study from

Abbreviations: CI, confidence interval; DM, diabetes mellitus; OR, odds ratio.

Sweden identified increased risk of gastric and skin carcinomas, and leukemias in patients with type 1 DM.[11] These risks were higher in females compared to males and were more significant in those >10 years of age.[11] In a study of type 1 DM in people from Australia, Scandinavia, and Scotland, there was an increased risk for gastric, liver, pancreatic, and renal cancer in both men and women, and increased risk of endometrial cancer in women.[12] In this study, the risk of cancer decreased with increased duration of DM.[12] A meta-analysis of type 1 DM patients from Europe, the United States, Australia, and Asia found a general increased risk of neoplasia, and increased risk of gastric, lung, pancreatic, liver, ovary, and renal neoplasia in particular.[13] Finally, a Taiwanese study reported an overall 13% increase in risk of cancer in type 1 DM, with increased incidence of cancer in men compared to women. The highest risk was associated with pancreatic cancer in both men and women.[14]

The risk distribution of cancer in humans with type 2 DM is different. A study from the United States found that the overall risk of cancer in type 2 diabetics was higher in men than in women, and, as opposed to findings in type 1 DM, that the risk of cancer increased with duration of DM.[15] Exogenous insulin administration also was identified as a risk for cancer in this study.[15] The most common forms of cancer reported in type 2 DM in various studies from different parts of the world are liver and pancreatic cancer.[1,16-18]

The risk of cancer in dogs is unknown, although dogs with DM were reported to have a significant association with benign mammary tumors compared to age and sex matched dogs with other endocrinopathies.[19] This study did not identify a significant association between DM and malignant mammary tumors.[19] The methodology used to diagnose benign and malignant tumors in this 1982 study was not reported.[19] Our aim was to determine if dogs with DM have increased overall risk of cancer and risk for specific forms of cancer compared to dogs without DM. It was hypothesized that dogs with DM have increased risk for certain types of neoplasia, compared to dogs without DM.

2 | MATERIALS AND METHODS

2.1 | Case selection

Medical records from a university teaching hospital were electronically searched to identify dogs evaluated for DM between January 2010 and August 2020. All records of dogs with a medical diagnosis of DM were reviewed by 1 person (SAM) to determine the accuracy of DM diagnosis. Case dogs were confirmed to have DM if they were treated with insulin, or if there was a clear reason for lack of insulin treatment such as euthanasia upon diagnosis or referral elsewhere for treatment. For dogs that were not insulin-treated, inclusion criteria included the presence of clinical signs such as polyuria, polydipsia, polyphagia, persistent hyperglycemia (blood glucose concentration ≥250 mg/dL), and glucosuria. Exclusion criteria included an incorrect diagnosis (such as diabetes insipidus), incomplete medical record in which signalment, blood glucose concentrations, or urinalysis were unavailable for review, a suspicion for secondary DM associated with corticosteroid or cyclosporine use, diestrus, hepatocutaneous syndrome, or surgical resection of insulinoma, and euthanasia at the time of diagnosis without confirmation of persistent hyperglycemia and glucosuria.

Medical records also were searched to identify control dogs without DM examined during the same time period. Stratified sampling was performed to select the same number of control dogs as the number of diabetic case dogs from each study year. Matching was stratified by year to account for any variation in use of diagnostic tests over the years. Control dogs without DM were breed, age, and sex matched to case dogs, in that order. If more than 1 control dog per year was breed, age, and sex matched to a specific case dog, potential control dogs were sorted by date of birth, and the first dog on the list was selected as a control dog. If the breed of a dog with DM could not be matched, a similar breed was selected using a breed cladogram.[20] If age could not be matched, a control dog closest in age to the case dog was selected. If neuter status could not be matched, dogs were matched by sex.

2.2 | Data retrieval

Data extracted from medical records included signalment, absence or presence of a DM diagnosis, and concurrent illness. Imaging findings documented were based on formal reports signed by a board-certified radiologist and included reports of abdominal and thoracic radiographs, ultrasonographic examinations, computed tomography, and magnetic resonance imaging. Cytology and histopathology findings were documented based on formal reports signed by a board-certified clinical pathologist or anatomic pathologist, respectively. Results of endoscopic and surgical biopsies were included. Adrenal axis testing (Immulite 2000, Siemens, Washington, District of Columbia), flow cytometry, and polymerase chain reaction antigen receptor rearrangement were performed and interpreted as previously described,[21,22] and *BRAF* mutation examinations (Antech Diagnostics, Fountain Valley, California) also were recorded. Type of insulin and duration of insulin treatment were documented for dogs with DM. Duration of insulin treatment was defined as the time from DM diagnosis, if available, until the time of the most recent documented clinic visit. If the date of DM diagnosis was unknown, the earliest known date of insulin administration was utilized to define the start of insulin treatment.

2.3 | Definition of neoplasia

Masses were classified as neoplastic or benign based on location, imaging findings, cytology, and histopathology. Intraabdominal masses were classified as neoplastic if cytology or histopathology confirmed such a diagnosis, or if the formal ultrasonographic report clearly prioritized a neoplastic differential diagnosis over a benign diagnosis. Specifically, adrenal masses were defined as neoplastic only if the ultrasonographic report unambiguously prioritized neoplasia over hyperplasia or benign enlargement. Adrenal nodules and bilaterally

enlarged adrenal glands were not classified as neoplastic. Mammary, testicular, and anal sac gland masses were classified as neoplastic, and if histopathology was available, specific diagnoses were recorded. Eyelid and dermal masses were considered benign unless a biopsy indicated that a neoplastic process was present. Intraocular pigmented masses, gingival masses, and masses extending from articular surfaces (eg, carpus) were considered neoplastic, and if histopathology was available, specific diagnoses were recorded.

2.4 | Sample size calculation

A 2-sample comparison of proportions test was used to determine the number of dogs with and without DM required to detect a significant difference between the prevalence of cancer in each group. The calculation was based on findings from a previous study in humans in which the prevalence of cancer among 23 358 patients with diabetes was 6.3%, whereas the prevalence of cancer among 383 799 individuals without diabetes was 2.6%.[17] The calculation, aimed at detecting a similar difference, resulted in a required sample size of 700 dogs in each of the 2 groups. The calculation was performed assuming a power of 0.9 and a type 1 error rate of 0.05.

2.5 | Statistical analysis

Most continuous variables were not normally distributed as determined visually and by skewness and kurtosis tests for normality. Therefore, results are reported as median (and range) and the 2-sample Wilcoxon rank sum (Mann-Whitney) test was used for comparison of continuous variables between dogs with and without DM. Case and control dogs were matched at a 1 : 1 ratio by year of examination and breed, age, and sex and each pair of case and control dogs was assigned a unique pair identification number. Conditional logistic regression was stratified by this unique paired identification number. Conditional logistic regression was used to calculate odds ratios (OR), corresponding 95% confidence intervals (CI), and *P*-values, to determine if dogs with DM had increased odds of developing cancer compared to dogs without DM. Odds ratios were calculated for the specific types of neoplasia identified most commonly in study dogs. Logistic regression also was employed to examine the relationship between the binary variable of presence or absence of cancer and continuous variables. A *P*-value <.05 was considered significant for all tests. All statistical evaluations were performed using a statistical software package (Stata 14.0 for Mac, Stata Corporation, College Station, Texas).

3 | RESULTS

3.1 | Study population

Eight-hundred and eighteen records of dogs with DM were available for review. One-hundred and eighteen cases were excluded because of an erroneous medical record diagnosis and an actual medical diagnosis of diabetes insipidus (41 dogs), an incomplete medical record (32 dogs), corticosteroid or cyclosporine treatment at the time of DM diagnosis (28 dogs), an erroneous medical record diagnosis other than diabetes insipidus (7 dogs), concurrent hepatocutaneous syndrome (4 dogs), concurrent diestrus (3 dogs), development of DM after treatment for insulinoma (2 dogs), and 1 case of a cat. Most dogs with DM (673/700, 96%) were treated with insulin, but 27/700 (4%) dogs with a confirmed diagnosis of DM that were not yet treated with insulin also were included in the study. Ultimately, 700 dogs with DM and 700 breed, age, and sex matched control dogs were included in the study. The signalment of study dogs is reported in Table 1. The findings reported in Table 1 confirm that control dogs without DM were successfully breed, age, and sex matched to case dogs with DM.

The median age at the time of initial DM diagnosis was 9 years (range, 0.4-19 years) and median duration of insulin treatment in dogs with DM was 0.8 years (range, 0-10.3 years). The median time between the initial diagnosis of DM and the cancer diagnosis was 73.5 days (range, 0-3162 days). The total number of dogs examined at the teaching hospital during the study period was 75 108 and the study period hospital prevalence for DM in dogs was therefore 0.93%.

3.2 | Neoplasia

Neoplasia was diagnosed in 137/700 (19.6%) dogs with DM and in 138/700 (19.7%) dogs without DM. The study period hospital prevalence for neoplasia in dogs was 0.37% ([137 + 138]/75 108). The overall odds of developing neoplasia in dogs with DM were 0.99 times the odds of developing neoplasia in dogs without DM, and this difference was not significant. The odds of developing neoplasia in neutered males, intact males, neutered females, and intact females with DM were not significantly different than the odds of developing neoplasia in dogs in the same sex category without DM.

The most common types of neoplasia documented among 275 neoplasms identified in all 1400 study dogs were mammary mass (21 dogs, 7.6%), splenic mass (18 dogs, 6.5%), hepatic mass (19 dogs, 6.9%), adrenal gland tumor (15 dogs, 5.4%), and cutaneous mast cell tumor (14 dogs, 5.1%). The odds of developing these forms of neoplasia in dogs with and without DM are reported in Table 2.

Mammary masses included 10 histopathologically-confirmed mammary carcinomas (7 in dogs without DM and 3 in dogs with DM), 10 mammary masses of undetermined etiology (1 in a dog without DM and 9 in dogs with DM), and 1 histopathologically-confirmed mammary hemangiosarcoma (in a dog without DM). Splenic masses were ultrasonographically described as heterogenous in 13/18 dogs (72%), poorly organized with disrupted splenic capsule in 7/18 (39%), cavitated in 5/18 (27%), highly vascular in 4/18 (22%), multilobular in 2/18 (11%), and mineralized in 1/18 (5.6%). There was evidence of peritoneal effusion in 5/18 dogs (28%) with splenic masses. Hepatic masses were ultrasonographically described as heterogenous in 12/19 dogs (63%), cavitated in 8/19 (42%), irregularly marginated in 3/19

TABLE 1 Signalment of study dogs including breeds represented by ≥10 dogs

Characteristic[a]	Dogs with diabetes mellitus (700)	Dogs without diabetes mellitus (700)
Age at the time of cancer diagnosis (years, median, range)	11 (3-19)	10 (4-18)
	Number (%) of dogs with diabetes mellitus	Number (%) of dogs without diabetes mellitus
Breed		
Mixed breed	179 (25.6%)	179 (25.6%)
Labrador Retriever	47 (6.7%)	47 (6.7%)
Pug	41 (5.9%)	41 (5.9%)
Maltese	32 (4.6%)	32 (4.6%)
Miniature Schnauzer	32 (4.6%)	32 (4.6%)
Yorkshire Terrier	29 (4.1%)	29 (4.1%)
Bichon Frise	26 (3.7%)	26 (3.7%)
Miniature Pinscher	25 (3.6%)	25 (3.6%)
Chihuahua	18 (2.6%)	18 (2.6%)
Unspecified	18 (2.6%)	18 (2.6%)
Shih Tzu	17 (2.4%)	17 (2.4%)
Dachshund	17 (2.4%)	17 (2.4%)
Rottweiler	16 (2.3%)	16 (2.3%)
West Highland White Terrier	14 (2.0%)	14 (2.0%)
Jack Russell Terrier	14 (2.0%)	14 (2.0%)
Miniature Poodle	13 (1.9%)	13 (1.9%)
Pomeranian	12 (1.7%)	12 (1.7%)
Cairn Terrier	11 (1.6%)	11 (1.6%)
Husky	11 (1.6%)	11 (1.6%)
Sex		
Neutered male	373 (53.3%)	385 (55%)
Neutered female	246 (35.15%)	252 (36%)
Intact male	38 (5.4%)	33 (4.7%)
Intact female	43 (6.15%)	30 (4.3%)

[a]There were no significant differences between age at the time of cancer diagnosis, sex distribution, and breed of dogs with or without diabetes mellitus.

(16%), multilobular in 2/19 (11%), and highly vascular in 2/19 (11%). One dog with a hepatic mass had evidence of peritoneal effusion. No cytology or histopathology was performed to further characterize any of the splenic or hepatic masses. Cutaneous mast cell tumors were diagnosed by cytology in 6/14 dogs (43%) and by histopathology in 8/14 dogs (57%).

Adrenal masses were identified in 12 dogs with DM and in 3 dogs without DM. Seven dogs had left-sided masses, 7 had right-sided masses, and 1 dog had bilateral adrenal gland involvement. Median adrenal length reported in 15 dogs with an adrenal mass was 21 mm (range, 6.7-46 mm) and median adrenal width reported in 12 dogs was 26 mm (range, 8-46 mm). Seven of 15 dogs (46%) had ultrasonographic findings consistent with loss of normal adrenal shape and architecture, 4/15 (27%) had neoplastic invasion into the caudal vena cava, 9/15 (60%) had no sonographic evidence of mass invasion into adjacent vasculature, and in 2/15 (13%) the caudal vena cava could not reliably be evaluated for invasion. Eight of 15 (53%) dogs with adrenal masses had loss of normal adrenal shape and architecture, invasion into the caudal vena cava, or both. In the remaining 7 of 15 dogs (47%), median adrenal length was 22 mm (range, 11-37 mm) and median adrenal width reported in 5 of these dogs was 22.5 mm (range, 10.7-32 mm). Adrenal mass echogenicity in these 7 dogs was characterized as heteroechoic (3 dogs), hyperechoic (3 dogs), or hypoechoic (1 dog).

Most dogs with adrenal masses (9 of 15, 60%) did not have adrenal axis testing. However, 6 of 15 dogs (40%) with adrenal masses, all of which had DM, had adrenal axis testing performed. An adrenocorticotropic hormone stimulation test confirmed a diagnosis of hyperadrenocorticism in 4 dogs, whereas a low-dose-dexamethasone-suppression test excluded a diagnosis of hyperadrenocorticism in 1 dog. The sixth dog had unknown initial adrenal axis test results because of incomplete referral records but was treated with trilostane.

In dogs with DM, the diagnosis of neoplasia was based on abdominal ultrasonographic findings (58 of 137, 42.3%), histopathology (28 of 137, 20.4%), cytology (22 of 137, 16.1%), physical examination (17 of 137, 12.4%), thoracic radiographs (5 of 137, 3.7%), computed tomography (3 of 137, 2.2%), magnetic resonance imaging (1 of 137, 0.73%), endoscopy (1 of 137, 0.73%), other radiographs (1 of 137, 0.73%), and echocardiography (1 of 137, 0.73%). The types of neoplasia identified in 17 dogs by physical examination alone were mammary masses in 9/17 dogs (52.9%), followed by unilateral anal sac gland masses (n = 4, 23.5%), unilateral testicular mass (n = 1, 5.9%), gingival mass (n = 1, 5.9%), intraocular pigmented mass (n = 1, 5.9%), and carpal mass (n = 1, 5.9%). In dogs without DM, the diagnosis of neoplasia was based on histopathology (60 of 138, 43.4%), cytology (29 of 138, 21%), abdominal ultrasonographic findings (23 of 138, 16.6%), chest radiographs (8 of 138, 5.8%), other radiographs (5 of 138, 3.6%), magnetic resonance imaging (3 of 138, 2.2%), physical examination (2 of 138, 1.5%), echocardiogram (2 of 138, 1.5%), computed tomography (2 of 138, 1.5%), *BRAF* mutation examination (2 of 138, 1.5%), flow cytometry (1 of 138, 0.72%), and necropsy (1 of 138, 0.72%). The types of neoplasia identified in 2 dogs by physical examination alone were mammary mass (50%) and testicular mass (50%).

The most common insulin types used for treatment of dogs with DM were neutral protamine Hagedorn (NPH; 503/673, 74.7%) and glargine (19/673, 2.8%). The type of insulin used was unknown in 99/673 (14.7%) of dogs, and 52 dogs (7.8%) were treated with 1 of

TABLE 2 Odds of developing different types of neoplasia in dogs with and without diabetes mellitus

Neoplasia	Number (%) of dogs with neoplasia and diabetes mellitus	Number (%) of dogs with neoplasia and without diabetes mellitus	Odds ratio	95% confidence interval	*P*-value
All neoplasia	137 (19.6%)	138 (19.7%)	0.99	[0.75-1.3]	.95
Mammary mass	12 (1.7%)	9 (1.3%)	1.37	[0.55-3.4]	.51
Splenic mass	13 (1.9%)	5 (0.7%)	1.2	[0.99-1.39]	.07
Hepatic mass	10 (1.4%)	9 (1.3%)	1	[0.91-1.12]	.82
Adrenal mass	12 (1.7%)	3 (0.43%)	4	[1.13-14.17]	.03
Cutaneous mast cell tumor	6 (0.9%)	8 (1.1%)	0.96	[0.82-1.12]	.59

4 other insulin products. Among dogs with DM, the odds of neoplasia in dogs receiving NPH or glargine were 1.1 and 2 times greater than the odds of neoplasia in dogs receiving a different insulin preparation, respectively, but these differences were not significant ($P = .6$ and $P = .2$, respectively). Among dogs with DM, logistic regression did not identify a significant association between the risk of neoplasia and duration of DM.

4 | DISCUSSION

We found that dogs with DM had increased odds of developing adrenal neoplasia compared to breed, age, and sex matched dogs without DM. Adrenal neoplasia is not among the most common neoplastic comorbidities reported in humans with DM. However, a recent study in humans found a significant association between incidental adrenal masses and DM, and approximately half of the patients with incidental adrenal masses had adrenal axis testing consistent with hyperadrenocorticism.[23] Hyperadrenocorticism was confirmed in only 4/15 (27%) dogs with adrenal masses in our study. However, only 6/15 (40%) dogs had adrenal axis testing performed, and thus the true prevalence of hyperadrenocorticism could be underestimated in our study. Although an association between hyperadrenocorticism and DM has been reported previously in dogs, to our knowledge, ours is the first report of increased risk of adrenal tumors in dogs with DM.[24,25] Previous studies in dogs have linked pituitary-dependent hyperadrenocorticism or undifferentiated hyperadrenocorticism to DM.[24,25] One of these previous studies lacked a control group, and the other matched control dogs to case dogs on the basis of age, but not on the basis of breed and sex.[24,25]

Although the odds of a splenic mass in dogs with DM were 1.2 times higher than the odds of a splenic mass in dogs without DM, this difference was not significant. In humans with DM, there is no increased risk for splenic neoplasia, but this finding warrants further investigation in dogs because of the difference in the general prevalence of sarcomas in these 2 species. In humans, it is estimated that approximately 50% of cancer-related deaths are attributed to various types of carcinomas, whereas in dogs it is estimated that most malignant cancers are a combination of carcinomas and sarcomas.[26]

Neoplasia was diagnosed in approximately 20% of dogs with and without DM and at a much higher prevalence than that reported in humans. One study in humans reported a cancer prevalence of 6.3% in patients with DM compared to a 2.6% prevalence of cancer among individuals without DM.[17] This finding is consistent with other reports in which it is estimated that the incidence of cancer in dogs is over 10 times that of the human population.[26] The high prevalence of cancer in the control groups is likely attributable to age matching of control dogs to case dogs. In contrast to the control group, the overall period hospital prevalence for neoplasia in a population of dogs that included all ages was only 0.37%. The sample size calculation of our study was based on the prevalence of neoplasia in humans with and without DM, because before our study was performed, these numbers were unavailable in dogs. Based on the findings reported in our study, the prevalence of neoplasia in dogs with and without DM is very similar, and a larger sample size is needed to detect a difference in the general prevalence of neoplasia in dogs with and without DM. However, the samples size was large enough to detect significant differences in the risk for adrenal neoplasia between dogs with and without DM. Our study will allow for more accurate sample size calculations for future studies investigating the prevalence of neoplasia in dogs with DM.

Histopathology and cytology were the most common diagnostic tools used for diagnosis of neoplasia and were utilized in over 60% of dogs without DM. However, in dogs with DM, ultrasound was most commonly utilized for establishing a diagnosis of neoplasia, and histopathology and cytology were used in only 36% of cases. This finding also was apparent specifically in regard to mammary masses, for which a histopathologic diagnosis was available more commonly in dogs without DM. This finding could reflect owner and clinician reluctance to sedate dogs with DM or subject them to an invasive procedure. Indeed, a limitation of our study is a lack of histologically-confirmed neoplasia in many of the study dogs. Limiting the inclusion of dogs to those that have histopathologically or cytologically confirmed neoplasia could have biased the study to underestimate the prevalence of neoplasia, and including dogs without histopathologically or cytologically confirmed neoplasia could have resulted in overestimation of the prevalence of neoplasia. However, the same inclusion and exclusion criteria were applied to case and control dogs. Therefore, the selection criteria would have influenced the definition

of neoplasia equally in all study dogs, decreasing the risk of biasing the OR of neoplasia in dogs with and without diabetes. These inclusion criteria do increase the generalizability of the study findings because in the clinical setting veterinarians might have to establish a diagnosis of cancer without the benefit of histopathologic or cytologic confirmation.

Case dogs were breed, age, and sex matched to control dogs. Dogs were not matched for primary reason of examination because most case dogs were examined primarily for DM, whereas control dogs, by design, did not have DM. However, matching dogs by age ensured that all study dogs were examined for complex medical issues that develop in middle to older age dogs and require a similar in-depth diagnostic evaluation. Matching dogs by breed ensured that breeds at risk for cancer were represented equally in the case and control groups. Matching was stratified by year because the use of diagnostic testing changes over time. Doing so ensured that novel tests such as magnetic resonance imaging, computed tomography, *BRAF* mutation examination, and flow cytometry were available equally in case and control dogs. This approach does not eliminate the chance for verification bias but applies the risk of verification bias equally to case and control dogs. Stratification by year and matching by breed, age, and sex was accounted for by performing conditional regression analysis.

Glargine insulin has been implicated as a possible carcinogen in humans.[1,15,27] However, a large study of over 12 000 people followed for approximately 6 years did not find evidence to support the hypothesis that glargine insulin has a carcinogenic effect.[27] In our study, no insulin type, including glargine, was associated with increased odds of neoplasia. Our study also did not identify a significant association between the risk of neoplasia and duration of DM. In humans with type 1 DM, there is decreased risk of cancer with increased duration of DM whereas in humans with type 2 DM, the risk of cancer increases with the duration of DM.[12,15] Our study was not powered to detect a carcinogenic effect of exogenous insulin or an association between duration of DM and neoplasia. Also, in our study, the median time between the initial diagnosis of DM and the cancer diagnosis was approximately 2.5 months, which is probably not enough time for insulin to have a carcinogenic effect. It is possible that in dogs, as in humans, exogenous insulin is not associated with risk of cancer. However, additional studies focused on the association between duration of DM and neoplasia as well as exogenous insulin treatment and neoplasia are warranted to determine if such associations exist in dogs.

The limitations of our study are related to the retrospective study design. Not all of the dogs had histologically or cytologically confirmed neoplasia, and the diagnosis of neoplasia was based on other diagnostic tools in many cases. Other diagnostic test results also were not available in all dogs, as demonstrated by the lack of adrenal axis testing in some dogs with adrenal masses. Furthermore, some masses were characterized by physical examination only and intraocular pigmented masses, gingival masses, and masses extending from articular surfaces (eg, carpus) noted in 1 dog each were defined as neoplastic without histopathologic confirmation. Mammary, testicular, and anal sac gland masses also were classified as neoplastic, if histopathology was unavailable. Of 21 mammary masses noted in this study, 10 were histopathologically classified as carcinoma, 10 had no histopathology, and 1 was histopathologically classified as hemangiosarcoma. A previous study noting an association between DM and benign but not malignant mammary masses included a diabetic population in which 57% of females were intact females.[19] Intact female dogs are at risk for secondary DM because of high growth hormone concentration and are also at risk for mammary tumors.[28,29] This previous study included 15 hospitals and uniformity or criteria for diagnosing mammary masses or differentiating benign from malignant masses in any of these institutions were not reported.[19] Furthermore, no review of records was conducted to ascertain the accuracy of the diagnosis of a mammary mass.[19] It is therefore difficult to compare the results of this previous study to the results of our study, in which only 15% of diabetic female dogs were intact and medical records were reviewed for the accuracy of a mammary mass diagnosis. Additional studies in which histopathologic evaluation of all tumors is available are needed to advance our understanding of the risk of histopathologically-defined tumors in dogs with DM. Our study also was not powered to detect some of the negative findings, such as a lack of an association between exogenous insulin or duration of DM and risk of neoplasia. Therefore, it is not known if these negative findings are a consequence of small sample size or true lack of association.

Our study reported the prevalence or proportion of dogs with or without DM that had cancer during the study period. Our study did not investigate the incidence or number of new cancer diagnoses in dogs with or without DM. It is possible that some of the study dogs classified as not having cancer will develop cancer in the future. However, this would not impact the period hospital prevalence for neoplasia in dogs reported here.

Another study limitation is that correction for multiple comparisons was not performed. The goal of multiple comparisons correction is to decrease the number of false positives that might arise from performing a large number of tests. However, an unfortunate outcome of correcting for multiple comparisons is that such corrections can increase the number of false negatives, where a significant difference is not detected statistically. In an exploratory study such as ours, which is intended to serve as a basis for future longer and larger studies, it is paramount to avoid false negatives and facilitate future research.[30]

In summary, dogs with DM are at increased risk for adrenal neoplasia. An understanding of the increased risk of adrenal neoplasia among dogs with DM can facilitate timely diagnostic testing and treatments and improve the health of dogs with DM.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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