JAVMA

AVMA

Low prevalence of occult cancer diagnosis when screening healthy, higher-risk, middle-aged to older dogs

Jenna H. Burton, DVM, MS, DACVIM[1*]; David M. Vail, DVM, MS, DACVIM[2,3]; Jennifer L. Willcox, DVM, DACVIM[4]; Sami Al-Nadaf, DVM, DACVIM[4]; Sarah Adrianowycz, DVM[2]; Danielle Biggs, BS, RVT[1]; Rubi Hayim, BS[3]; Kara Magee, DVM, DACVIM[3]; Rachel McMahon, DVM, DACVIM[3]; Irene Mok, BA[1]; Ann Marie Picone, DVM[3]; Jessica Ralston, BS[1]; Brittany M. Smith, BS[5]; Rachel Uyehara, DVM[3]; Amanda L. Willis, MS[1]; Stephen Albert Johnston, PhD[6,7]; Douglas H. Thamm, VMD, DACVIM[1]

[1]Flint Animal Cancer Center, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO
[2]Carbone Cancer Center, University of Wisconsin-Madison, Madison, WI
[3]Department of Medical Sciences, School of Veterinary Medicine, University of Wisconsin-Madison, Madison, WI
[4]Department of Surgical and Radiological Sciences, School of Veterinary Medicine, University of California-Davis, Davis, CA
[5]Veterinary Center for Clinical Trials, School of Veterinary Medicine, University of California-Davis, Davis, CA
[6]Calviri Inc, Phoenix, AZ
[7]Center for Innovations in Medicine, Biodesign Institute, Arizona State University, Tempe, AZ

*Corresponding author: Dr. Burton (jhburton@colostate.edu)

OBJECTIVE
To determine the prevalence of undiagnosed malignant neoplasms in a cohort of healthy middle-aged to older dogs.

METHODS
Healthy, client-owned dogs between the ages of 5.5 and 11.5 years and of mixed breed or breeds overrepresented for death due to cancer were screened for eligibility to participate in the Vaccination Against Canine Cancer Study at 3 study sites from May 6, 2019, to June 21, 2022. Physical examination with rectal evaluation and aspiration cytology of dermal and subcutaneous masses, CBC, biochemical profile, urinalysis, 3-view thoracic radiographs, and abdominal ultrasound were performed to identify occult cancer or other serious disease in all patients prior to study enrollment.

RESULTS
902 dogs were screened for participation in the Vaccination Against Canine Cancer Study. At the time of screening, 24 dogs (2.7%) were diagnosed with cancer, while another 30 dogs (3.3%) had abnormalities identified for which malignant neoplasia could not be ruled out but was not definitively confirmed. The prevalence of confirmed cancer in this population was 2.7% and 6.0% when cases in which malignant neoplasia was suspected were included. For the 24 dogs definitively diagnosed with cancer, the diagnosis was made on the basis of physical examination with aspiration cytology of a dermal or subcutaneous mass for 20 dogs (83%).

CONCLUSIONS
Routine physical examination was able to detect the majority of the malignant tumors in this population of dogs.

CLINICAL RELEVANCE
A thorough physical examination, including rectal examination, with aspiration cytology of dermal or subcutaneous lesions is a critical component of cancer screening for middle-aged and older dogs.

Keywords: cancer, screening, healthy dogs, prevalence, malignant neoplasm

Cancer screening is commonly used in physician-based medicine to identify preneoplastic lesions and neoplastic disease prior to development of cancer-related symptoms. Cancer screening for people may occur through physical examination (eg, skin or breast examination), laboratory-based tests such as Pap smears and prostate-specific antigen testing, imaging procedures such as mammography or colonoscopy, or genetic screening in higher-risk populations for specific cancers to identify genetic mutations that are associated with increased risk of tumor development. The major benefit of cancer screening is detection of malignancies at an earlier and often more treatable stage of disease, ideally resulting in improved long-term patient outcomes.

For cancer screening to be effective, a test or procedure must be able to detect cancers prior to the

Received July 24, 2024
Accepted October 24, 2024
Published online November 22, 2024

doi.org/10.2460/javma.24.07.0463

development of cancer-related symptoms and evidence must exist that treatment initiated earlier as a consequence of screening results in improved patient outcomes.[1] Additionally, the potential harms that may result from cancer screening including test-related complications, false-positive and false-negative results, and overdiagnosis of malignancies that would never become clinically apparent to the patient must be balanced with the potential benefit of earlier detection.[2] The balance of benefit to harm is more favorable to individuals at higher risk for development of a specific cancer, and to best strike this balance, evidence-based screening guidelines exist that provide risk-based recommendations for cancer screening indications for people.[3] Cancer screening recommendations for people are based on a combination of gender, age, location of cancer development, as well as familial, lifestyle, and/or genetic risk factors.[3]

There is growing interest in cancer screening in veterinary medicine. Cancer is the leading cause of death in older dogs,[4] and some veterinary patients may have an improved outcome when their cancer is detected and treated at an earlier stage of disease.[5–8] There are several multicancer screening tests currently available for dogs that are commercially available to pet owners with reported specificity and sensitivity for these assays to help users understand the benefits and limitations of these tests.[9–11] However, it is challenging to understand the positive predictive value (PPV) of any veterinary screening test, as the prevalence of the underlying and undiagnosed cancer in the target population being screened needs to be known to calculate PPV.[12] This information is readily available in human medicine through programs such as the National Cancer Institute Surveillance, Epidemiology, and End Results Program,[13] but a lack of national veterinary cancer registries has prevented our full understanding of the true prevalence of cancer in dogs in the US.

More recently, the Dog Aging Project (DAP) reported a 3.0% prevalence of malignant tumor diagnosis within a cohort of 27,541 dogs enrolled in the DAP, which is lower than the prevalence reported from other countries that maintain veterinary cancer registries.[14] These cancer diagnoses were owner-reported, and cytologic or histological confirmation was not required, which may have led to either under- or overreporting of malignant tumor diagnoses. Still, these data begin to fill a critical gap in our knowledge regarding the prevalence of cancer diagnosis in dogs in the US.

To further address the gap in our knowledge regarding the prevalence of cancer in dogs, we sought to review the prevalence of occult cancer in a population of middle- to older-aged dogs screened for eligibility for participation in a cancer preventative clinical trial. The primary objective of this study was to determine the prevalence of previously undiagnosed malignant neoplasms in a cohort of healthy middle-aged to older dogs. A secondary objective was to determine the diagnostic methods by which these neoplasms were most frequently identified.

Methods

Healthy dogs aged 5.5 to 11.5 years were recruited for enrollment into the Vaccination Against Canine Cancer Study (VACCS) from May 6, 2019, to June 21, 2022, at the Colorado State University Flint Animal Cancer Center, University of Wisconsin-Madison School of Veterinary Medicine, and University of California-Davis School of Veterinary Medicine. To be eligible for the study, dogs needed to be of mixed breed or one of the following breeds: Afghan Hound, Airedale Terrier, Alaskan Malamute, Basset Hound, Beagle, Bernese Mountain Dog, Boxer, Briard, Bullmastiff, Cocker Spaniel, Corgi, English Setter, Field Spaniel, Flat-Coated Retriever, French Bulldog, German Shorthaired Pointer, Giant Schnauzer, Golden Retriever, Gordon Setter, Irish Setter, Irish Water Spaniel, Spinone Italiano, Keeshond, Labrador Retriever, Leonberger, Newfoundland, Norwegian Elkhound, Nova Scotia Duck Tolling Retriever, Old English Sheepdog, Petit Basset Griffon Vendéen, Rhodesian Ridgeback, Rottweiler, Saluki, Siberian Husky, Staffordshire Bull Terrier, Standard Poodle, Tibetan Terrier, and Vizsla. These breeds have been previously reported to be overrepresented for death due to cancer.[15] Additionally, dogs at increased risk of developing specific tumor types were also eligible, including Scottish Terrier, West Highland White Terrier, and Shetland Sheepdog (urothelial carcinoma)[16]; Borzoi, Great Pyrenees, Irish Wolfhound, and Deerhound (osteosarcoma)[17,18]; German Shepherd Dog (hemangiosarcoma)[19]; Springer Spaniel (mammary carcinoma)[20]; and Boston Terrier (mast cell tumor).[21] Mixed-breed dogs were included, as they are frequently the most commonly represented "breed" in oncology studies and have been shown to have a similar predisposition to cancer development in a large-scale study.[14,22] Dogs could not have been previously diagnosed with cancer or have had significant comorbidities that would prevent obtaining 5 years of follow-up. Owners were required to live within 150 miles from one of the study sites to enroll their pet. The full eligibility criteria and clinical trial design have been previously published elsewhere.[23] The VACCS trial was approved by and carried out in accordance with the IACUC and/or Clinical Review Board at all 3 sites (Colorado State University approval No. 585; University of Wisconsin-Madison approval No. V-006039; University of California-Davis approval No. 20463); informed owner consent was obtained for all dogs enrolled.

To assess dogs for occult neoplasia prior to enrollment into the clinical trial, a physical examination was performed by a study veterinarian with measurement, fine-needle aspiration, and cytologic assessment of dermal and subcutaneous masses. Initial cytologic assessment was performed by either an oncologist or oncology specialty intern or resident; if concerning cells were noted, the sample was recommended to be submitted for evaluation by a clinical pathologist. If a definitive diagnosis could not be obtained with cytology, biopsy and histopathology were recommended. A CBC, chemistry panel, urinalysis, and prothrombin time/partial thromboplastin time test were performed as well as 3-view thoracic radiographs and abdominal

ultrasound; diagnostic images were evaluated by a board-certified radiologist. If a lesion was noted on imaging and a malignant neoplastic process could not be ruled out, sampling was offered or reimaging to reassess the lesion(s) was performed in 4 to 6 weeks. If the lesions were unchanged, resolved, or cytologically benign, these dogs were eligible for inclusion into the VACCS. Dogs were excluded from the study if the lesions had progressed during that time or if owners declined reassessment of the abnormalities. Dogs with a previous history or current diagnosis of a benign tumor were still eligible for enrollment.

Age, weight, sex, and breed were abstracted for all dogs screened for the VACCS. Cancer diagnosis or lesion of concern was reported for dogs definitively diagnosed or suspected to have cancer, respectively. The method of detection was also reported for all suspected or definitively diagnosed cancers. For dogs in which cancer was not definitively diagnosed, 2 investigators (JB and the site primary investigator [DT, DV, or SA]) independently assigned a degree of suspicion of high, moderate, or low that the lesion was malignant. If the 2 initial reviewers were not in agreement, the case information was reviewed by all 4 investigators to reach consensus regarding the designation of high, moderate, or low suspicion.

Statistical analysis

Continuous data were assessed for normality with a Shapiro-Wilk test and reported as mean and SD or median and IQR. Categorical data were reported as percentages. Differences in age and weight between dogs without cancer and dogs suspected or diagnosed with cancer were assessed with a 2-tailed, unpaired Mann-Whitney test, and differences in sex were assessed with a Fisher exact test. Statistical analysis was performed in Prism (version 10.2.0; GraphPad Software), and *P* values < .05 were considered statistically significant.

Results

Of the 902 dogs screened for enrollment into the VACCS, 97 (10.8%) were determined to be ineligible to participate in the clinical trial **(Figure 1)**.

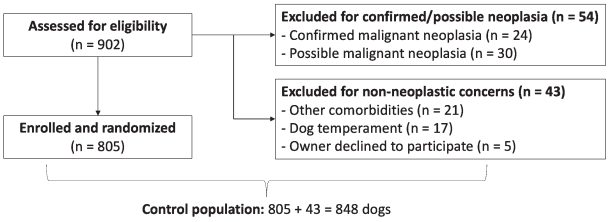

Figure 1—Flow diagram for the 902 healthy dogs aged 5.5 to 11.5 years that were screened for enrollment into the Vaccination Against Canine Cancer Study, a randomized, blinded, placebo-controlled clinical trial investigating a cancer preventative vaccine. Mixed-breed dogs or breeds at higher risk of dying from cancer were screened for occult neoplasia at 1 of 3 study sites—Colorado State University, University of Wisconsin-Madison, and University of California-Davis—from May 6, 2019, to June 21, 2022.

Fifty-four dogs were excluded because of confirmation or concern for cancer; 24 dogs (2.7%) were diagnosed with a malignant neoplasm and 30 (3.3%) were excluded as malignant neoplasia was not definitively diagnosed but could not be excluded. Twenty-one dogs (2.3%) were excluded because of bloodwork abnormalities or other diseases that may have impacted follow-up of these dogs for 5 years **(Supplementary Table S1)**, 17 dogs (1.9%) were excluded due to fearful or aggressive temperament, and 5 dogs (0.5%) were not enrolled due to owner decision. The 805 dogs that enrolled in the VACCS clinical trial as well as the 43 dogs that were excluded for reasons other than confirmed or suspected neoplasia served as the control group in this study (n = 848).

The demographics of dogs screened for the study are reported in **Table 1**. Age, weight, and sex were compared between dogs without overt cancer (n = 848) and dogs with or suspected to have malignant neoplasia (54). Dogs diagnosed with or suspected to have cancer at screening were significantly older (8.0 years; IQR, 7.0 to 9.5 years) than dogs without cancer detected (7.0 years; IQR, 6.0 to 9.0 years; $P < .01$). There was no significant difference in weight, sex, or neuter status between the groups.

As diagnosis of malignant neoplasia excluded dogs from further participation in the VACCS, not all dogs had all diagnostic tests performed. Of the 902 dogs screened for the study, 16 dogs (1.8%) did not have screening bloodwork and urinalysis performed, 18 dogs (2.0%) did not have thoracic radiographs performed, and 22 dogs (2.4%) did not have an abdominal ultrasound performed.

For the 24 dogs diagnosed with a malignant neoplasm at screening, mast cell tumors were diagnosed most commonly (10 [41.7%]). Other tumors diagnosed included apocrine gland anal sac adenocarcinoma (3 [12.5%]), soft tissue sarcoma (3 [12.5%]), thyroid carcinoma (2 [8.3%]), dermal hemangiosarcoma (2 [8.3%]), and 1 case each of urothelial carcinoma, histiocytic sarcoma, B-cell chronic lymphocytic leukemia, and basal cell carcinoma. Twenty of these 24 malignancies (83%) were detected by physical examination, 2 were detected by bloodwork abnormalities (lymphocytosis [n = 1] and hypercalcemia [1]), 1 (4.2%) was detected via abdominal ultrasound, and 1 (4.2%) was detected on thoracic radiographs **(Table 2)**. Cytologic and/or histologic assessment was performed by a board-certified pathologist, except for 3 dogs diagnosed with mast cell tumor, in which the diagnosis was made by cytologic review by a board-certified medical oncologist.

Thirty dogs had lesions identified at screening for which malignant neoplasia could not be excluded, and these included pulmonary masses or nodules (6 [20.0%]), splenic nodules (6 [20.0%]), adrenal mass/nodule (5 [16.7%]), suspected skin cancer (4 [13.3%]), urinary bladder mass (2 [6.7%]), splenic mass/nodules with peritoneal effusion (2 [6.7%]), and 1 (3.3%) each of anal sac nodule, kidney nodule, mammary mass, retroperitoneal mass, and prostatic mass. Eleven dogs (36.7%) were considered to

Table 1—Demographics of 902 healthy dogs aged 5.5 to 11.5 years that were screened for enrollment into the Vaccination Against Canine Cancer Study, a randomized, blinded, placebo-controlled clinical trial investigating a cancer preventative vaccine. Mixed-breed dogs or breeds at higher risk of dying from cancer were screened for occult neoplasia at 1 of 3 study sites—Colorado State University, University of Wisconsin-Madison, and University of California-Davis—from May 6, 2019, to June 21, 2022. Dogs were grouped on the basis of whether they had no evidence of malignant neoplasia (n = 848), had definitive diagnosis of malignant neoplasia (24), or were suspected to have malignant neoplasia at the time of screening (30).

	Dogs without neoplasia at screening (n = 848)	Dogs excluded for diagnosed neoplasia (n = 24)	Dogs excluded for possible neoplasia (n = 30)
Median (IQR) weight (kg)	27.7 (21.0–34.1)	25.2 (17.9–32.5)	31.0 (25.7–38.0)
Not recorded	3 (0.4)	0	0
Median (IQR) age (y)	7.0 (6.0–9.0)	8.5 (7.0–9.9)	8.0 (7.0–9.0)
Sex			
Female, intact	20 (2.4)	1 (4.2)	2 (6.7)
Female, spayed	430 (50.7)	7 (29.2)	15 (50)
Male, intact	43 (5.1)	1 (4.2)	2 (6.7)
Male, neutered	355 (41.9)	15 (62.5)	11 (36.7)
Breed			
Mixed breed	369 (43.5)	13 (54.2)	12 (40.0)
Golden Retriever	134 (15.8)	2 (8.3)	3 (10.0)
Labrador Retriever	93 (11.0)	1 (4.2)	2 (6.7)
German Shepherd Dog	19 (2.2)	—	—
Bernese Mountain Dog	17 (2.0)	—	4 (13.3)
German Shorthair Pointer	17 (2.0)	—	—
Vizsla	14 (1.7)	—	1 (3.3)
Standard Poodle	12 (1.4)	—	—
Beagle	11 (1.3)	—	—
Flat-Coated Retriever	10 (1.2)	—	—
Corgi	9 (1.1)	—	—
Leonberger	9 (1.1)	1 (4.2)	1 (3.3)
Newfoundland	9 (1.1)	—	—
Boston Terrier	8 (0.9)	1 (4.2)	—
Spinone Italiano	8 (0.9)	—	—
Shetland Sheepdog	8 (0.9)	—	1 (3.3)
Siberian Husky	8 (0.9)	—	—
Springer Spaniel	8 (0.9)	—	1 (3.3)
Boxer	7 (0.8)	3 (12.5)	1 (3.3)
English Setter	7 (0.8)	—	—
French Bulldog	7 (0.8)	1 (4.2)	—
Rottweiler	6 (0.7)	—	1 (3.3)
West Highland White Terrier	6 (0.7)	1 (4.2)	—
Bullmastiff	5 (0.6)	—	—
Alaskan Malamute	4 (0.5)	—	—
Cocker Spaniel	4 (0.5)	—	—
Gordon Setter	4 (0.5)	—	—
Basset Hound	3 (0.4)	—	—
Borzoi	3 (0.4)	—	—
Great Pyrenees	3 (0.4)	—	1 (3.3)
Irish Wolfhound	3 (0.4)	—	—
Saluki	3 (0.4)	—	—
Staffordshire Bull Terrier	3 (0.4)	—	—
Airedale Terrier	2 (0.2)	—	1 (3.3)
Field Spaniel	2 (0.2)	1 (4.2)	—
Keeshond	2 (0.2)	—	1 (3.3)
Rhodesian Ridgeback	2 (0.2)	—	—
Scottish Terrier	2 (0.2)	—	—
Tibetan Terrier	2 (0.2)	—	—
Giant Schnauzer	1 (0.1)	—	—
Irish Setter	1 (0.1)	—	—
Irish Water Spaniel	1 (0.1)	—	—
Norwegian Elkhound	1 (0.1)	—	—
Other; Australian Cattle Dog	1 (0.1)	—	—

Data are presented as number (%) of dogs unless otherwise specified.

have a low suspicion that the lesion identified was malignant neoplasia, 12 dogs (40%) were considered to have a moderate suspicion, and 7 dogs (23.3%) were considered to have a high degree of suspicion that the lesion identified on screening was malignant neoplasia. Abnormalities in these 30 dogs were detected by physical examination in 6 dogs (20%), thoracic radiographs in 6 dogs (20%), and abdominal ultrasound in 18 dogs (60%) (Table 2).

Malignant neoplasia was definitively diagnosed at a prevalence of 2.7% and could not be ruled out in another 3.3% of the 902 dogs screened for the VACCS trial. When

Table 2—Prevalence of definitively diagnosed or suspected malignant neoplasia and method of detection for the 902 dogs described in Table 1.[23] Abnormalities noted on the various detection methods led to additional diagnostic testing, such as cytology or histopathology, to reach a definitive diagnosis of neoplasia.

	Definitive diagnosis of cancer	Definitive diagnosis + high suspicion	Definitive diagnosis + moderate to high suspicion	Definitive diagnosis + any suspicion
No. (%) of dogs	24 (2.7)	31 (3.4)	43 (4.8)	54 (6.0)
Method of detection				
Physical examination	20 (83.3)	21 (67.7)	25 (58.1)	27 (50.0)
CBC, biochemical profile, and urinalysis	2 (8.3)	0	0	2 (3.7)
Thoracic radiographs	1 (4.2)	4 (12.9)	6 (14.0)	7 (13.0)
Abdominal ultrasound	1 (4.2)	6 (19.4)	12 (27.9)	21 (38.9)

Table 3—Prevalence of cancer in the population of dogs described in Table 1 compared between the overall population of dogs screened for the Vaccination Against Canine Cancer Study as compared to breeds at higher risk for cancer development that included Golden Retrievers (n = 134), Boxers (7), Bernese Mountain Dogs (17), and mixed-breed dogs (394). As some dogs were not definitively diagnosed with cancer but had lesions for which neoplasia remained a differential diagnosis, 3 separate analyses were performed to evaluate dogs that had been definitively diagnosed with cancer, dogs with a definitive diagnosis and that had lesions that were highly suspicious for cancer, and dogs that were definitely diagnosed and had any degree of suspicion that cancer was present.

	All dogs (n = 902)		Higher-risk breeds (n = 171)		Mixed-breed dogs (n = 394)		
	n	Prevalence (%)	n	Prevalence (%)	n	Prevalence (%)	*P* value
Definitive diagnosis of cancer	24	2.7	5	2.9	13	3.3	.85
Definitive diagnosis + high suspicion	31	3.4	6	3.5	15	3.8	.98
Definitive diagnosis + any suspicion	54	6.0	13	7.6	25	6.3	.74

dogs with a definitive diagnosis or a high suspicion of cancer were considered, the prevalence of detection was 3.4%; when all dogs with definitive or suspected cancer were included, the prevalence of cancer detected was 6.0% in this population **(Table 3)**. Breeds considered at highest risk for cancer development—Golden Retrievers, Bernese Mountain Dogs, and Boxers—were analyzed separately to determine whether the prevalence of cancer detection would be different for these breeds (Table 3); results were not statistically different when compared to the overall study population or to mixed-breed dogs.

Discussion

This study found that the prevalence of occult malignant neoplasia in this population of 902 older, healthy dogs is in the range of 2.7% to 6.0%, with the latter including dogs both definitively diagnosed and suspected to have underlying cancer. The majority of these tumors were identified on physical examination and the diagnosis confirmed with fine-needle aspiration and cytology, emphasizing the importance of routine physical examination in the detection of cancer in dogs and conveyance to the owner of the importance of aspiration of all accessible masses with analysis by an evaluator with cytologic expertise. Neoplastic conditions were identified by routine bloodwork for 2 dogs in this population, in addition to identification of other health conditions such as azotemia and hepatopathies.

Dogs diagnosed or suspected to have cancer were statistically older than dogs screened for VACCS that were not suspected to have cancer with a median age of 8 and 7 years, respectively. This age is similar to what is reported by Rafalko et al,[24] who determined the median age of cancer diagnosis to be 8.8 years when they analyzed the age of cancer diagnosis in > 3,400 dogs, with a mean of 8.0 years when age analysis was limited to purebred dogs. Weight was not different between the dogs screened and not diagnosed with cancer versus those that were confirmed or suspected to have malignant neoplasia in this study, whereas increased body size based on size class (toy or small, medium, standard, and large or giant) has been associated with cancer development in a previous study.[14] This finding may have been due to the breed restrictions for VACCS enrollment, as these dogs tended to be larger-breed dogs. Additionally, there was a minimum weight requirement of 5.0 kg for VACCS enrollment due to the blood volume collected at study visits, and this requirement likely skewed this study population to heavier dogs as well.

The frequency that cancer was definitively diagnosed by physical examination combined with cytologic assessment of dermal and subcutaneous masses was 83% but dropped to 50% when definitive diagnoses and suspected neoplastic conditions were evaluated together. This is potentially due to the increased cost and perceived invasiveness of obtaining a diagnosis with percutaneous ultrasound-guided aspirates resulting in clients declining these procedures

for their pets. Additionally, full staging with thoracic radiographs and abdominal ultrasound was not always completed for every dog screened for the VACCS if cancer was identified on examination, as they had already failed the screening process. It is possible that additional and potentially unrelated neoplastic conditions may have been identified if all screening diagnostic tests had been performed for every dog. However, detection of neoplastic conditions by physical examination in the majority of dogs diagnosed with cancer in this study emphasizes the importance of this fundamental skill in detecting cancer in aging dogs. As apocrine gland anal sac adenocarcinomas were the second most commonly diagnosed tumor after mast cell tumors, performing a rectal examination as part of a routine physical examination is essential for earlier detection of these tumors specifically. Dogs with small (< 3.2-cm) nonmetastatic apocrine gland anal sac adenocarcinoma are reported to have median survival times of > 3 years when treated only with surgical removal of the primary tumor, highlighting the potential benefit of detection of these tumors prior to lymph node metastasis developing, which is associated with survival times of about 1.5 years with surgery with or without chemotherapy.[7,25,26] However, it is also important to note that 20% of dogs with < 2-cm apocrine gland anal sac adenocarcinomas have lymph node metastasis at the time of diagnosis, indicating that detection of a primary tumor at a smaller size is not necessarily reflective of the overall tumor behavior.[27]

There were several limitations to this study. Cancers arising from the skin and subcutaneous tissues or within thoracic and abdominal cavities could be assessed; however, bone or CNS tumors were unlikely to be detected with these methods prior to development of clinical signs. The oral cavity can also be a challenging location to evaluate fully. Dogs enrolled in the VACCS needed to be amenable to repeated examinations and venipuncture; therefore, a thorough oral examination was able to be performed in this patient population. It is important to note that these findings may not be widely applicable to other populations of dogs due to the inclusion/exclusion criteria of the VACCS and that the owners of this group of dogs had the time and resources to consider participation in a clinical trial that would require multiple visits over 5 years.

Another limitation to this study was how the cytologic assessment was performed during the screening process. Initial cytologic assessment performed by a medical oncology specialist or trainee could have led to the possibility that some malignant masses were interpreted to be benign. As all but 3 mast cell tumors were submitted for evaluation by a clinical pathologist, it is unlikely that benign tumors would have been classified as malignant. The cytologic agreement with histopathology for neoplastic conditions is very good, with a sensitivity of 89.3% and specificity of 97.9%,[28] but there does not exist information in our profession regarding the accuracy of veterinarians to diagnose a lipoma or other common benign lesions, which represent the majority of dermal and subcutaneous lesions assessed during the screening process. However, if there was clinical concern that a lesion may be malignant on the basis of appearance, reported growth by client, and/or location and could not be readily confirmed by cytologic assessment, further workup with biopsy and histopathology was recommended prior to enrollment. If owners chose not to pursue these additional diagnostics, these dogs were not enrolled in the study but were captured in the study population for which malignant neoplasia could not be ruled out.

The prevalence of diagnosed or suspected cancer was not higher in Golden Retrievers, Bernese Mountain Dogs, and Boxers compared to the overall population or mixed-breed dogs screened for the VACCS. This finding was likely due to the VACCS eligibility requirements, which limited enrollment to mixed breeds and breeds at higher risk for cancer development. A study[22] of > 27,000 dogs examined a variety of inherited disorders, including cancer, and results suggested that purebred dogs were not more predisposed to develop cancer as compared to mixed-breed dogs, which goes against the widely held assumption that mixed-breed dogs are at lower risk of cancer development than purebred dogs. Another possibility is limited statistical power to assess this due to the small number of cases in each group as well as the predominance of mixed-breed dogs enrolled (43% of the study population). It is possible that, as the VACCS continues and enrolled dogs are followed over the 5-year study period, we may see differences in cancer development between these different groups; analysis is planned at the completion of the VACCS trial.

There were limitations to this study that prevent broad application of our findings to all dogs. As the VACCS eligibility criteria had restrictions on breeds that could be enrolled and required a minimum body weight of 5.0 kg, these data do not reflect the canine population as a whole. The aforementioned study criteria could have led to an overestimation of occult cancer prevalence in a more diverse canine population. Alternatively, the knowledge that VACCS enrollment was for dogs that were healthy with no current or previous cancer diagnosis may have caused owners to self-select out from eligibility screening if they were concerned that their dog may have had some underlying but undiagnosed health condition, which ultimately may have led to underestimation of the prevalence of cancer in this study population. However, the prevalence of definitive cancer diagnosis in this population of 2.7% and up to 3.4% when dogs highly suspected to have cancer were included was in line with the 3.0% prevalence reported by the DAP group and lower than the 8% to 10% prevalence of cancer in dogs screened for cancer estimated for the PPV calculation for one of the blood-based assays previously available for cancer screening in dogs.[9] We note that the prevalence is dependent on the sensitivity of the test applied. Given the difference between studies and prevalence estimates, the question of the best value to use for PPV calculations is still open.

In conclusion, the prevalence of occult malignant neoplasia in healthy middle-aged to older dogs appears low, and many of these cancers can be detected with a thorough physical examination that includes a rectal examination. Aspiration and cytologic evaluation of subcutaneous and dermal masses identified on examination provided a diagnosis for the majority of dogs in this study population.

Acknowledgments

None reported.

Disclosures

Drs. Johnston and Thamm are shareholders in Calviri Inc, which is commercializing the frameshift vaccination technology and diagnostics used in the Vaccination Against Canine Cancer Study. Dr. Willcox is currently an employee if Antech Diagnostics, Mars Petcare Science and Diagnostics.

No AI-assisted technologies were used in the generation of this manuscript.

Funding

This study was funded by Open Philanthropy, Calviri Inc, and the Barbara A. Suran Comparative Research Endowment.

ORCID

J. H. Burton https://orcid.org/0000-0002-1895-8298
D. H. Thamm https://orcid.org/0000-0002-8914-7767

References

1. PDQ Screening and Prevention Editorial Board. PDQ cancer screening overview. National Cancer Institute. Updated October 16, 2023. Accessed February 16, 2024. https://www.cancer.gov/about-cancer/screening/hp-screening-overview-pdq
2. Smith RA. The development of cancer screening guidelines. *Med Clin North Am*. 2020;104(6):955–970. doi:10.1016/j.mcna.2020.08.009
3. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2019: a review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin*. 2019;69(3):184–210. doi:10.3322/caac.21557
4. Fleming JM, Creevy KE, Promislow DE. Mortality in North American dogs from 1984 to 2004: an investigation into age-, size-, and breed-related causes of death. *J Vet Intern Med*. 2011;25(2):187–198. doi:10.1111/j.1939-1676.2011.0695.x
5. Chang SC, Chang CC, Chang TJ, Wong ML. Prognostic factors associated with survival two years after surgery in dogs with malignant mammary tumors: 79 cases (1998–2002). *J Am Vet Med Assoc*. 2005;227(10):1625–1629. doi:10.2460/javma.2005.227.1625
6. Wendelburg KM, Price LL, Burgess KE, Lyons JA, Lew FH, Berg J. Survival time of dogs with splenic hemangiosarcoma treated by splenectomy with or without adjuvant chemotherapy: 208 cases (2001–2012). *J Am Vet Med Assoc*. 2015;247(4):393–403. doi:10.2460/javma.247.4.393
7. Skorupski KA, Alarcón CN, de Lorimier LP, LaDouceur EEB, Rodriguez CO, Rebhun RB. Outcome and clinical, pathological, and immunohistochemical factors associated with prognosis for dogs with early-stage anal sac adenocarcinoma treated with surgery alone: 34 cases (2002–2013). *J Am Vet Med Assoc*. 2018;253(1):84–91. doi:10.2460/javma.253.1.84
8. Tuohy JL, Selmic LE, Worley DR, Ehrhart NP, Withrow SJ. Outcome following curative-intent surgery for oral melanoma in dogs: 70 cases (1998–2011). *J Am Vet Med Assoc*. 2014;245(11):1266–1273. doi:10.2460/javma.245.11.1266
9. Flory A, Kruglyak KM, Tynan JA, et al. Clinical validation of a next-generation sequencing-based multi-cancer early detection "liquid biopsy" blood test in over 1,000 dogs using an independent testing set: the CANcer Detection in Dogs (CANDiD) study. *PLoS One*. 2022;17(4):e0266623. doi:10.1371/journal.pone.0266623
10. Wilson-Robles H, Miller T, Jarvis J, et al. Evaluation of nucleosome concentrations in healthy dogs and dogs with cancer. *PLoS One*. 2020;15(8):e0236228. doi:10.1371/journal.pone.0236228
11. Selting KA, Sharp CR, Ringold R, Knouse J. Serum thymidine kinase 1 and C-reactive protein as biomarkers for screening clinically healthy dogs for occult disease. *Vet Comp Oncol*. 2015;13(4):373–384. doi:10.1111/vco.12052
12. Pinsky PF. Principles of cancer screening. *Surg Clin North Am*. 2015;95(5):953–966. doi:10.1016/j.suc.2015.05.009
13. Surveillance, Epidemiology, and End Results Program. National Cancer Institute. Accessed February 29, 2024. https://seer.cancer.gov/
14. Schwartz SM, Urfer SR, White M, Megquier K, Shrager S, Ruple A; Dog Aging Project Consortium. Lifetime prevalence of malignant and benign tumours in companion dogs: cross-sectional analysis of Dog Aging Project baseline survey. *Vet Comp Oncol*. 2022;20(4):797–804. doi:10.1111/vco.12839
15. Dobson JM. Breed-predispositions to cancer in pedigree dogs. *ISRN Vet Sci*. 2013;2013:941275. doi:10.1155/2013/941275
16. Knapp DW, Ramos-Vara JA, Moore GE, Dhawan D, Bonney PL, Young KE. Urinary bladder cancer in dogs, a naturally occurring model for cancer biology and drug development. *ILAR J*. 2014;55(1):100–118. doi:10.1093/ilar/ilu018
17. Ru G, Terracini B, Glickman LT. Host related risk factors for canine osteosarcoma. *Vet J*. 1998;156(1):31–39. doi:10.1016/S1090-0233(98)80059-2
18. Phillips JC, Stephenson B, Hauck M, Dillberger J. Heritability and segregation analysis of osteosarcoma in the Scottish Deerhound. *Genomics*. 2007;90(3):354–363. doi:10.1016/j.ygeno.2007.05.001
19. Prymak C, McKee LJ, Goldschmidt MH, Glickman LT. Epidemiologic, clinical, pathologic, and prognostic characteristics of splenic hemangiosarcoma and splenic hematoma in dogs: 217 cases (1985). *J Am Vet Med Assoc*. 1988;193(6):706–712.
20. Moe L. Population-based incidence of mammary tumours in some dog breeds. *J Reprod Fertil Suppl*. 2001;57:439–443.
21. Villamil JA, Henry CJ, Bryan JN, et al. Identification of the most common cutaneous neoplasms in dogs and evaluation of breed and age distributions for selected neoplasms. *J Am Vet Med Assoc*. 2011;239(7):960–965. doi:10.2460/javma.239.7.960
22. Bellumori TP, Famula TR, Bannasch DL, Belanger JM, Oberbauer AM. Prevalence of inherited disorders among mixed-breed and purebred dogs: 27,254 cases (1995–2010). *J Am Vet Med Assoc*. 2013;242(11):1549–1555. doi:10.2460/javma.242.11.1549
23. Burton JH, Johnston SA, Vail DM, et al. Design of a randomized, placebo-controlled study evaluating efficacy and safety of a cancer preventative vaccine in dogs. *Vet Immunol Immunopathol*. 2024;267:110691. doi:10.1016/j.vetimm.2023.110691
24. Rafalko JM, Kruglyak KM, McCleary-Wheeler AL, et al. Age at cancer diagnosis by breed, weight, sex, and cancer type in a cohort of more than 3,000 dogs: determining the optimal age to initiate cancer screening in canine patients. *PLoS One*. 2023;18(2):e0280795. doi:10.1371/journal.pone.0280795
25. Williams LE, Gliatto JM, Dodge RK, et al; Veterinary Cooperative Oncology Group. Carcinoma of the apocrine glands of the anal sac in dogs: 113 cases (1985–1995). *J Am Vet Med Assoc*. 2003;223(6):825–831. doi:10.2460/javma.2003.223.825
26. Morello EM, Cino M, Giacobino D, et al. Prognostic value of Ki67 and other clinical and histopathological factors in canine apocrine gland anal sac adenocarcinoma. *Animals (Basel)*. 2021;11(6):1649. doi:10.3390/ani11061649
27. Jones AE, Wustefeld-Janssens BG. A relatively high proportion of dogs with small apocrine gland anal sac adenocarcinoma (AGASACA) primary tumours present with locoregional lymph node metastasis. *Vet Comp Oncol*. 2023;21(2):327–331. doi:10.1111/vco.12890
28. Ghisleni G, Roccabianca P, Ceruti R, et al. Correlation between fine-needle aspiration cytology and histopathology in the evaluation of cutaneous and subcutaneous masses from dogs and cats. *Vet Clin Pathol*. 2006;35(1):24–30. doi:10.1111/j.1939-165X.2006.tb00084.x

Supplementary Materials

Supplementary materials are posted online at the journal website: avmajournals.avma.org.