

Evaluation of the risk and age of onset of cancer and behavioral disorders in gonadectomized Vizslas

M. Christine Zink, DVM, PhD; Parvene Farhooody, MA; Samra E. Elser, BS; Lynda D. Ruffini; Tom A. Gibbons, MS; Randall H. Rieger, PhD

Objective—To investigate associations between age at gonadectomy and estimated risk or age at diagnosis of neoplastic and behavioral disorders in Vizslas.

Design—Retrospective cohort study.

Animals—2,505 Vizslas born between 1992 and 2008.

Procedures—Data on demographics, gonadectomy status, and age at diagnosis of disease or disorder were obtained with an anonymous online survey and analyzed.

Results—Dogs gonadectomized at ≤ 6 months, between 7 and 12 months, or at > 12 months of age had significantly increased odds of developing mast cell cancer, lymphoma, all other cancers, all cancers combined, and fear of storms, compared with the odds for sexually intact dogs. Females gonadectomized at ≤ 12 months of age and males and females gonadectomized at > 12 months of age had significantly increased odds of developing hemangiosarcoma, compared with the odds for sexually intact dogs. Dogs gonadectomized at ≤ 6 months of age had significantly increased odds of developing a behavioral disorder. The younger the age at gonadectomy, the earlier the mean age at diagnosis of mast cell cancer, cancers other than mast cell, hemangiosarcoma, lymphoma, all cancers combined, a behavioral disorder, or fear of storms.

Conclusions and Clinical Relevance—Additional studies are needed on the biological effects of removing gonadal hormones and on methods to render dogs infertile that do not involve gonadectomy. Veterinarians should discuss the benefits and possible adverse effects of gonadectomy with clients, giving consideration to the breed of dog, the owner's circumstances, and the anticipated use of the dog. (*J Am Vet Med Assoc* 2014;244:309–319)

Veterinarians, breeders, and owners have a particular interest in the health of purebred dogs. Estimating the risk of various diseases in a given breed can be helpful in guiding diagnostic decisions of veterinarians and can identify factors that might contribute to or accompany these disease conditions. Such knowledge can also guide breeders in selection and testing of breeding pairs, help national breed clubs direct their fundraising efforts to support research on the most common diseases that affect their specific breeds of dog, and inform the public regarding health issues that might be encountered when purchasing or adopting dogs of a specific breed.

From Zink Integrative Sports Medicine, 12701 Folly Quarter Rd, Ellicott City, MD 21042 (Zink); the Department of Psychology, Division of Mathematics and the Natural Sciences, Queens College, Flushing, NY 11367 (Farhooody); Veterinary Medical Scientist Training Program, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA 19104 (Elser); Moravia Veterinary Hospital, 68 Central St, Moravia, NY 13118 (Ruffini); and West Chester Statistics Institute (Gibbons, Rieger) and the Department of Mathematics and Statistics, College of Arts and Sciences (Rieger), West Chester University, West Chester, PA 19383. Ms. Ruffini's present address is Department of Psychology, Binghamton University, State University of New York, Binghamton, NY 13902. Mr. Gibbons' present address is Bogier Clinical and IT Solutions, 900 Ridgefield Dr, Raleigh, NC 27609.

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In 2008, the Vizsla Club of America Welfare Foundation sponsored and funded the Vizsla Health Survey to examine health issues in that breed.¹ The survey identified cancer and behavioral problems as the most prevalent diseases or disorders in the breed. Of the 2,505 dogs reported, 604 (24.1 %) had at least 1 type of cancer and 648 (25.9%) had behavioral disorders.¹ Cancer, specifically hemangiosarcoma and lymphoma, was listed as the most common cause of death in the Vizsla breed. Mast cell cancer, hemangiosarcoma, and lymphoma or lymphosarcoma were the leading types of cancer in the breed, and there was an association between gonadectomy and development of these cancers as well as between gonadectomy and behavioral problems.¹

Investigators in a number of studies have found associations between gonadectomy and an increased risk of various types of cancer, including hemangiosarcoma,^{2,3} prostate cancer,^{4–8} transitional cell carcinoma,^{6,9–11} and osteosarcoma.^{12–14} Investigators in other studies^{15–20} have found an association between gonadectomy and behavioral problems. Given the results of these studies and the association between cancer and behavioral problems and gonadectomy in Vizslas,¹ we were interested in determining whether there was a relationship between the risk of these problems and age at gonadectomy. Cancer was of particular interest because it is a major veterinary expense for owners and one of the most common causes of early death in dogs.²¹

Studies on the association between gonadectomy and orthopedic conditions, such as cranial cruciate ligament insufficiency,^{22–25} hip dysplasia,^{20,26} and patellar luxation,²⁷ have been published. Orthopedic disorders are uncommon in Vizslas.¹ The association between various orthopedic conditions and gonadectomy has been studied extensively in breeds more prone to such disorders; thus, we did not believe it necessary to evaluate the relationship between orthopedic conditions and gonadectomy in Vizslas.

Whether the increased risks for cancer and behavioral problems differ between male and female Vizslas gonadectomized at various ages was also considered important. This information would allow veterinarians and breeders to make recommendations regarding the optimal age at which dogs should undergo gonadectomy. This is particularly important for female dogs because it is thought that there is an increasing risk for mammary gland cancer^{28,29} and pyometra^{30–32} in bitches that remain sexually intact for a longer period before gonadectomy.

Therefore, the purpose of the study reported here was to examine data obtained in the study¹ on Vizslas to determine whether age at gonadectomy or sex of gonadectomized dogs altered the risks of cancer or behavioral problems or age of onset of these conditions. We hypothesized that even though the study¹ on Vizslas revealed differences in the estimated risk of cancer and behavioral problems between sexually intact dogs and dogs gonadectomized at any age, gonadectomy after puberty might not be associated with an increased risk. In other words, the associations detected in that study might have been a function of only prepubertal gonadectomy. In addition, we considered that analysis of age at diagnosis might provide additional information to support or refute findings in that study¹ of an increased risk of cancer and behavioral problems in gonadectomized dogs.

Materials and Methods

Data collection—Data on estimated risk and age of diagnosis of mast cell tumor, hemangiosarcoma, lymphoma or lymphosarcoma, all other cancers, and all cancers combined as well as estimated risk and age at diagnosis of behavioral problems were obtained for Vizslas from a survey conducted on that breed in 2008.¹ The survey was designed by statisticians at the West Chester Statistics Institute and administered via an anonymous online questionnaire at a site hosted by West Chester University Internet Presentations Group. There was a direct link to that site from the Vizsla Club of America website, and the survey was advertised in a variety of email lists, websites, magazines, and newsletters to which Vizsla owners would have access. Responses were allowed to be posted between January 21 and December 15, 2008.

Respondents were asked to indicate the age of their dogs at gonadectomy. Respondents could choose from the following options: gonadectomized at ≤ 6 months of age (the age at which many veterinarians recommend gonadectomy for pet dogs), between 7 and 12 months of age, or at > 12 months of age or not gonadectomized.

For each diagnosis, dogs were grouped into categories of males and females gonadectomized at ≤ 6

months, between 7 and 12 months, or at > 12 months of age or that remained sexually intact. This allowed us to investigate the effect of age at gonadectomy for each sex on the estimated risk of these conditions as reported by Vizsla owners.

Statistical analysis—All data were collected, tabulated, and statistically analyzed with the aid of statistical analysis software.^{a,b} The effect of sex as well as the interaction between sex and age at gonadectomy were considered in all analyses. An alternative analysis that coded gonadectomy as a dichotomous variable (yes or no), controlled for sex, was also conducted for each outcome. Logistic regression with parametric methods (or nonparametric methods when data did not have a normal distribution) was used to perform these analyses. In addition to logistic regression analyses, a survival analysis was conducted on each outcome. The analyses examined relationships between sex and gonadectomy status and mast cell cancer, hemangiosarcoma, lymphoma or lymphosarcoma, all other cancers, all cancers combined, death from all causes, all behavioral disorders combined, and fear of storms (the most commonly reported behavioral problem).

In addition to the most common types of cancer, there was a category for other cancers with an input field for text responses. If the other cancers category was selected but the text in the input field indicated that the disorder was a benign type of tumor (eg, lipoma), the disorder was considered noncancerous for the particular outcome being evaluated. If the other cancers category was selected but there was no reference to a specific type of cancer, this response was considered an outcome of interest only for the overall cancer outcome.

Gonadectomy may be used as a treatment for some behavioral problems and is often recommended as a means of ensuring that genetic material from dogs with behavioral problems does not enter the gene pool. Therefore, data of all dogs for which a behavioral problem was identified prior to gonadectomy were deleted during the analysis of the relationship between gonadectomy and all behavioral problems. Excluding dogs that might have been gonadectomized because of a behavioral problem eliminated a confounding factor that could have incorrectly suggested a stronger association between gonadectomy and behavioral problems. Because gonadectomy is not considered to be a treatment for fear of storms, the analysis for this disorder included all dogs.

The analyses for cancer included all dogs because gonadectomy is most often performed early in life, whereas cancer is generally a disease associated with advanced age. Furthermore, gonadectomy is not generally considered to be a treatment for cancer, except for cancers of the reproductive tract and some types of mammary gland cancer.

Kaplan-Meier time-to-event curves were used for comparisons among gonadectomy age categories as well as between male and female Vizslas. Significant differences between the unadjusted time to age of onset for each diagnosis was compared with a log rank test. Cox proportional hazard regression analysis was then performed to further investigate the effect of age at gonadectomy and sex on the age at diagnosis. Values of $P \leq 0.05$ were considered significant.

The survey included a field for the age at diagnosis for each disorder. However, for Vizslas that did not have a disorder of interest, age was imputed. For Vizslas reported as deceased but not having a disorder of interest, the age at time of death was used in the analysis. For Vizslas reported as alive but without a disorder of interest, age was calculated on the basis of the date the survey was completed and January 1 of the year of birth for that Vizsla. The direction of any possible bias in age imputation was to overestimate the age of Vizslas (both gonadectomized and sexually intact) that did not have a diagnosis, thereby causing Vizslas (both gonadectomized and sexually intact) that did not have a diagnosis to appear to have lived longer in the analysis.

Results

Sample—As reported elsewhere,¹ detailed health information for 2,505 purebred Vizslas born between 1992 and 2008 was obtained. At least 1 response was submitted from each of 25 countries. The majority of the responses were from the United States (86.7%), the United Kingdom (4.0%), Canada (3.5%), and Australia (2.6%).

Of the 1,431 dogs that were gonadectomized at the time of the survey, 362 (25.3%) were gonadectomized at

≤ 6 months of age, 298 (20.8%) were gonadectomized between 7 and 12 months of age, and 771 (53.9%) were gonadectomized at > 12 months of age. Of the 362 dogs that were gonadectomized at ≤ 6 months of age, 209 were females and 153 were males. Of the 298 dogs that were gonadectomized between 7 and 12 months of age, 157 were females and 141 were males. Of the 771 dogs that were gonadectomized at > 12 months of age, 459 were females and 312 were males. Frequencies of mast cell tumor, hemangiosarcoma, lymphoma or lymphosarcoma, all other cancers, all cancers combined, death (all causes), behavioral disorders, and fear of storms in female and male Vizslas on the basis of age at gonadectomy were tabulated (Table 1).

Mast cell cancer—Logistic regression analysis of the relationships among gonadectomy, sex, and mast cell cancer revealed that the odds of a male having mast cell cancer were not significantly ($P = 0.393$) different from the odds of a female having that cancer. When controlling for sex, the odds of a gonadectomized Vizsla having mast cell cancer were significantly ($P < 0.001$) higher (3.5 times as high) than were the odds for sexually intact dogs (Table 2). Dogs gonadectomized at ≤ 6 months, between 7 and 12 months, or at > 12 months

Table 1—Frequency (%) of various conditions in gonadectomized and sexually intact Vizslas.

Condition	Females				Males			
	≤ 6 months	7–12 months	> 12 months	Sexually intact	≤ 6 months	7–12 months	> 12 months	Sexually intact
Mast cell cancer	17 (0.7)	10 (0.4)	48 (1.9)	14 (0.6)	8 (0.3)	5 (0.2)	33 (1.3)	13 (0.5)
Hemangiosarcoma	7 (0.3)	5 (0.2)	28 (1.1)	3 (0.1)	0 (0)	3 (0.1)	16 (0.6)	11 (0.4)
Lymphoma or lymphosarcoma	4 (0.2)	3 (0.1)	15 (0.6)	3 (0.1)	4 (0.2)	3 (0.1)	10 (0.4)	4 (0.2)
All other cancers*	35 (1.6)	28 (1.2)	87 (3.9)	21 (0.9)	24 (1.1)	30 (1.3)	55 (2.5)	32 (1.4)
All cancers combined	63 (2.5)	46 (1.8)	174 (7.0)	40 (1.6)	36 (1.4)	40 (1.6)	109 (4.4)	59 (2.4)
Death (all causes)	29 (1.2)	25 (1.0)	122 (4.9)	43 (1.7)	22 (0.9)	26 (1.0)	77 (3.1)	58 (2.3)
All behavioral disorders	40 (1.8)	24 (1.1)	53 (2.4)	86 (3.9)	30 (1.4)	21 (1.0)	44 (2.0)	77 (3.5)
Fear of storms	30 (1.2)	22 (0.9)	57 (2.3)	19 (0.8)	11 (0.4)	17 (0.7)	31 (1.2)	14 (0.6)

Data were obtained from a survey¹ reported previously. Total number of dogs was not calculated because some dogs had > 1 condition.
*Other than mast cell cancer, hemangiosarcoma, and lymphoma or lymphosarcoma.

Table 2—The OR (95% confidence interval [CI]) for diseases or disorders in gonadectomized Vizslas.

	< 6 months		7–12 months		> 12 months		All ages	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Mast cell cancer	2.8 (5.0–1.6)	< 0.001	2.0 (3.9–1.1)	0.030	4.5 (7.0–2.9)	< 0.001	3.5 (5.4–2.3)	< 0.001
Hemangiosarcoma								
Females	6.0 (21.3–1.7)*	0.006	—	—	11.5 (38.5–3.5)	< 0.001	9.0 (29.4–2.8)	< 0.001
Males	2.0 (7.3–0.6)*	0.283	—	—	5.3 (18.2–1.5)	0.009	0.6 (1.4–0.3)	0.249
Lymphoma or lymphosarcoma	3.5 (9.6–1.3)	0.017	3.1 (9.4–1.0)	0.041	5.2 (12.0–2.2)	< 0.001	4.3 (9.7–1.9)	< 0.001
All other cancerst	4.1 (6.1–2.8)	< 0.001	5.0 (7.5–3.4)	< 0.001	5.4 (7.5–3.9)	< 0.001	5.0 (6.8–3.6)	< 0.001
All cancers combined								
All dogs	3.7 (5.1–2.7)	< 0.001	4.0 (5.5–2.9)	< 0.001	5.7 (7.4–4.4)	< 0.001	—	—
Females	—	—	—	—	—	—	6.5 (9.2–4.5)	< 0.001
Males	—	—	—	—	—	—	3.6 (4.9–2.6)	< 0.001
Behavioral disorder after gonadectomy	1.8 (2.4–1.3)	< 0.001	1.3 (1.9–0.9)	0.171	1.1 (1.4–0.8)	0.694	1.3 (1.6–1.0)	0.035
Fear of storms	3.9 (6.3–2.4)	< 0.001	4.7 (7.6–2.9)	< 0.001	4.0 (6.0–2.6)	< 0.001	4.1 (6.0–2.8)	< 0.001

Data were obtained from a survey¹ reported previously.
The referent category was sexually intact dogs. The OR was recorded for each sex when the values differed significantly ($P < 0.05$) between males and females.
*Data are for dogs gonadectomized at ≤ 12 months of age. †Other than mast cell cancer, hemangiosarcoma, and lymphoma or lymphosarcoma.
— = Not determined.

of age all had significantly greater odds (OR, 2.8, 2.0, and 4.5, respectively) of having mast cell cancer than the odds for sexually intact dogs.

In a separate analysis, the age at which a diagnosis of mast cell cancer was established was examined for dogs that were gonadectomized at various ages or remained sexually intact. This analysis revealed that mast cell cancer was diagnosed at a significantly ($P = 0.024$) younger age in gonadectomized dogs than in sexually intact dogs (Figure 1). There was no significant ($P = 0.502$) difference between females and males for the age at time of diagnosis of mast cell cancer.

Hemangiosarcoma—None of the male Vizslas gonadectomized at ≤ 6 months of age developed hemangiosarcoma; thus, the interaction between sex and age of gonadectomy could not be reliably analyzed on the basis of the aforementioned age categories (gonadectomy at ≤ 6 months, between 7 and 12 months, or at > 12 months of age). Therefore, dogs were assigned to 3 categories: gonadectomized at ≤ 12 months of age, gonadectomized at > 12 months of age, or remained sexually intact. Logistic regression analysis revealed that there were differences in the estimated odds of hemangiosarcoma for these age categories depending on whether the dogs were male or female. Overall, the odds of gonadectomized females having hemangiosarcoma were 9.0 times as high as ($P < 0.001$) the odds for sexually intact females (Table 2); there was no significant ($P = 0.249$) difference in the overall odds of gonadectomized males having hemangiosarcoma, compared with the odds for sexually intact males. The odds of females gonadectomized at ≤ 12 months of age or at > 12 months of age having hemangiosarcoma were significantly higher than those for sexually intact females (OR, 6.0 [$P = 0.006$] and 11.5 [$P < 0.001$], respectively). Males gonadectomized at > 12 months of age had a significantly ($P = 0.009$) higher OR (OR, 5.3) for hemangiosarcoma than did sexually intact males.

There was no significant ($P = 0.733$) difference in the age at diagnosis of hemangiosarcoma in gonadectomized or sexually intact Vizslas (Figure 2). There also was no significant ($P = 0.943$) difference in the age at diagnosis of hemangiosarcoma between males and females.

Lymphoma or lymphosarcoma—Logistic regression analysis revealed that there was no significant ($P = 0.724$) difference in the odds of male Vizslas having lymphoma or lymphosarcoma, compared with the odds for females. When controlling for sex, the odds of a gonadectomized Vizsla having lympho-

ma or lymphosarcoma were significantly ($P < 0.001$) higher (4.3 times as high) than those for sexually intact dogs (Table 2). Dogs that were gonadectomized at ≤ 6 months of age, between 7 and 12 months of age, or at > 12 months of age had significantly higher odds (OR, 3.5 [$P = 0.017$], 3.1 [$P = 0.041$], and 5.2 [$P < 0.001$], respectively) of having lymphoma or lymphosarcoma than did sexually intact dogs.

There was no significant ($P = 0.425$) difference in the age at diagnosis of lymphoma or lymphosarcoma in gonadectomized dogs, compared with the age in sexually intact dogs (Figure 3). Similarly, there was no

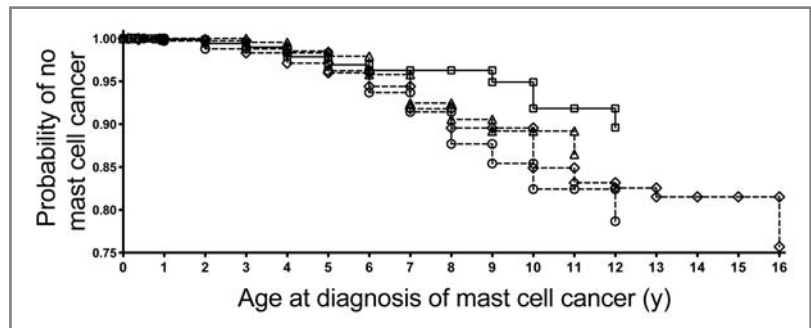


Figure 1—Kaplan-Meier curve of age at gonadectomy (≤ 6 months [circles], 7 to 12 months [triangles], or > 12 months [diamonds] or sexually intact [squares]) and age at diagnosis of mast cell cancer in 148 Vizslas. Mast cell cancer was diagnosed at a significantly ($P = 0.024$) younger mean age in gonadectomized dogs than in dogs that remained sexually intact.

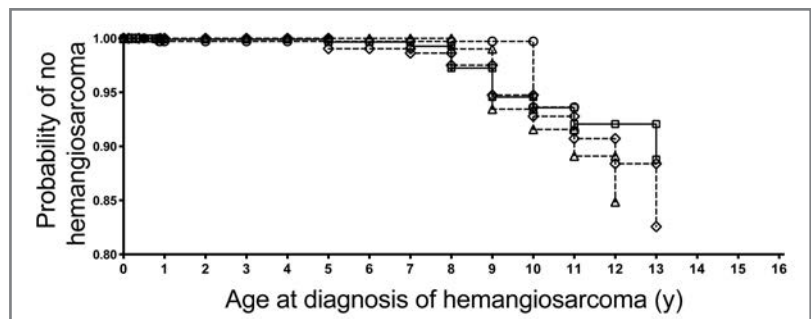


Figure 2—Kaplan-Meier curve of age at gonadectomy and age at diagnosis of hemangiosarcoma in 73 Vizslas. There was no significant ($P = 0.733$) difference in the age of gonadectomized and sexually intact dogs at which hemangiosarcoma was diagnosed. See Figure 1 for remainder of key.

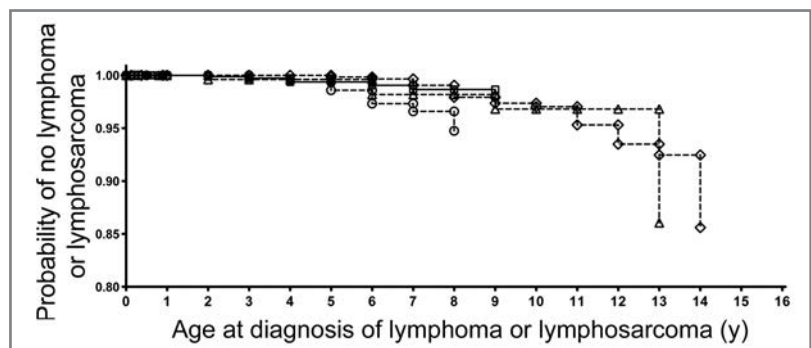


Figure 3—Kaplan-Meier curve of age at gonadectomy and age at diagnosis of lymphoma or lymphosarcoma in 46 Vizslas. There was no significant ($P = 0.425$) difference in the age of gonadectomized and sexually intact dogs at which lymphoma or lymphosarcoma was diagnosed. See Figure 1 for remainder of key.

significant ($P = 0.535$) difference in age at diagnosis of lymphoma or lymphosarcoma between males and females (data not shown).

Cancers other than mast cell cancer, hemangiosarcoma, or lymphoma or lymphosarcoma—There was no significant ($P = 0.741$) difference in the odds of male Vizslas having cancers other than mast cell cancer, hemangiosarcoma, or lymphoma or lymphosarcoma, compared with the odds for females. When controlling for sex, the odds of a gonadectomized Vizsla having cancers other than mast cell cancer, hemangiosarcoma, or lymphoma or lymphosarcoma were significantly ($P < 0.001$) higher (5.0 times as high) than those for sexually intact dogs (Table 2). In addition, dogs that were gonadectomized at ≤ 6 months of age, between 7 and 12 months of age, or at > 12 months of age had significantly ($P < 0.001$) higher odds (OR, 4.1, 5.0, and 5.4, respectively) of having cancers other than mast cell cancer, hemangiosarcoma, or lymphoma or lymphosarcoma than did sexually intact dogs.

Analysis revealed that the younger a dog was at the time of gonadectomy, the earlier the cancers other than mast cell cancer, hemangiosarcoma, or lymphoma or lymphosarcoma were diagnosed ($P < 0.001$; Figure 4). There was no significant ($P = 0.701$) difference in the age at which a diagnosis of cancers other than mast cell cancer, hemangiosarcoma, or lymphoma or lymphosarcoma was made for females, compared with the age at cancer diagnosis for males (data not shown).

All cancers combined—Logistic regression analysis revealed that there was no significant ($P = 0.799$) difference in the odds of male Vizslas having cancer of any kind, compared with the odds for females. When controlling for sex, the odds of a spayed female Vizsla having cancer were significantly ($P < 0.001$) higher (6.5 times as high) than the odds for sexually intact females, and the odds of neutered male Vizslas having cancer were significantly ($P < 0.001$) higher (3.6 times as high) than the odds for sexually intact males (Table 2). Dogs gonadectomized at ≤ 6 months, between 7 and 12 months, or at > 12 months of age all had significantly ($P < 0.001$) greater odds of having cancer (OR, 3.7, 4.0, and 5.7, respectively) than did sexually intact dogs.

The younger a dog was at the time of gonadectomy, the earlier cancer was diagnosed ($P < 0.001$; Figure 5). There was no significant ($P = 0.777$) difference in the age at which cancer was diagnosed for females, compared with the

age at which cancer was diagnosed in males (data not shown).

Relationships between gonadectomy, sex, and death (all causes)—When controlling for sex, the odds of a gonadectomized Vizsla being deceased were not significantly ($P = 0.990$) different for dogs that were gonadectomized, compared with the odds for sexually intact dogs, regardless of the age at which the dog was spayed or neutered. There was no significant ($P = 0.595$) difference in the longevity of gonadectomized Vizslas, compared with the longevity for those that remained sexually intact (Figure 6).

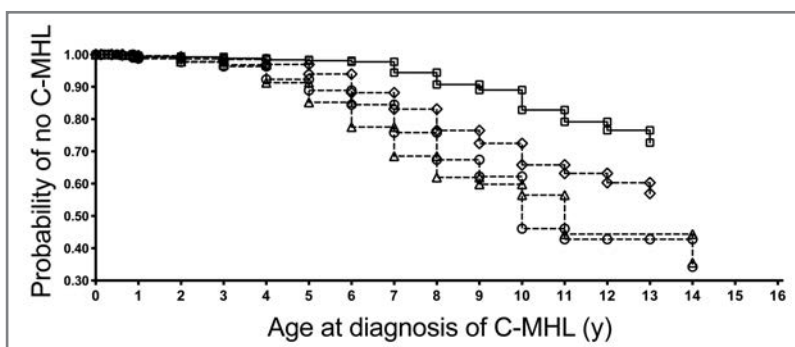


Figure 4—Kaplan-Meier curve of age at gonadectomy and age at diagnosis of cancers other than mast cell cancer, hemangiosarcoma, or lymphoma or lymphosarcoma (C-MHL) in 312 Vizslas. The C-MHL was diagnosed at a significantly ($P < 0.001$) younger mean age in gonadectomized dogs than in dogs that remained sexually intact. See Figure 1 for remainder of key.

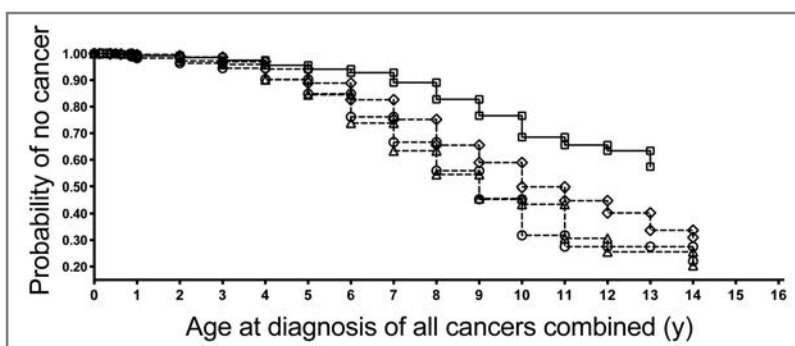


Figure 5—Kaplan-Meier curve of age at gonadectomy and age at diagnosis of all types of cancers in 567 Vizslas. All types of cancer were diagnosed at a significantly ($P < 0.001$) younger mean age in gonadectomized dogs than in dogs that remained sexually intact. See Figure 1 for remainder of key.

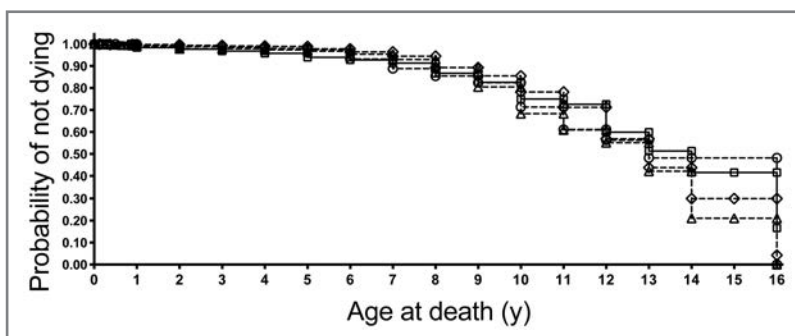


Figure 6—Kaplan-Meier curve of age at gonadectomy and age at death in 402 Vizslas. There was no significant ($P = 0.595$) difference in the age at death between Vizslas that remained sexually intact and Vizslas that were gonadectomized. See Figure 1 for remainder of key.

All behavioral disorders—Logistic regression analysis revealed that the odds of gonadectomized Vizslas having behavioral problems (fear of storms, separation anxiety, fear of noises, fear of gunfire, timidity, excitability, submissive urination, aggression, hyperactivity, and fear biting) after gonadectomy were significantly ($P = 0.035$) higher than the odds for sexually intact dogs (OR, 1.3; Table 2). When controlling for sex, the odds of dogs gonadectomized at ≤ 6 months of age having a behavioral disorder after gonadectomy were significantly ($P < 0.001$) higher (1.8 times as high) than those of sexually intact dogs. There was no significant difference in the odds that dogs gonadectomized between 7 and 12 months of age or at > 12 months of age would have a behavioral disorder diag-

nosed after gonadectomy, compared with the odds for sexually intact dogs. Thus, the significant difference in the odds of gonadectomized Vizslas having a behavioral problem, compared with the odds for sexually intact dogs, was entirely influenced by the fact that dogs gonadectomized at ≤ 6 months of age had a greater risk of behavioral problems. Analysis of age at first diagnosis of a behavioral disorder revealed that the younger a dog was at the time of gonadectomy, the earlier a behavioral problem was diagnosed ($P < 0.001$; Figure 7).

Fear of storms—In the original health survey,¹ fear of storms was the most frequent of all behavioral disorders. Thus, we examined the relationships between age at gonadectomy and fear of storms separately. Overall,

when controlling for sex, the odds of dogs gonadectomized at any age having fear of storms were significantly ($P < 0.001$) higher (4.1 times as high) than the odds for sexually intact dogs (Table 2). In addition, the odds of female Vizslas having fear of storms were significantly ($P = 0.028$) higher (1.4 times as high) than the odds for males.

Females had a significantly ($P = 0.021$) earlier onset of fear of storms, regardless of whether they were gonadectomized or sexually intact, than did males (Figure 8). The younger a dog was at the time of gonadectomy, the earlier a fear of storms was diagnosed ($P < 0.001$; Figure 9).

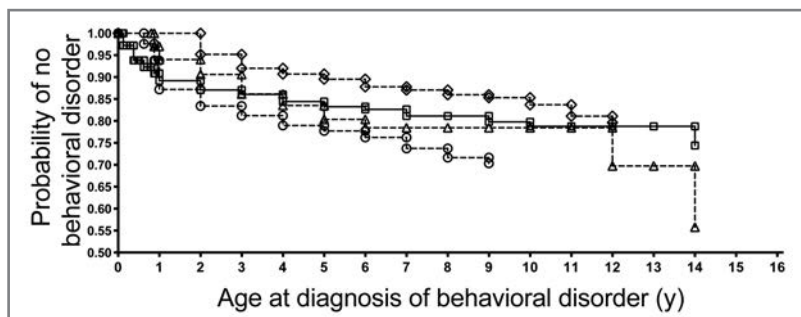


Figure 7—Kaplan-Meier curve of age at gonadectomy and age at diagnosis of a behavioral disorder in 375 Vizslas. Behavioral problems were diagnosed at a significantly ($P < 0.001$) younger mean age in gonadectomized dogs than in dogs that remained sexually intact. See Figure 1 for remainder of key.

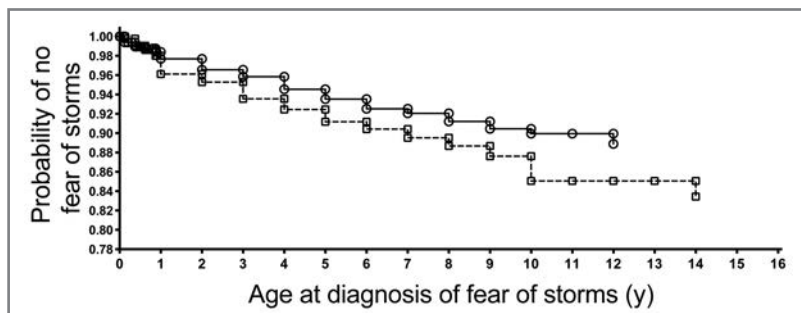


Figure 8—Kaplan-Meier curve for age at diagnosis of fear of storms in 201 Vizslas grouped on the basis of sex (female [squares] and male [circles]). Fear of storms was diagnosed at a significantly ($P = 0.021$) younger mean age in female dogs than in male dogs, regardless of gonadectomy status.

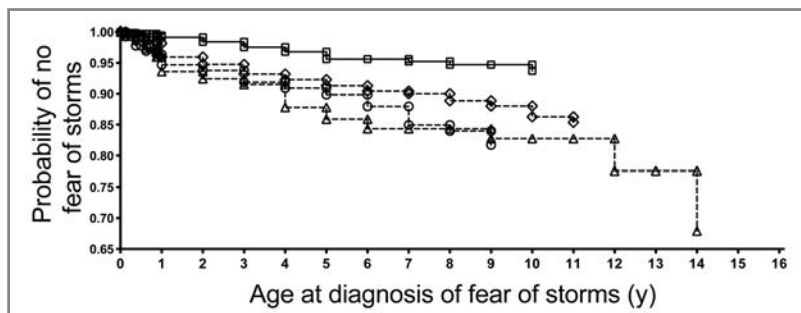


Figure 9—Kaplan-Meier curve for age at gonadectomy and age at diagnosis of fear of storms in 201 Vizslas. Fear of storms was diagnosed at a significantly ($P < 0.001$) younger mean age in gonadectomized dogs than in dogs that remained sexually intact. See Figure 1 for remainder of key.

Discussion

The present study, which was conducted with data from a survey¹ of health conditions in 2,505 Vizslas, revealed that gonadectomized dogs had significantly higher odds than did sexually intact dogs of having mast cell tumor, hemangiosarcoma, lymphoma or lymphosarcoma, all other cancers, all types of cancer combined, or behavioral disorders, regardless of the age at which the dog was gonadectomized. The 2 exceptions were that male dogs gonadectomized at ≤ 12 months of age did not have a higher risk of developing hemangiosarcoma and dogs gonadectomized at > 6 months of age did not have a higher risk of developing a behavioral disorder, other than fear of storms. In addition, for gonadectomized dogs, regardless of age at gonadectomy, the age at diagnosis of mast cell cancer; cancers other than mast cell cancer, hemangiosarcoma, and lymphoma or lymphosarcoma; all cancers combined; behavioral disorders diagnosed after gonadectomy; or fear of storms, the onset was significantly earlier than for sexually intact dogs.

Associations between gonadectomy and various diseases have been examined in several studies.²⁻¹⁴ Most of those

studies involved retrospective examination of veterinary clinical records, and age at gonadectomy generally was not considered in the analyses. Data on whether the dogs were spayed or neutered most typically were included because such information is routinely recorded in the signalment, but gonadectomy was not a primary focus of the studies. The present study is one in which the relationships among age at gonadectomy, sex, and various disease conditions were specifically analyzed.

The association between gonadectomy and various neoplasms in dogs has been examined in several studies.^{15–20} Mammary gland cancer is an important condition in female dogs, with approximately 20% to 50% of the tumors being histologically malignant.^{33,34} It is commonly believed that gonadectomized female dogs have a reduced risk of mammary gland cancer and that the earlier a dog is gonadectomized, the lower the risk.^{28,29,34,35} However, authors of a recent systematic review³⁶ of all reports in peer-reviewed journals on the associations among neutering, age at neutering, and mammary gland tumors concluded that the evidence that neutering reduces the risk of mammary gland neoplasia is weak and not a sound basis for firm recommendations on neutering because of limited evidence and bias in published results.

The present study included 1,360 female dogs, 535 of which were sexually intact. Only 11 dogs had mammary gland neoplasia; all but one of these were spayed at > 5 years of age. Given that mammary gland cancer is seen more commonly in female dogs and 54.3% of the dogs in the survey were female, this would still have been equivalent to only 20 dogs in the study having mammary gland cancer, had the cancer affected both sexes equally. In comparison, 267 dogs in the study had diagnoses of mast cell cancer ($n = 148$), hemangiosarcoma (73), or lymphoma or lymphosarcoma (46). There is a breed predilection for development of mammary gland neoplasia,³⁷ and analysis of results of the present study suggested that mammary gland cancer is not a major concern in Vizslas, regardless of gonadectomy status.

In contrast to the association of mammary gland neoplasia and sexually intact status in female dogs, gonadectomy has been associated with an increased risk of other types of neoplasia. A recent study³⁸ of 759 Golden Retrievers revealed that neutering dogs before 12 months of age was associated with an increased incidence of lymphosarcoma in both sexes and that neutering after 12 months of age was associated with development of mast cell tumor and hemangiosarcoma in females.

A number of other studies have also found an increased risk of other types of cancer in gonadectomized dogs, including prostate cancer,^{4–8} transitional cell carcinoma,^{6,9–11} and osteosarcoma.^{12–14} Of concern, studies^{2,3,38,39} have found an increased risk of hemangiosarcoma, a common tumor that frequently leads to fatal outcomes, in gonadectomized dogs, which is in concurrence with findings for the present study.

If there is a causative relationship between gonadectomy and increased development of various types of neoplasia, the mechanism for this effect must be considered. There is a large body of literature on the impor-

tant nonreproductive effects of sex steroids, particularly on the immune system.⁴⁰ Estrogen, progesterone, and testosterone regulate growth, differentiation, survival, and function of many cells involved in homeostasis and immunity. It is thought that this might be through the ability of estrogens and androgens to increase telomerase activity.⁴¹ The T-effector and T-regulatory lymphocytes as well as other immune cells, such as natural killer cells and macrophages, have estrogen receptors that mediate T-cell activation and differentiation.^{42–44} In 1 study,⁴⁵ ovariectomized female rhesus macaques had accelerated immune senescence and reduced responses to vaccination. Results of that study⁴⁵ suggested that sex hormones may play a role in maintaining ongoing immune surveillance for cancer cells. Early removal of the sex hormones by gonadectomy would interfere with this immune function. This is a potential explanation for the increased incidence of multiple types of cancers in the gonadectomized dogs of the present study. Given the number of dogs that undergo prepubertal gonadectomy in North America, studies are needed to elucidate the interactions between sex hormones and the immune system of dogs.

The increased risk of cancer in gonadectomized dogs in the present study was not the result of a longer life span because there was no difference in the life span of gonadectomized versus sexually intact dogs. The finding that sexually intact and gonadectomized Vizslas have similar life spans is in contrast to results of a recent multibreed study⁴⁶ in which investigators found that neutered dogs lived longer than sexually intact dogs. For the study reported here, conclusions regarding life span may be specific to Vizslas, or there could have been confounding variables affecting results of that multibreed study.⁴⁶

The present study also revealed an increased risk of behavioral problems that developed in dogs after they were gonadectomized. It should be mentioned that the most common behavioral problems in Vizslas in this study did not include sexual behaviors (eg, mounting and urine marking). Instead, behavioral problems were primarily fears and anxiety, such as fear of storms and gunshots, as well as increased arousal, such as aggression and hyperactivity. These findings contrast with the commonly held belief that undesirable behaviors are reduced by gonadectomy. This belief arises partly from 2 studies^{47,48} in which there was a reduction in sexually dimorphic behaviors (eg, mounting and urine marking) in gonadectomized male dogs. However, in one of those studies,⁴⁸ which is often cited to support gonadectomy to improve dog behavior, investigators found no effect of castration on aggression toward unfamiliar people. Furthermore, they also found in that study⁴⁸ that although there was a pattern of improvement in urine marking, mounting, and roaming in dogs following castration, the difference was not significant. Most importantly, that study⁴⁸ did not involve use of a control group of dogs with behavioral problems that were not gonadectomized. Similarly, investigators in the other study⁴⁷ did not use a control group of sexually intact dogs. Because of the lack of a control group (nongonadectomized dogs), neither of these studies^{47,48} can distinguish between the effects of gonadectomy and other

factors on alterations of behavior. Problem behaviors in the dogs of those studies may have improved as a result of increase in age, improved training, or other unidentified factors, rather than as a result of gonadectomy. Additionally, in one of those studies,⁴⁷ owners were asked to report on their dog's behavioral changes via telephone interview conducted a mean of 27 months after gonadectomy, which provided a highly subjective and potentially biased set of data on behavior.

A number of studies^{15–20,24,49,50} have revealed increases in problem behaviors in gonadectomized dogs. In 1 study,²⁰ dogs gonadectomized before 5 months of age had an increase in noise phobias. That same study²⁰ found an increase in aggressive and sexual behaviors, excessive barking, and a greater likelihood of separation anxiety in gonadectomized dogs. Interestingly, the authors attributed these findings to type II error because of limited support in their data for a causal relationship between gonadectomy and these behavioral problems.

In 1 prospective study,¹⁷ ovariohysterectomized bitches had an increase in reactivity toward humans and aggression toward family members, compared with the behavior of bitches that remained sexually intact. Similar findings have been described in other studies.^{18,19} An increase in aggressive behavior in spayed females and an inverse relationship between age at gonadectomy and aggression were found in 1 study.¹⁸ Investigators in another study⁴⁹ concluded that the only behavioral differences between sexually intact and spayed females were that spayed females had increased aggression toward owners and indiscriminate eating patterns. Investigators in both of those studies^{18,49} found that increases in aggressive behavior were more extreme in females that had displayed aggression before gonadectomy and that aggression did not increase in any female spayed after 1 year of age.

Additionally, a study¹⁵ of 1,644 dogs revealed significant increases in the percentage of neutered male dogs admitted to a veterinary teaching hospital behavioral clinic with aggression (directed at humans and other animals) and phobias, compared with the percentage of neutered male dogs in the general population of dogs admitted to other departments of the same hospital. Two other studies,^{24,50} involving > 1,500 and 3,000 dogs, respectively, found that neutered male dogs were more aggressive and spayed females were more fearful than sexually intact dogs. In another study¹⁶ involving > 3,000 dogs, the likelihood that a dog had bitten a member of the household was highest for neutered males and decreased (in rank order) for spayed females, sexually intact males, and sexually intact females. Similar patterns were seen for growling and possessive aggression. One of the largest training centers for assistance dogs performed a prospective study^c on the effects of prepubertal gonadectomy in 1990 and found that gonadectomized dogs had significant increases in failure rates attributable to behavioral problems.

These findings deserve attention from the veterinary community and suggest a need to reexamine the recommendation of gonadectomy for dogs with behavioral problems. This is particularly important because behavioral problems are the most common reason for relinquishment of dogs to shelters.^{51,52} Although pup-

pies from unwanted breedings may contribute to dogs entering shelters, the primary problem is that dogs are not succeeding as pets in their homes, as evidenced by the fact that more adult dogs than puppies are relinquished to shelters.⁵² Although it should be emphasized to owners that dogs with behavioral problems are not ideal candidates for a breeding program, this recommendation need not be synonymous with gonadectomy since other means by which to prevent procreation, such as vasectomy or behavioral management, are available.

Similar to other studies that involve data obtained with a survey instrument, the present study has a number of limitations. First, these data indicate an association, not causation. Additional studies will be required to provide information on the mechanisms by which removal of specific combinations of hormones secreted by the gonads affects target organs and body systems.

Self-directed surveys have the potential for selection bias. The dogs of the present study were owned predominantly by members or friends of members of local and national Vizsla clubs.¹ Twenty-four percent of respondents learned of the Vizsla Health Survey through the V-Talk email list; 17% through the Vizsla Club of America website; 13% through a breeder, friend, or associate; 13% through national Vizsla club newsletters; 11% through local club newsletters or websites; and 4% through a magazine advertisement. This suggested that approximately 75% of the respondents were members of or associated with a local or national Vizsla club.

Biased sample selection was a potential concern for the survey. This likely was a fairly uniform population of dog owners that probably were of at least moderate socioeconomic status. It is possible that purebred dogs kept sexually intact for breeding purposes might be more likely to be socialized and trained for show events, which potentially reduces the likelihood of behavioral problems. However, only 53% of the sexually intact dogs in the present study had been bred, so it is likely that not all sexually intact dogs were kept sexually intact primarily for breeding purposes. The potential that sexually intact dogs receive more socialization and training might be offset by the likelihood that educated owners of Vizslas would adhere to advice of veterinarians to spay or neuter their dogs in the belief that it is the responsible course of action. This population of owners might also recognize the importance of basic obedience training for their dogs, which could reduce the likelihood of behavioral problems.

It was possible that owners who adhered to a veterinarian's advice to spay or neuter their pet dogs were also more likely to take their dogs to a veterinarian if they had signs of illness or were more likely to pursue diagnostic testing. This additional veterinary care could have resulted in an increase in the diagnosis of cancer or behavioral disorders in gonadectomized dogs. However, this relies on the assumption that dogs were allowed to remain sexually intact because their owners did not seek veterinary advice (and thus were unaware of the common recommendation of gonadectomy) or could not afford gonadectomy or other veterinary care. However, approximately 75% of respondents in this

survey were associated with a local or national Vizsla club, which indicated a higher-than-typical amount of involvement with their dogs. Sexually intact status of dogs in the survey was unlikely to reflect neglect or lack of veterinary care, considering that most Vizslas used for show and competition events receive a high level of attention from their owners and handlers. It is improbable that the increase in cancer diagnoses in gonadectomized dogs in the present study was attributable to more veterinary care.

It is possible that some Vizslas were allowed to remain sexually intact and selected as future breeding prospects because of their health and medical histories. However, it is impossible to accurately predict those dogs that will develop various forms of cancer; thus, it is doubtful that dogs from a specific litter were selected for breeding or to become pets solely on the basis of their likelihood of not developing neoplasia. Some dogs originally allowed to remain sexually intact for breeding may have been gonadectomized as adults because a closely related dog developed cancer. Breeders may choose to not breed a dog closely related to dogs that have developed early-onset cancer or another serious health condition. This might explain the substantially higher ORs for mast cell cancer and hemangiosarcoma in dogs gonadectomized at > 12 months of age, compared with the ORs for dogs gonadectomized at ≤ 12 months of age. Nonetheless, this kind of selection bias does not explain the finding that the younger the dogs were when they were gonadectomized, the younger the dogs were when mast cell cancer; cancers other than mast cell cancer, hemangiosarcoma, and lymphoma or sarcoma; and all cancers combined were diagnosed.

Information bias was also a potential concern. In the present study, the survey was used to collect data about dogs during a 16-year period. Quality of health-care practices would be expected to change during that time, so the stringency of criteria for diagnoses might have differed for dogs recently examined, as opposed to dogs examined earlier. Furthermore, the memories of owners for reporting disease conditions of dogs born as many as 16 years previously may have been faulty. Additionally, the criteria used to diagnose neoplasia and other diseases, including behavioral disorders, were not included in the survey. It is possible that owners were provided with a tentative rather than a definitive diagnosis of neoplasia by veterinarians without confirmation via examination of a biopsy specimen. Owners may also have made diagnoses relating to behavioral problems without consultation with a behavioral specialist or veterinarian. However, all of these potential areas of bias should have applied equally to the owners of gonadectomized and sexually intact dogs.

Another limitation was that the study reported here involved only a single breed of dog. Given that dogs are a single species, it would seem that hormonal discrepancies between breeds should be minor, but whether the effects of gonadal hormones might differ in Vizslas remains unknown. In veterinary medicine, studies of drugs and vaccines are often performed in a single breed (often Beagles) and extrapolated to all breeds. Widespread use of a drug may subsequently reveal that other breeds or individual dogs respond differently to

certain drugs. One notable example is those breeds in which the MDR-1 mutation is highly prevalent.⁵³ However, single-breed studies of vaccines and drugs continue to be commonplace. In addition, results of a study³⁸ of the effects of gonadectomy in Golden Retrievers are similar to results of the present study, particularly with regard to finding sex and age differences in the risk for hemangiosarcoma in gonadectomized dogs. The Golden Retriever study³⁸ provides further evidence that the effects of gonadectomy may be similar in various dog breeds, at least within sporting dogs. However, it is possible that the effects of gonadectomy differ among breeds, and additional studies should be conducted to investigate the effects of gonadectomy in a variety of dogs, including mixed-breed dogs.

Potential sources of confounding bias include, for example, a tendency for respondents to recall more recent disease conditions in their dogs, which might have paralleled an increase in the prevalence of gonadectomy in the population. Confounding also may have been the result of some unmeasured factor that differentiated owners who gonadectomized their dogs from those who did not. It is difficult to know whether these types of bias influenced the present study.

An additional potential source of confounding was that behavioral differences between sexually intact and gonadectomized dogs could have been attributable to being subjected to hospitalization and surgery at a young age, rather than to the hormonal changes conferred by gonadectomy. A prospective, randomized, blinded study with a control (sham) surgery could be performed to distinguish between these 2 scenarios.

Despite its inherent limitations, results of the present study emphasized the importance of initiating further investigations into the effects of gonadectomy on cancer and behavior. They also support the need for veterinarians to practice individualized medicine and to thoroughly discuss the various benefits and disadvantages of gonadectomy in male and female dogs with their clients, rather than to recommend gonadectomy (particularly prepubertal gonadectomy) for all dogs not destined for use as breeding animals. Factors that should be considered include the breed of dog, origin of the dog, knowledge and commitment of the owner, and intended use of the dog (eg, pet, athletic competitions, or working dog). For a dog obtained from responsible breeders, the medical history of related dogs can also be evaluated to help determine that dog's predisposition for various health problems. Pet owners might find it difficult to manage a sexually intact dog to prevent unwanted breedings, and breeding procedures and pregnancy pose health risks and expenses that pet owners may want to avoid. It is important for veterinarians to thoroughly discuss all aspects of care and management to help owners make the best decision for each dog.

Alternative options to render dogs infertile should be examined by the veterinary profession. Vasectomy is a surgical technique for male dogs that maintains the hormonal status but prevents fertile reproduction. This surgery is no more invasive than castration and could become common practice among small animal veterinarians. Hysterectomy is a potential surgical option for female dogs and could be taught to veterinarians as

readily as ovariohysterectomy. Hysterectomy should involve removal of the entire uterus to minimize the risk of stump pyometra. However, it is not known whether hysterectomized females typically display signs of estrus or vaginal discharge, because this surgical means of rendering bitches infertile has not been systematically evaluated.

Analysis of the present study suggested that gonadectomy does not inevitably result in a healthier, more temperamentally stable dog. This study also emphasized the need for additional studies to examine effective means of population control that do not involve removal or ablation of the gonads.

- a. SAS, version 9.2, SAS Institute Inc, Cary, NC.
- b. West Chester Statistics Institute, West Chester University, West Chester, Pa.
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From this month's AJVR

Pharmacokinetics of meloxicam administered orally to rabbits (*Oryctolagus cuniculus*) for 29 days

Katie W. Delk et al

Objective—To determine the pharmacokinetics and safety of meloxicam in rabbits when administered orally for 29 days.

Animals—6 healthy rabbits.

Procedures—Meloxicam (1.0 mg/kg, PO, q 24 h) was administered to rabbits for 29 days. Blood was collected immediately before (time 0) and 2, 4, 6, 8, and 24 hours after drug administration on days 1, 8, 15, 22, and 29 to evaluate the pharmacokinetics of meloxicam. On day 30, an additional sample was collected 36 hours after treatment. Plasma meloxicam concentrations were quantified with liquid chromatography–mass spectrometry, and noncompartmental pharmacokinetic analysis was performed. Weekly plasma biochemical analyses were performed to evaluate any adverse physiologic effects. Rabbits were humanely euthanized for necropsy on day 31.

Results—Mean \pm SD peak plasma concentrations of meloxicam after administration of doses 1, 8, 15, 22, and 29 were 0.67 ± 0.19 μ g/mL, 0.81 ± 0.21 μ g/mL, 1.00 ± 0.31 μ g/mL, 1.00 ± 0.29 μ g/mL, and 1.07 ± 0.19 μ g/mL, respectively; these concentrations did not differ significantly among doses 8 through 29. Results of plasma biochemical analyses were within reference ranges at all time points evaluated. Gross necropsy and histologic examination of tissues revealed no clinically relevant findings.

Conclusions and Clinical Relevance—Plasma concentrations of meloxicam for rabbits in the present study were similar to those previously reported in rabbits that received 1.0 mg of meloxicam/kg, PO, for 5 days. Results suggested that a dosage of 1.0 mg/kg, PO, every 24 hours for up to 29 days may be safe for use in healthy rabbits. (*Am J Vet Res* 2014;75:195–199)



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