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Household Chemical Exposures and the Risk of Canine Malignant Lymphoma, a Model for Human Non-Hodgkin's Lymphoma

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Abstract

Background—Epidemiologic studies of companion animals offer an important opportunity to identify risk factors for cancers in animals and humans. Canine malignant lymphoma (CML) has been established as a model for non-Hodgkin's lymphoma (NHL). Previous studies have suggested that exposure to environmental chemicals may relate to development of CML.

Methods—We assessed the relation of exposure to flea and tick control products and lawn-care products and risk of CML in a case-control study of dogs presented to a tertiary-care veterinary hospital (2000–2006). Cases were 263 dogs with biopsy-confirmed CML. Controls included 240 dogs with benign tumors and 230 dogs undergoing surgeries unrelated to cancer. Dog owners completed a 10-page questionnaire measuring demographic, environmental, and medical factors.

Results—After adjustment for age, weight, and other factors, use of specific lawn care products was associated with greater risk of CML. Specifically, the use of professionally applied pesticides

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Conflict of interest
None declared

was associated with a significant 70% higher risk of CML (odds ratio(OR)=1.7; 95% confidence interval (CI)=1.1–2.7). Risk was also higher in those reporting use of self-applied insect growth regulators (OR = 2.7; 95% CI=1.1–6.8). The use of flea and tick control products was unrelated to risk of CML.

Conclusions—Results suggest that use of some lawn care chemicals may increase the risk of CML. Additional analyses are needed to evaluate whether specific chemicals in these products may be related to risk of CML, and perhaps to human NHL as well.

Keywords

Lymphoma; Non-Hodgkin; Dogs; Epidemiology; Case-Control Studies; Specialty Uses of Chemicals

1. Introduction

In 2010, it was estimated that 65,540 men and women would be diagnosed with Non-Hodgkin's Lymphoma (NHL) in the United States (Howlader, et al. 2010). Incidence of NHL has doubled since the 1970s, making it the sixth most common cancer, with a five year overall survival rate of 67%. Numerous studies have considered the potential association between agricultural chemical exposure and NHL, with inconsistent results (Hooiveld, et al. 1998; McDuffie, et al. 2001; Thorn, et al. 2000) in part due to the likelihood of misclassification of exposure dose in population-based studies, and the possibility of confounding by other environmental risk factors.

Epidemiologic studies of companion animals provide an opportunity to study the health effects of environmental risk factors that may be difficult to assess in humans, including herbicide and pesticide exposures. Canine cancers have been well established as appropriate models for studies of human cancers (Hayes 1978). In particular, canine malignant lymphoma (CML) exhibits common clinical, pathologic, and histologic features as human NHL and responds similarly to treatment (Teske 1994). The present study sought to evaluate the association between exposure to common household chemicals and risk of CML. The close interaction and shared household environment of dogs and their human owners provides a unique opportunity for evaluating how herbicide and pesticide exposure may contribute to human NHL. Only a small number of previous studies have evaluated whether herbicide and/or pesticide exposure increases risk of CML (Garabrant and Philbert 2002; Gavazza, et al. 2001; Kaneene and Miller 1999), most focusing on the impact of 2,4-dichlorophenoxyacetic acid. However, results have been inconsistent and the association between other types of household chemicals and CML remains unknown.

2. Materials and Methods

Between December 2006 and July 2007, we conducted a case-control study of CML at the Foster Hospital for Small Animals at Cummings School of Veterinary Medicine at Tufts University. The Foster Hospital is a large veterinary teaching hospital in central Massachusetts and serves as the referral hospital for the region. The institutional review boards and animal care and use committees at Tufts University and the University of Massachusetts Amherst reviewed and approved the protocol used in this study.

Case and Control Identification

Eligible cases were all dogs diagnosed with biopsy-confirmed malignant lymphoma presenting to the Foster Small Animal Hospital between January 2000 and December 2006 identified through review of oncology service records (n = 624). Owners of eligible cases

were mailed a questionnaire measuring demographic, environmental, and medical factors. After 2–3 months, non-responders were sent a second copy of the questionnaire. After two mailings, completed questionnaires were received from 263 (42%) of case owners.

We identified two groups of control dogs, which were individually matched to cases on age (+/-1 year) and date of diagnosis (+/-3 months). First, dogs with histologically confirmed benign tumors were identified through systematic hand-review of pathology department records. To select a match, we chose the similarly-aged dog diagnosed closest in time to each CML case. Second, dogs with non-neoplastic chronic diseases were identified through hand-review of surgery department records. To select a match, we chose the similarly-aged dog treated closest in time to each CML case. After two questionnaire mailings, completed questionnaires were received from owners of 245 (39%) benign tumor controls and 233 (37%) chronic disease control owners.

Exposure and covariate assessment

We sent the owners of eligible cases and controls a 10-page questionnaire inquiring about demographic and health-related characteristics and environmental exposures of their pet in the specified 1-year period prior to their dog's year of diagnosis. We first asked about the dog's year of birth, sex, breed (purebred, and specified breed or mix of breeds), when the dog was acquired, and the source of the dog (shelter, breeder, pet shop, stray, or other). Physical characteristics queried included owner's assessment of hair length (naturally short, groomed short, medium, or long), nose length (very short [i.e., brachycephalic], average [i.e., mesocephalic], or very long [i.e., dolichocephalic]), weight, body type (thin, average, slightly overweight, or overweight), and grooming care (less than 1/month, 1/month, 2–3/month, weekly or more). We asked about history of 19 types of health conditions including allergies, arthritis, thyroid disease, and kidney disease, and the date conditions were first diagnosed. Finally, we assessed the use of 40 common medications including glucosamine, chondroitin, cosequin, carprofen/Rimadyl, predniose, and oral antibiotics.

We assessed household exposure to a variety of environmental chemicals, including lawn-care products, flea and tick-control products, and other household chemicals via questionnaire. Owners were asked if their lawn was treated by a professional company and to specify the frequency of treatment, the types of products used (fertilizer, weed killer, insect killer, insect growth regulators, fungus killer, and/or rodent killer), and to indicate whether the products employed were "organic". For self-applied lawn care products, owners were asked about the type of products used (fertilizer, weed killer, insect killer, insect growth regulators, fungus killer, and/or rodent killer), the frequency of use, and to specify the brand used from a list of commonly-available products.

We asked owners if they used flea/tick control products on their pet, and if so, to identify the type (flea or tick collar, powder/spray, shampoo, dip, pills, and drops) and frequency of use. For drops, we asked about the brand used (Frontline, Frontline Plus, or Frontline Top Spot; Advantage, K9 Advantix, or Biospot; Revolution; and/or other).

Finally, we asked about other aspects of the pet's living environment that might modify their exposure to environmental chemicals. Factors queried included household smoking, house size, house location, the amount of time the dog spent outdoors in summer and winter, and the dog's physical activity level.

Statistical analysis

We first compared demographic and health-related characteristics of the two control groups of dogs to determine if the groups were homogeneous and could be combined for

comparison with CML cases for our main analyses. We compared mean ages between groups using a t-test and compared proportions using chi-square tests.

We then evaluated the association of household chemical exposures and CML risk using odds ratios and calculated 95 percent confidence intervals. Although cases and controls were initially matched by date of diagnosis and age, we chose to use unconditional logistic regression due to the relatively low response rates obtained, and adjusted for the matching factors (date of diagnosis and age) in our regression model. Multivariable logistic regression was used to further adjust for confounders. We retained a covariate in our regression model if its inclusion changed the odds ratio for the main exposure variable by ≥ 10 percent or if it was independently associated with risk of CML ($P < 0.20$). Our final multivariable model included age at diagnosis (6 years or younger vs. older than 6 years), reference year (continuous), weight (less than 50 pounds vs. 50 pounds or heavier), body type (thin/average vs. overweight), previous history of cancer (ever vs. never), and use of any of three medications prior to reference year (chondroitin, cosequin, and prednisone). Other variables measured by questionnaire were evaluated but were not included in the analysis because they were not associated with chemical exposures or risk of malignant lymphoma in multivariable models, including location of residence and household smoking.

We conducted stratified analyses to determine if the relations between household chemical exposures and CML risk varied by subject characteristics (age, sex, weight, pure vs. mixed breed), behaviors that may affect level of chemical exposure (time spent outdoors on lawns, reference year/time of exposure). Finally we performed sensitivity analyses comparing CML cases to each control group individually.

For all analyses, two-sided P values < 0.05 were considered statistically significant. With an alpha type-1 error set at 0.05, one association in twenty is expected to be significant by chance alone. All analyses were performed with STATA Version 10.1 (Stata software system; StataCorp, College Station, Texas)

3. Results

Characteristics of CML cases, benign tumor controls (BNG) and chronic disease controls (CHR) are presented in table 1. Common diagnoses in the BNG group included lipoma, fibroma, sebaceous hyperplasia, trichoepithelioma, papilloma, nevus, adenoma, keratosis, and epithelioma. Common diagnoses and surgical procedures reported for dogs in the CHR group included cranial cruciate ligament rupture, medial patellar luxation, hepatic shunt and degenerative myopathy.

The two control groups were similar with respect to all factors considered, with the exception of weight ($p=0.001$). Because of the similarity between BNG and CHR controls, we pooled these groups for all comparisons with cases. CML cases did not differ from controls in terms of most characteristics. However, CML cases were more likely to weigh greater than 50 pounds compared to controls ($p<0.001$).

Age-adjusted and multivariable odds ratio for CML by exposure to flea and tick control products are presented in Table 2. CML cases and controls were similar in their use of any flea/tick control products, as well as their use of specific types of products including collars, powders or sprays, shampoos, dips, pills, or one-spot drops. In addition, CML cases were not more likely than controls to report the use of multiple types of flea/tick control products.

Age-adjusted and multivariable odds ratio for malignant lymphoma associated with exposure to professionally-administered lawn care products, self-applied lawn products, and either type of use are presented in Table 3. CML cases and controls did not differ in their

overall exposure to lawn care products (any vs. none). However, cases were more likely to come from homes reporting use of professionally applied pesticides (odds ratio = 1.7, 95% confidence interval (CI) = 1.1–2.7; P = 0.02). CML risk was higher in dogs exposed to herbicides, though results were marginally significant (OR = 1.4; 95% CI = 1.0–2.1, P=0.06). Exposure to other types of professionally applied lawn care chemical was not associated with increased risk, though we observed the suggestion of a trend with the total number of professionally applied products used (P = 0.06). CML cases were more likely to come from homes self-application of insect growth regulators (OR = 2.7; 95% CI = 1.1–6.8; 0.03). Other self-applied lawn care products including pesticides and herbicides were not associated with risk of CML. When professionally and self-applied use of products were evaluated simultaneously, we observed a positive association between use of pesticides and CML risk (OR = 1.4; 95% CI = 1.1–2.0; P = 0.05).

We saw no evidence of effect modification of the relationship between lawn care chemical exposure and CML by factors including reference year, time spent outdoors, weight, breed, sex, or age (results not shown). Results from sensitivity analyses comparing CML cases with each control group separately were very similar to the main analyses (results not shown). For example, CML cases reported more frequent exposure to professionally applied lawn care pesticides than both benign tumor controls (OR = 1.7; 95% CI = 1.0 – 2.8; P= 0.05) and chronic disease controls (OR = 1.7; 95% CI = 1.0 – 3.0; P = 0.06).

4. Discussion

In this case-control study of pet dogs, we observed evidence that exposure to specific lawn care chemicals was associated with greater risk of CML. In contrast, we did not find any association between use of any flea and tick control products and CML.

A small number of previous studies have evaluated the association between exposure to lawn care chemicals and risk of CML. A study by Hayes and colleagues (Hayes, et al. 1991) observed a significant 30% increase in risk of CML in dogs living in homes where 2,4-dichlorophenoxyacetic acid had ever been applied to lawns by either the homeowner or a professional lawn care company. Relative risks were slightly higher when both types of application were reported (OR for owner and professional application vs. none = 1.39; 95% CI = 0.95–1.87). In a subsequent analysis of these data aimed at addressing criticism raised by others (Carlo, et al. 1992), results from analyses stratified by type of control group (tumors vs. non-tumors), method of data collection (mailed questionnaire vs. telephone interview), and specific herbicidal agent were similar to the original results (Hayes, et al. 1995). However, a reanalysis of the study data by another research group did not support the authors' original conclusion that herbicide use modestly increased risk (Kaneene and Miller 1999). A recent case-control study in Italy did not observe an increase in risk of CML in dogs exposed to pesticides (Gavazza, et al. 2001), but did find a significant increase in risk in dogs of owners with occupations requiring chemical use and those living in urban areas.

Though the relationship between use of flea control products and risk of NHL in humans or CML in dogs had not been previously evaluated, several studies have reported increases in risk of other cancers in humans and companion animals (Bertone, et al. 2003; Davis, et al. 1993; Glickman, et al. 1989; Pogoda and Preston-Martin 1997). For example, Davis et al observed a significant increase in risk of brain cancer in children who were exposed to flea collars on pets, pesticide bombs in the home, and garden use of pesticides (Davis, et al. 1993). The use of both insecticides and flea and tick dips has previously been associated with increases in risk of canine bladder cancer (Glickman, et al. 1989). In addition, a recent case-control study by our research group observed an increase in risk of oral squamous cell carcinoma in domestic cats exposed to flea control products, especially flea collars (Bertone,

et al. 2003). We did not observe any association between use of flea and tick control products and risk of CML in the present study.

In our study, we asked dog owners to report use of lawn care and flea/tick control products in the specified 1-year period prior to the year of diagnosis. We hypothesized that the latency period between chemical exposure and the development of malignant lymphoma in dogs would be short, based on data from human studies reporting that patients with Hodgkin's disease have an increased risk of developing NHL within as little as 1 year after their primary diagnosis and treatment (Dong and Hemminki 2001; Royle, et al. 2010; Swerdlow, et al. 2000). Although owners may have had difficulty recalling chemical use occurring many years ago and some misclassification of exposure likely exists, exposure levels for pets with relatively short life spans may be consistent over time and thus more easily recalled by owners. For example, risk of CML was positively associated with residential exposure to electromagnentic fields (EMF) in a case-control study in Colorado (Reif, et al. 1995). While each dog's exposure to EMF was only assessed once based on levels at a single residence, this level represented approximately 65% of the dog's lifetime exposure because the subjects spent such a high proportion of their lives in a single home.

The validity of assessing dog's level of exposure to environmental chemicals has been assessed previously. Reynolds et al (1994) correlated level of urinary excretion of 2,4-D in dogs with known exposure to lawns treated with 2,4-D herbicides and found that exposed dogs absorbed, metabolized, and excreted a substantial biologic dose of herbicide chemicals, in proportion to reported exposure level (Reynolds, et al. 1994). In another study, dog owner's report of household smoking level by questionnaire correlated well with dog's urinary level of cotinine, a metabolite of nicotine (Bertone-Johnson, et al. 2008).

The response rate in our study was relatively low, likely because of the long interval between year of CML diagnosis and our questionnaire mailing for some animals; in fact, response rate of subjects with earlier reference years (2000 to 2003) was considerably lower than that for later reference years (2004 to 2006; 36% vs. 48%). We would not expect owner participation to bias our findings concerning household chemical exposures, as likelihood of response is unlikely to vary substantially by lawn care use, as it may for health-related behaviors such as smoking. In fact, dogs from responders and non-responders differed only slightly by age (7.4 vs. 8.0 years) and frequency of spay/neuter (94% vs. 85%), and response rates were comparable for cases, benign tumor controls and chronic disease controls (42%, 39%, and 37%, respectively). As control dogs were patients in the same tertiary care hospital as case dogs, we would expect similarities in demographic characteristics of case and control owners presenting their dogs for follow-up care after referral from a primary care veterinarian. Furthermore, analyses stratified by reference year did not indicate that the relation of flea/tick control products or lawn-care chemicals with CML risk varied with time, or because of differences in owner characteristics related to reference year.

Our study has notable strengths. Unlike studies focusing on a particular type of pesticide or herbicide, our study has evaluated a heterogeneous group of chemicals and the risk of lymphoma. In addition, we were able to control for confounding by important demographic and behavioral factors. Further, we included two distinct control groups of dogs with different types of disorders (tumor and non-tumor based) from the same tertiary care veterinary hospital to minimize the likelihood of selection and recall biases. While it is possible that recall bias may exist, as CML cases had a serious disease likely to be fatal while controls in general did not, we would expect this bias to apply similarly to all of the environmental factors assessed, and not just to a subset of the lawn care chemicals. Thus recall bias is an unlikely explanation for our findings.

Dogs may serve as sentinels for risks associated with environmental exposures for a variety of reasons (Gavazza, et al. 2001; Kelsey, et al. 1998). Dogs have environmental exposures similar to their owners because they share the same household. Dose of exposure to environmental chemicals such as lawn care products used at home may be substantial, especially for dogs spending a considerable amount of time outdoors on lawns. Studies of environmental risk factors for CML in dogs are facilitated by dogs having shorter life spans than humans, faster disease progression, and shorter latency periods between exposure and disease compared to humans (MacEwen 1990; Thrusfield 1988; Vail and MacEwen 2000). Because canine and human cancers such as CML and NHL share common etiologic factors (Hayes 1978; MacEwen 1990), results from studies of CML may provide insight into the development of human non-Hodgkin lymphoma.

Additional studies are needed to further assess the effects of commonly used household chemicals on risk of canine malignant lymphoma, including evaluations of exposure dose and frequency of exposure. In particular, studies using biochemical markers would be useful in disentangling the effects of different chemical components of lawn care products.

5. Conclusions

In summary, findings of this study suggest that exposure to certain types of lawn care chemicals may increase the risk of malignant lymphoma in dogs. Additional studies are needed to further evaluate the effects of specific chemical components of lawn care products on risk of canine malignant lymphoma, and may potentially contribute to human NHL as well.

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Highlights

- Case-control study of household environmental chemicals and risk of canine lymphoma.
- Two types of household environmental chemicals: flea/tick control and lawn care.
- Professionally applied pesticide significantly increased CML risk.
- Use of owner applied insect growth regulators significantly increased CML risk.
- Certain lawn care chemicals may increase risk of CML and potentially human NHL.

Table 1

Characteristics of canine malignant lymphoma cases, benign tumor controls, and chronic disease controls.

Characteristic	Benign Tumor Controls (N=245)	Chronic Disease Controls (N=233)	P-value[a]	Cases (N=266)	P-value[b]
Age at Diagnosis					
7 years or younger	123 (50.2%)	124 (53.2%)		147 (55.3%)	
Older than 7 years	122 (49.8%)	109 (46.8%)	0.51	119(44.7%)	0.35
Sex					
Male	120 (50.2%)	120 (52.6%)		144 (54.1%)	
Female	119 (49.8%)	108 (47.4%)	0.60	122 (45.9%)	0.48
Purebred					
No	50 (21.8%)	50 (22.3%)		65 (25.3%)	
Yes	179 (78.2%)	174 (77.7%)	0.90	192 (74.7%)	0.33
Hair length					
Short (natural)	86 (35.4%)	102 (44.0%)		106 (39.9%)	
Short (groomed)	41 (16.9%)	32 (13.8%)		38 (14.3%)	
Medium	91 (37.5%)	76 (32.8%)		102 (38.4%)	
Long	25 (10.3%)	22 (9.5%)	0.29	20 (7.5%)	0.64
Nose length					
Very Short or Average	218 (90.8%)	200 (86.6%)		244 (92.4%)	
Very Long	22 (9.2%)	31 (13.4%)	0.14	20 (7.6%)	0.11
Neutered/Spayed					
No	12 (5.1%)	17 (7.3%)		18 (6.9%)	
Yes	225 (94.9%)	215 (92.7%)	0.31	244 (93.1%)	0.72
Household smoking					
None	188 (80.3%)	187 (85.0%)		208 (80.3%)	
Any	46 (19.7%)	33 (15.0%)	0.19	51 (19.7%)	0.45
Location of residence					
Urban	21 (8.8%)	20 (8.9%)		23 (8.8%)	
Suburban	150 (62.8)	151 (67.1%)		178 (67.7%)	
Rural	64 (26.7%)	52 (23.1%)		53(20.2%)	
Farm	4 (1.7%)	2 (0.9%)	0.68	9 (3.4%)	0.13

Characteristic	Benign Tumor Controls (N=245)	Chronic Disease Controls (N=233)	P-value[a]	Cases (N=266)	P-value[b]
Type of residence					
Apartment or Multi-family	21 (8.9%)	25 (11.1%)		30 (8.7%)	
Single-family house	216 (91.1%)	200 (88.9%)	0.41	241 (91.3%)	0.58
History of cancer					
None	195 (79.6%)	200 (85.8%)		206 (77.4%)	
Any	50 (20.4%)	33 (14.2%)	0.07	60 (22.6%)	0.09
Body type					
Thin or Average	162 (67.8%)	168 (74.3%)		188 (71.2%)	
Slightly Overweight or Overweight	77 (32.3%)	58 (25.7%)	0.12	76 (28.8%)	0.94
Weight					
< 50 lbs	84 (35.0%)	115 (50.4%)		75 (28.7%)	
≥ 50 lbs	156 (65.0%)	113 (49.6%)	0.001	186 (71.3%)	<0.001
Time spent outdoors, cold days					
< 1 hour per day	104 (62.7%)	107 (60.8%)		123 (69.1%)	
≥ 1 hour per day	62 (37.4%)	69 (39.2%)	0.72	55 (30.9%)	0.10
Time spent outdoor, warm days					
< 1 hour per day	34 (21.7%)	50 (30.7%)		58 (33.0%)	
≥ 1 hour per day	123 (78.3%)	113 (69.3%)	0.07	118 (67%)	0.11
Cosequin use					
No	234 (95.5%)	218 (93.6%)		250 (97.7%)	
Yes	11 (4.5%)	15 (6.4%)	0.35	6 (2.3%)	0.04
Chondrotin use					
No	232 (94.7%)	215 (92.3%)		257 (96.6%)	
Yes	13 (5.3%)	18 (7.7%)	0.28	9 (3.4%)	0.07
Prednisone use					
No	235 (95.9%)	228 (97.9%)		250 (94.0%)	
Yes	10 (4.1%)	5 (2.2%)	0.23	16 (6.0%)	0.06

[a] P-value comparing benign tumor and chronic disease control groups, based on chi-square test for categorical variables

[b] P-value comparing cases and pooled control groups, based on chi-square test for categorical variables

Table 2

Age-adjusted and multivariate odds ratios for the association between exposure to flea/tick control products and canine malignant lymphoma, N=744

Exposure	Cases (N=266)	Controls (pooled) (N=478)	Age-Adjusted OR[a] (95% CI)	Multivariate OR[a] (95% CI)
Use of any flea/tick control products				
No	41 (15.9%)	74 (15.9%)	1.0 (0.7–1.5)	1.1 (0.7–1.7)
Yes	217 (84.1%)	391 (84.1%)		
Number of flea/tick control products used				
None	71 (26.7%)	154 (32.2%)	1	1
1	161 (60.5%)	261 (54.6%)	1.3 (0.9–1.9)	1.3 (0.9–1.9)
2	27 (10.2%)	50 (10.5%)	1.2 (0.7–2.0)	1.2 (0.7–2.1)
≥3	7 (2.6%)	13 (2.7%)	1.2 (0.4–3.1)	0.8 (0.4–3.0)
P_{trend}			0.36	0.41
Type of Flea/Tick control product				
Collar				
No	238 (89.5%)	432 (90.4%)	1.1 (0.7–1.8)	1.2 (0.7–2.0)
Yes	28 (10.5%)	46 (9.6%)		
Powder/Spray				
No	256 (96.2%)	465 (97.3%)	1.4 (0.6–3.2)	1.5 (0.6–3.6)
Yes	10 (3.8%)	13 (2.7%)		
Shampoo				
No	241 (90.6%)	435 (91.0%)	1.1 (0.6–1.8)	1.0 (0.6–1.8)
Yes	25 (9.4%)	43 (9.0%)		
Dip				
No	260 (97.7%)	466 (97.5%)	0.9 (0.3–2.4)	0.9 (0.3–2.6)
Yes	6 (2.3%)	12 (2.5%)		
Pills				
No	250 (94.0%)	450 (94.1%)	1.0 (0.5–1.9)	1.1 (0.6–2.0)
Yes	16 (6.0%)	28 (5.9%)		
Drops				
No	115 (43.2%)	220 (46.0%)	1.1 (0.8–1.5)	1.1 (0.8–1.5)
Yes	151 (56.8%)	258 (54.0%)		
Brand of Drops				
Frontline, Frontline Plus, or Frontline TopSpot	138 (78.4%)	252 (78.0%)	1	1
Advantage, K9 Advantix, or Biospot	31 (17.6%)	54 (16.7%)	1.0 (0.6–1.7)	1.1 (0.6–1.7)
Revolution	3 (1.7%)	9 (2.8%)	0.6 (0.2–2.3)	0.6 (0.2–2.4)
Other	4 (2.3%)	8 (2.5%)	1.0 (0.7–1.5)	0.9 (0.3–3.0)

[a] OR, odds ratio. CI, confidence interval. Multivariate relative risks were adjusted for age, reference year, weight, history of cancer, and use of cosequin, chondroitin and prednisone.

Table 3

Age-adjusted and multivariate odds ratios for the association between exposure to professional and self-treated lawn products and canine malignant lymphoma

	Professionally applied products		Self-applied products		Professionally or self-applied products	
Exposure	**Cases: Controls**	**OR (95% CI)[a]**	**Cases: Controls**	**OR (95% CI)[a]**	**Cases: Controls**	**OR (95% CI)[a]**
Use of any lawn care products						
No	182: 341	1.2 (0.9–1.7)	149: 262	1.0 (0.7–1.3)	94: 173	1.1 (0.8–1.6)
Yes	74: 113		102: 182		162: 273	
Number of lawn care products used						
None	191: 365	1	194: 333	1	137: 242	1
1	8: 26	0.6 (0.3–1.4)	23: 77	0.5 (0.3–0.8)	19: 89	0.4 (0.2–0.7)
2	28: 41	1.4 (0.8–2.3)	27: 41	1.2 (0.7–2.0)	51: 73	1.3 (0.8–1.9)
≥3	38: 46	1.5 (0.9–2.5)	22: 27	1.2 (0.7–2.3)	59: 74	1.3 (0.8–1.9)
P_{trend}		0.06		0.81		0.15
Type of lawn care product						
Herbicide						
No	204: 395	1.4 (1.0–2.1)	222: 403	1.0 (0.7–1.5)	165: 326	1.3 (0.9–1.8)
Yes	62:83		44: 75		101: 152	
Pesticide						
No	221: 429	1.7 (1.1–2.7)	226: 420	1.2 (0.7–1.8)	189: 376	1.4 (1.1–2.0)
Yes	45: 49		40: 58		77: 102	
Insect Growth Regulators						
No	254: 460	1.2 (0.6–2.6)	253: 470	2.7 (1.1–6.8)	244: 453	1.6 (0.8–2.9)
Yes	12: 18		13: 8		22: 25	
Fungicide						
No	257: 470	1.8 (0.7–4.8)	264: 472	0.7 (0.1–3.8)	255: 464	1.4 (0.6–3.2)
Yes	9: 8		2: 6		11: 14	
Rodenticide						
No	264: 473	0.8 (0.2–4.2)	265: 474	0.3 (0.04–3.1)	263: 470	0.6 (0.2–2.4)
Yes	2: 5		1: 4		3: 8	
Fertilizer						

	Professionally applied products		Self-applied products		Professionally or self-applied products	
Exposure	**Cases: Controls**	**OR (95% CI)[a]**	**Cases: Controls**	**OR (95% CI)[a]**	**Cases: Controls**	**OR (95% CI)[a]**
No	197: 372	1.2 (0.8–1.7)	216: 383	0.9 (0.6–1.4)	157: 289	1.0 (0.8–1.4)
Yes	69: 106		50: 95		109: 189	

[a]OR, odds ratio from multivariate model; CI, confidence interval. Multivariate relative risks were adjusted for age, reference year, weight, history of cancer, and use of cosequin, chondroitin and prednisone.