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Environmental Tobacco Smoke and Risk of Malignant Lymphoma in Pet Cats

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Feline malignant lymphoma occurs commonly in domestic cats and may serve as a model for non-Hodgkin's lymphoma in humans. Several studies have suggested that smoking may increase the risk of non-Hodgkin's lymphoma. To evaluate whether exposure to household environmental tobacco smoke (ETS) may increase the risk of feline malignant lymphoma, the authors conducted a case-control study of this relation in 80 cats with malignant lymphoma and 114 controls with renal disease diagnosed at a large Massachusetts veterinary teaching hospital between 1993 and 2000. Owners of all subjects were sent a questionnaire inquiring about the level of smoking in the household 2 years prior to diagnosis. After adjustment for age and other factors, the relative risk of malignant lymphoma for cats with any household ETS exposure was 2.4 (95 percent confidence interval: 1.2, 4.5). Risk increased with both duration and quantity of exposure, with evidence of a linear trend. Cats with 5 or more years of ETS exposure had a relative risk of 3.2 (95 percent confidence interval: 1.5, 6.9; p for trend = 0.003) compared with those in nonsmoking households. These findings suggest that passive smoking may increase the risk of malignant lymphoma in cats and that further study of this relation in humans is warranted. *Am J Epidemiol* 2002;156:268–73.

cat diseases; lymphoma; smoke; smoking; tobacco smoke pollution

Abbreviations: CI, confidence interval; ETS, environmental tobacco smoke; TUSVM, Tufts University School of Veterinary Medicine.

Malignant lymphoma is a common malignancy in domestic cats and is histologically similar to non-Hodgkin's lymphoma in humans (1, 2). Previously, feline malignant lymphoma was believed to be largely the result of infection by feline leukemia virus, because the majority of cats diagnosed with malignant lymphoma also tested positive for feline leukemia virus (3). However, in recent years, increased frequency of vaccination against feline leukemia virus has greatly reduced the prevalence of this infection in domestic cats, and the proportion of malignant lymphoma cases with concurrent feline leukemia virus infection has decreased substantially (1, 4). The reduced role of feline leukemia virus in the etiology of feline malignant lymphoma raises questions about whether lifestyle and environmental factors may influence disease risk in pet cats, as they do in humans.

Several recent studies in humans have suggested that smoking may increase the risk of non-Hodgkin's lymphoma, although results have been inconsistent. Of the four known cohort studies (5–8) to evaluate this association, three (5–7) observed a significant increase in risk of incident non-Hodgkin's lymphoma in current smokers, with relative risks ranging from 1.4 (5) to 3.8 (6). A positive association between smoking and non-Hodgkin's lymphoma has also been suggested by the results of several (9–14) but not all (15–19) case-control studies. In addition, while few studies have evaluated the role of exposure to environmental tobacco smoke (ETS) in the development of non-Hodgkin's lymphoma, several have suggested a relation between parental smoking prior to a child's birth and risk of childhood lymphoma (20–23).

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In sharing their living environment with humans, pet cats are exposed to many of the same environmental contaminants as their owners, including ETS (24). Exposure levels in cats continuously kept indoors may actually be higher than those in human household members, who often spend extended periods of time outside the house. Routes of ETS exposure in cats may be through inhalation and oral ingestion during grooming of particulate matter deposited on the fur; feline exposure patterns thus may mimic those of young children living in smoking households, who may both inhale ETS and orally ingest particulate matter by mouthing contaminated objects (25). As humans do, cats exposed to household ETS metabolize nicotine into cotinine and demonstrate urinary cotinine levels that increase with exposure dose (E. R. Bertone, unpublished data). To assess whether household exposure to ETS may increase the risk of malignant lymphoma in pet cats, we conducted a hospital-based case-control study of this exposure in animals presenting to the Tufts University School of Veterinary Medicine (TUSVM).

MATERIALS AND METHODS

The Foster Small Animal Hospital at TUSVM is a large veterinary teaching hospital in central Massachusetts and serves as the referral hospital for the region. The institutional review board at TUSVM reviewed and approved the protocol used in this study.

Case definition

Eligible cases for this study included all cats diagnosed with biopsy-confirmed malignant lymphoma at the Harrington Oncology Clinic of the Foster Small Animal Hospital at TUSVM between January 1993 and June 2000 ($n = 124$). In June 2000, letters were then sent to owners of all eligible cases at their last known address acknowledging a previous diagnosis of malignant lymphoma in their pet and explaining the general purpose of the study but not its objectives. Owners were asked to complete a short questionnaire inquiring about general characteristics of the case's care and home environment and to return the questionnaire to TUSVM in the enclosed, postage-paid envelope. Owners who had not responded by mail within 2 months were sent a second copy of the introduction letter and questionnaire. Nonrespondents to the second mailing were telephoned by study staff and asked to complete the questionnaire over the phone. Complete questionnaire information was obtained from 80 (64.5 percent) of the owners of cases. Of the nonrespondents, 10 (8.1 percent) refused to participate, 11 (8.9 percent) could not be reached by telephone, and 23 (18.5 percent) were no longer living at their last known address and could not be located.

Control definition

Eligible controls were 168 cats diagnosed with renal failure at TUSVM between January 1993 and June 2000. Controls were originally chosen for a concurrent study of risk factors for oral squamous cell carcinoma. These animals were selected as controls because renal disease is a nonmalignant, serious condition but is not known to be etiologically associated with passive smoking in either cats or humans. In addition, cats with renal disease diagnosed at TUSVM were thought to be more representative than healthy controls would be of the population that gave rise to the malignant lymphoma cases, because cat owners who bring their pets to a large teaching hospital for clinical evaluation and laboratory testing are likely to differ substantially from the general population of cat owners. The diagnosis of renal failure in all potential controls was based on low urine specific gravity (specific gravity < 1.018) and the presence of concurrent azotemia (elevated serum creatinine). Mailing procedures were identical to those used in the case group. Completed questionnaire responses were ultimately obtained from 114 (67.9 percent) owners of controls, 14 (8.3 percent) refused participation, 13 (7.7 percent) could not be reached by telephone, and 27 (16.1 percent) were no longer living at their last known address and could not be located.

Exposure and covariate assessment

The owners of eligible cases and controls were sent a two-page questionnaire inquiring about the characteristics, care, and home environment of their pet during a specific year, corresponding to 2 years prior to the diagnosis of malignant lymphoma or renal disease. Questions on characteristics of the subject included age, birth year, sex, breed, hair length, reproductive status (i.e., neutered/spayed vs. reproductively intact), and general medical history. Other questions inquired about aspects of the cat's care and home living environment, such as number of years owned; usual diet; use of flea-control products including collars, shampoos, drops, and pills; frequency of grooming, bathing, and toothbrushing; amount of time spent outside during the day and at night; house size; house location; and primary heating source.

Questions pertaining to exposure to ETS 2 years prior to diagnosis asked whether the cat had ever lived in the same household as a smoker, the types of tobacco products household members used (cigarettes, cigars, pipes), the number of years the cat had lived with a smoker, the total number of smokers in the household, and the average number of cigarettes smoked per day by all household members combined.

Statistical analysis

Cats were divided into categories based on their level of exposure to ETS, as reported by their owners via questionnaire. Aspects of ETS exposure evaluated included ever versus never exposed, duration of exposure (none, <5 years, ≥5 years), number of household smokers (0, 1, ≥2), and average total number of cigarettes smoked per day by all household members (0, 1–19, ≥20). To consider the effects of duration and intensity of exposure simultaneously, we created an ETS exposure index by multiplying the years of exposure by the average number of cigarettes smoked in the house per day; subjects were then divided into categories (0, 1–99, ≥100).

Odds ratios were used to estimate the relative risk of malignant lymphoma over categories of ETS exposure, and 95 percent confidence intervals were calculated. Multivariable logistic regression modeling (SPSS software system; SPSS Inc., Chicago, Illinois) was used to adjust all risk estimates for confounders; a covariate was considered a confounder and was included in the regression model if its inclusion altered the relative risk for the ETS–malignant lymphoma association by 10 percent or more. The final multivariable model included terms for age at diagnosis (continuous), location of residence (suburban vs. other), and hair length (long vs. short). Other variables measured by questionnaire were evaluated but were not included in the analysis because they were not associated with either exposure to ETS or risk of malignant lymphoma.

Tests for trend were performed over categories of ETS exposure, and the median values of the categories were modeled as a single continuous variable. Subanalyses were also conducted to evaluate whether an association between ETS and malignant lymphoma might be limited to subsets of the study population, including older animals (aged ≥10 years at diagnosis), indoor cats (0 hours spent outside per day), and animals living in smaller houses (<6 rooms). In addition, to evaluate whether the length of time between diagnosis and owner recall of ETS exposure may have affected the relative risk, a subanalysis limited to cases and controls diagnosed in recent years (January 1996–June 2000) was also performed.

RESULTS

Age-adjusted relative risks for the association between malignant lymphoma and selected characteristics are presented in table 1. Cases and controls did not differ in terms of age (mean age of cases, 11.2 years; mean age of controls, 11.0 years) or number of years living with their current owner (mean for cases, 10.8 years; mean for controls, 10.4 years). Sex, breed, use of flea-control products, number of years owned, indoor/outdoor status, and average house size were also unrelated to the risk of malignant lymphoma. Risk was slightly, but nonsignificantly elevated for cats fed moist, canned food as the main component of their diet. Long hair length, intact reproductive status, and living in a nonsuburban location were inversely associated with malignant lymphoma risk, although results were not statistically significant.

Multivariable relative risks for malignant lymphoma associated with household exposure to passive smoking are presented in table 2. Cats with any history of household exposure to tobacco smoke had a significant twofold increase in risk of malignant lymphoma (relative risk = 2.4, 95 percent confidence interval (CI): 1.2, 4.5). Duration of exposure was also significantly associated with malignant lymphoma risk. Cats with 5 or more years of ETS exposure had a relative risk of 3.2 (95 percent CI: 1.5, 6.9) compared with those with no exposure, with evidence of a linear trend (p for trend = 0.003). Risk of malignant lymphoma appeared linearly related to the number of smokers living in the house, with a relative risk of 1.9 (95 percent CI: 0.9, 3.9) for cats living with one smoker and 4.1 (95 percent CI: 1.4, 12.1) for those living with two or more smokers (p for trend = 0.005), although confidence limits were wide. When total number of cigarettes smoked in the household was evaluated, risk was similarly elevated. Cats living in households in which a pack or more of cigarettes was smoked per day had a relative risk of 3.3 (95 percent CI: 1.3, 8.1; p for trend = 0.006) compared with those living in nonsmoking households. To assess the effects of duration and quantity of ETS exposure simultaneously, we created an ETS exposure index by multiplying years of exposure by number of cigarettes smoked by all household members. Cats in the highest category of this index had a nearly fourfold increase in malignant lymphoma risk compared with those with no ETS exposure (relative risk = 3.8, 95 percent CI: 1.4, 9.8; p for trend = 0.008).

Although our power to evaluate the association between ETS exposure and risk of malignant lymphoma in subsets of the population was relatively low, results from subanalyses limited to older cats, indoor cats, and cats living in smaller houses were similar to those of the main study (results not shown). When we limited our analysis to the 64 cases and 89 controls diagnosed recently (January 1996–June 2000), results were also similar to those of the main analysis; cats exposed to household ETS for 5 or more years had a relative risk of 4.0 (95 percent CI: 1.6, 9.9; p for trend = 0.003) compared with those with no exposure.

DISCUSSION

Results from our case-control study suggest that pet cats exposed to household ETS have a significantly increased risk of malignant lymphoma. Risk was positively associated with both duration and quantity of ETS exposure. Cats living in households in which a pack or more of cigarettes was smoked per day had a significant threefold increase in risk compared with cats with no household exposure, although confidence intervals were wide. To our knowledge, our study is the first to examine the association between household ETS exposure and risk of malignant lymphoma in cats or other domestic animals.

While few epidemiologic studies of risk factors for disease in cats have been conducted, several have considered the relation between factors such as ETS and cancer in pet dogs, which have been proposed as appropriate sentinels for environmental health hazards in humans (24, 26). In two case-control studies based in a Colorado veterinary teaching hospital (27, 28), Reif et al. evaluated the associations between household exposure to ETS and risk of lung, nasal, and sinus cancers in pet dogs. Dogs exposed to ETS demonstrated a nonsignificant 60 percent increase in risk of lung cancer (27). Risk of nasal cancer was significantly higher for long-nosed dogs exposed to household ETS than for unexposed animals, although there was no evidence of an increase in risk for short-nosed breeds (28).

To our knowledge, previous studies have not addressed the association between ETS and malignant lymphoma in pets. While no clear mechanism has been proposed to explain an association between active or passive smoking and the development of non-Hodgkin's lymphoma in humans, several components of tobacco smoke may be carcinogenic to lymphoid tissue and may cause mutation in lymphocyte

TABLE 1. Age-adjusted relative risks and 95 percent confidence intervals for the association between selected characteristics and feline malignant lymphoma, Massachusetts, 1993–2000

Characteristic	Cases (no.)	Controls (no.)	Age-adjusted* RR†	95% CI†
Age (continuous)			1.0	1.0, 1.1
No. of years owned (continuous)			1.0	0.9, 1.0
Sex				
Male	44	59	1.0	
Female	36	55	0.9	0.5, 1.6
Purebred				
No	71	103	1.0	
Yes	9	11	1.2	0.5, 3.0
Hair length				
Short	61	77	1.0	
Long	19	37	0.7	0.4, 1.3
Reproductive status				
Neutered/spayed	78	106	1.0	
Intact	2	8	0.4	0.1, 1.7
No. of rooms in house				
1 – 6	40	56	1.0	
7 – 9	32	48	0.9	0.5, 1.7
≥10	7	10	1.0	0.3, 2.7
Location of residence				
Suburban	42	49	1.0	
Urban	19	33	0.7	0.3, 1.4
Rural	18	31	0.7	0.3, 1.4
Allowed outdoors				
No	35	49	1.0	
Yes	45	65	1.0	0.5, 1.7
Use of flea-control products				
No	48	61	1.0	
Yes	31	52	0.8	0.4, 1.4
Main component of diet				
Dry food	38	67	1.0	
Moist, canned food	41	47	1.5	0.9, 2.7

* All relative risks (except age) were adjusted for age as a continuous variable.
† RR, relative risk; CI, confidence interval.

precursors (6–8). More than 40 mutagens and carcinogens in ETS have been identified, several of which have been implicated in human carcinogenesis (29, 30). In our population, the majority of malignant lymphomas were of gastrointestinal and nasal origin. Given this anatomic distribution, it seems biologically plausible that lymphoid tissues would be susceptible to the potentially harmful effects of inhaled and/or orally ingested ETS. This hypothesis is supported by the observation that tumor location varied slightly by ETS exposure status, with gastrointestinal tumors accounting for 56 percent of the malignant lymphomas in ETS-exposed cats compared with 39 percent in unexposed animals, although this difference was not statistically significant.

Cats with renal failure were chosen as controls because, to our knowledge, incident renal disease has not been associated with exposure to active or passive smoking in studies in either cats or humans. While it is possible that a previously unidentified association may exist between smoking and renal disease in cats, it is more likely that passive smoking would increase risk rather than be protective. In that instance, ETS exposure would be overrepresented in our control group compared with the general population, and the actual ETS–malignant lymphoma relation would be even stronger than we observed. In addition, cats diagnosed with renal failure at TUSVM are appropriate controls because they are likely to be representative of the underlying study base that gave rise

TABLE 2. Multivariate relative risks and 95 percent confidence intervals for the association between exposure to environmental tobacco smoke and feline malignant lymphoma, Massachusetts, 1993–2000

Exposure level	Cases (no.)	Controls (no.)	Multivariate RR*,†	95% CI*	*p* for trend‡
No exposure to household ETS*	47	82	1.00		
Any exposure to household ETS	33	32	2.4	1.2, 4.5	
No. of years of ETS exposure§					
>0–<5	9	16	1.3	0.5, 3.2	
≥5	24	16	3.2	1.5, 6.9	0.003
No. of smokers in household§					
1	22	24	1.9	0.9, 3.9	
≥2	11	7	4.1	1.4, 12.1	0.005
No. of cigarettes smoked/day in household§					
1–19	16	17	1.9	0.9, 4.3	
≥20	16	10	3.3	1.3, 8.1	0.006
ETS exposure index§,¶					
1–99	17	18	1.8	0.8, 4.0	
≥100	15	9	3.8	1.4, 9.8	0.008

* RR, relative risk; CI, confidence interval; ETS, environmental tobacco smoke.

† Multivariate relative risks were adjusted for age at diagnosis (continuous), location of residence (suburban, other), and hair length (short, long).

‡ Test for trend was calculated by using the median value of each category as a continuous variable in the regression model.

§ Reference group: cats with no household exposure to ETS.

¶ ETS exposure index: (years of exposure to ETS) × (no. of cigarettes smoked per day by all household members).

to the malignant lymphoma cases; pet owners who bring their cats to a large teaching hospital for clinical examination and laboratory tests, as were required for both malignant lymphoma and renal failure diagnoses, are likely to be similar in terms of demographic characteristics.

Response rates in our study were similar for cases (65 percent) and controls (68 percent), and they were similar to those reported in many case-control studies in human populations. As with any case-control study, incomplete participation by all eligible subjects may result in selection bias if participation is influenced by both exposure and disease status. In our population, study participation did not vary in terms of an animal's sex, reproductive status, year of birth, or year of malignant lymphoma or renal failure diagnosis. While cat owners who smoke may be less likely to participate than those who do not, participation is unlikely to also vary by disease diagnosis. To date, few studies have evaluated lifestyle risk factors for chronic disease in companion animals, so it is unlikely that owner participation would be influenced by previous knowledge of an association between household smoking and health in pets.

The lack of previous research in this area and selection of a control group with a serious illness should also have limited recall bias in our study; it is unlikely that owners of cats with malignant lymphoma and renal failure would misreport household smoking history differently. It is possible that inaccurate recall of smoking history by both case and control owners may have resulted in some exposure misclassification, because many owners were required to recall an exposure that occurred several years earlier. Research in humans suggests that misclassification of smoking status tends to be low (31) and that the effect of misclassification on risk estimates in studies of ETS and cancer is small (32, 33). We attempted to address this issue in our study by conducting a subanalysis limited to animals that had been diagnosed within 3.5 years of our exposure assessment. In this analysis, results were virtually identical to those of the main study. In addition, because any misclassification of smoking status is likely to have been nondifferential with respect to case status, we would expect it to have biased results toward the null value.

Exposure to passive smoking may be difficult to measure accurately, because the biologic dose a subject receives may be mediated by a large number of factors. We attempted to reduce misclassification of ETS exposure level by collecting information on the amount of time subjects spent outdoors and on house size, both of which may influence biologic dose (24, 34). Inclusion of these factors in multivariable regression models had no effect on risk estimates, and subanalyses limited to animals living in smaller houses and to indoor cats produced results identical to the main study. Furthermore, as explained above, we would expect misclassification of biologic dose to have attenuated our results.

In summary, our study suggests that exposure to household ETS may increase the risk of malignant lymphoma in pet cats. Similarities between feline malignant lymphoma and human non-Hodgkin's lymphoma, and the commonality of ETS exposure for all household members, suggests that further research into these relations may be warranted.

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