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Cancer of the Nasal Cavity and Paranasal Sinuses and Exposure to Environmental Tobacco Smoke in Pet Dogs

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A case-control study of nasal cancer in pet dogs was conducted to test the hypothesis that exposure to environmental tobacco smoke increases risk. Cases (n = 103) were selected from a teaching hospital during 1986–1990. Controls (n = 378) with other forms of cancer were selected from the same study base. Exposure to environmental tobacco smoke was evaluated by determining the number of smokers in the household, the packs of cigarettes smoked per day at home by each smoker, the number of years that each person smoked during the dog's lifetime, and the proportion of time spent indoors by the dog. The crude odds ratio for exposure to environmental tobacco smoke was 1.1 (95% confidence interval (CI) 0.7–1.8) and was unchanged after adjustment for confounders. Skull shape was found to exert a pronounced modifying effect; among dolichocephalic (long-nosed) dogs, the odds ratio for a smoker in the house was 2.0 (95% CI 1.0–4.1). A monotonic increase in the odds ratios across strata of total packs smoked and total indoor exposure to environmental tobacco smoke was found in this group of dogs, with risks of approximately 2.5 for the highest stratum. Conversely, all odds ratios for exposure to environmental tobacco smoke among short- and medium-length-nosed dogs were approximately 0.5. The data support an association between environmental tobacco smoke and canine nasal cancer. *Am J Epidemiol* 1998;147:488–92.

carcinoma; case-control studies; dogs; epidemiology; nasal cavity; nose neoplasms; tobacco smoke pollution

An association between cancers of the human nasal cavity and paranasal sinuses and cigarette smoking has been described in recent studies in the United States (1) and China (2). To date, limited evidence from two studies conducted in Japan suggests that exposure to environmental tobacco smoke is also a risk factor for nasal sinus cancer (3, 4). In a large cohort study, nonsmoking Japanese women married to smoking husbands had an elevated risk for cancer of the paranasal sinuses, which increased with the amount smoked by their husbands (3). In a case-control study (4), risk estimates for maxillary sinus tumors among nonsmoking women increased with the number of smokers in the home.

Spontaneous animal models of respiratory disorders may provide an important "sentinel" for the evaluation of effects of exposure to environmental tobacco smoke and other ambient environmental pollutants (5). Many forms of canine cancer resemble their human analogues in biologic behavior, pathologic expression, and recognized risk factors. Epidemiologic studies of environmental risk factors for cancer in pet dogs have been advocated because of relative freedom from confounding factors such as occupational exposures, the dogs' shorter life span, and restricted residential mobility (5). Although relatively uncommon among humans in the United States, nasal cancer is a common neoplasm in pet dogs, and is the most commonly diagnosed cancer of the respiratory system in that species (6). We recently reported an increased risk for lung cancer in dogs exposed to environmental tobacco smoke in the home (7). The study reported here was designed to test the hypothesis that exposure to environmental tobacco smoke in the home increases the risk for cancer of the nasal cavity and paranasal sinuses in pet dogs.

MATERIALS AND METHODS

Cases and controls

All cases of cancer of the nasal cavity and paranasal sinuses were selected from the oncology records system of the veterinary teaching hospital at Colorado State University, Fort Collins, Colorado, for the years 1986–1990. Unmatched controls with other forms of cancer were selected randomly from the same database

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Abbreviations: CI, confidence interval; OR, odds ratio.

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and time period. The major diagnostic categories among the control group were lymphoma (126), bone cancer (95), oral cancer (33), melanoma (19), splenic and hepatic hemangiosarcoma (15), and breast cancer (12). The diagnoses of nasal cancer and other forms of cancer in controls were histologically verified.

Exposure assessment

A telephone interview was conducted with the owners of all subjects. Interviews were conducted in a blinded manner with respect to case-control status. Demographic information was collected for each subject. Exposure to environmental tobacco smoke was evaluated by determining the number of smokers in the household, the packs of cigarettes smoked per day at home by each smoker, the number of years that each person smoked during the dog's lifetime, and the proportion of time (per 24-hour day) spent by the dog inside the home. An exposure index was created to obtain a quantitative estimate of lifetime exposure to environmental tobacco smoke by multiplying the number of packs smoked by all smokers in the home during the dog's lifetime by the proportion of time the dog spent inside the home. Subjects that lived in homes with no resident smokers were assumed to have received no exposure to environmental tobacco smoke.

Information on potential confounders and effect modifiers was collected during the interview. Socioeconomic status was evaluated from owner's years of education. A history of occupational exposure of the owner to substances associated with human respiratory tract cancer, such as asbestos, uranium, and wood dust, was obtained, since associations with owner's occupation have been identified in other studies of canine cancer (8). Lifetime residential histories were assessed for exposure to industrial sites. Potential exposure to other environmental risk factors, such as household pesticides, lawn herbicides and fertilizers, flea and tick control products, wood shavings, and dusts, was assessed.

Analysis

Odds ratios with approximate 95 percent confidence intervals were calculated to estimate risk. Multiple logistic regression analysis was used to control for possible confounding (9). Age, gender, and breed (purebred versus mixed) were included in each logistic regression model as possible confounders. Environmental and demographic variables which were associated with nasal cancer in crude analyses were screened for inclusion in logistic models at $p < 0.20$. Further analyses were stratified by skull shape. Dolichocephalic (long-nosed) breeds have been shown to be at increased risk for nasal cancer (10), and skull shape was found to exert an important modifying effect in our earlier study of canine lung cancer (7). Skull shape was assessed from the medical record by classifying dogs according to breed or to their description if not purebred. High risk breeds were identified from earlier analyses of nasal cancer in a national database of hospital diagnoses (6, 11), and this variable screened for inclusion in the logistic models. The linearity of trends in risk for levels of environmental tobacco smoke exposure was evaluated with Mantel's extension chi-square test (12).

RESULTS

The data analysis was based on 103 cases and 378 controls. Controls were similar to cases with respect to age, sex, purebred/mixed breed, high-risk breed, time spent outdoors, and owner's education (table 1). Participation rates for cases (74 percent) and controls (76 percent) were similar. At least one smoker had lived in the home of 46 percent of the subjects during their lifetimes. Crude odds ratios with 95 percent confidence intervals were calculated to screen environmental variables for an association with nasal cancer. Risk estimates for types of home construction, ventilation, heating, air conditioning, and urban/rural residence were not elevated. Potential exposures to industrial sites, hazardous waste sites, wood shavings, furniture building, woodworking, dusts, fireplace smoke, and owner's occupation were examined—no evidence of an association with nasal cancer was found.

Potential exposures to herbicides and insecticides used in lawn treatment and gardening were not associated with increased risk for nasal cancer. However, the use of topical insecticides for flea and tick control increased the risk (odds ratio (OR) = 2.0, 95 percent confidence interval (CI) 1.3–3.0). Since nasal cancer was associated with the use of flea control products, this variable was incorporated into the logistic regres-

TABLE 1. Characteristics of cases and controls from veterinary oncology records, Colorado, 1986–1990

Characteristic	Cases (n = 103)	Controls (n = 378)
Mean age (years)	11.0	9.7
Sex (% male)	49.5	45.5
Breed (%)		
Purebred	61.2	65.9
High-risk breed	38.8	39.7
Time outdoors (%)	33.6	33.5
Owner's education more than high school (%)	80.5	78.8

* As defined in (6, 11).

sion models as a potential confounder. Age, gender, and breed risk were also incorporated in all final models when they met the $p < 0.20$ criterion for inclusion.

The crude odds ratio for the presence of a smoker in the home and risk of nasal cancer was 1.1 (95 percent CI 0.7–1.8). The odds ratio remained unchanged after adjustment for age, gender, purebred/mongrel breed, and years of education of the owner. After further adjustment for the use of flea control products, the presence of a smoker was not related to nasal cancer risk (table 2). Similarly, the total pack-years of exposure to environmental tobacco smoke, which took into account the smoking pattern of all smokers in the home during the dog's lifetime, was unrelated to overall risk of nasal cancer. The exposure index, which incorporated the proportion of the day spent indoors by the dog, as well as total pack-years, was analyzed by assigning subjects to exposure tertiles based on the distribution of environmental tobacco smoke exposure in the control group. No evidence of increasing risk for nasal cancer was found across exposure strata.

The data were stratified according to skull shape to examine potential effect modification (table 3). In our earlier study of canine lung cancer, risk was restricted to short- and medium-length-nosed dogs (7). In contrast, long-nosed dogs have been found to be at increased risk for nasal cancer in previous studies (10, 11). Skull shape was found to exert a strong modifying effect on estimated risk for nasal cancer associated with exposure to environmental tobacco smoke (table 3). An increase in risk for a smoker in the house was restricted to long-nosed (dolichocephalic) dogs (OR = 2.0, 95 percent CI 1.0–4.1). Evidence of a dose-response relation to environmental tobacco smoke was found among long-nosed dogs. The adjusted risk estimates for the highest stratum of packs smoked (OR = 2.4, 95 percent CI 1.0–5.9) and the exposure index (OR = 2.5, 95 percent CI 1.1–5.7) were moderately strong. The test for trend in nasal cancer risk across strata of the exposure index was statistically significant ($p < 0.05$). Conversely, all odds ratios for exposure to environmental tobacco smoke among short- and medium-length-nosed dogs were approximately 0.5.

The exposure to environmental tobacco smoke for the group of 55 long-nosed dogs in the highest exposure index tertile was characterized further to provide a framework for interspecies comparisons. On average, these dogs were 10.4 years old and had lived in a home with two smokers. Collectively, these persons smoked an average of 36 cigarettes per day in the presence of their pets.

The risk for nasal cancer was also examined according to histologic type. Dogs with sarcomas had a higher adjusted risk (OR =2.0, 95 percent CI 0.8–5.2) than dogs with carcinomas (OR = 1.2, 95 percent CI 0.6–2.3) for the highest tertile of the exposure index.

TABLE 2. Adjusted odds ratios (ORs) for exposure to environmental tobacco smoke in canine nasal cancer, Colorado, 1986–1990

Risk factor	Cases exposed (n = 103)	Controls exposed (n = 378)	OR*	95% CI†
Smoker				
None	54	206	1.0	
Smoker	49	172	0.9	0.6–1.5
Pack-years				
None	54	206	1.0	
1 to <12	26	94	0.9	0.5–1.5
≥12	23	78	1.0	0.6–1.8
Exposure index				
None	56	214	1.0	
0 to ≤4.5	18	56	0.8	0.4–1.5
>4.5	29	108	1.1	0.6–1.8

* Adjusted for age, gender, high-risk breed, and use of flea control products.
† CI, confidence interval.

DISCUSSION

Cigarette smoking has been associated with human nasal and nasal sinus cancer (1, 2) as well as with nasopharyngeal cancer (13, 14). The highest risks are found for squamous cell carcinomas at both sites (1, 14). Tumors of the canine nasal cavity and paranasal sinuses are primarily adenocarcinomas, with squamous cell carcinoma comprising approximately 10–14 percent of cases (6, 11). Under experimental conditions, dogs exposed to cigarette smoke via tracheostomy developed rhinitis, as well as basal epithelial cell hyperplasia and squamous metaplasia in the turbinates (15). These lesions may be precursors to nasal cancer. Nasal carcinomas may also be induced in dogs by the inhalation of radionuclides (16, 17), suggesting that the dog's nasal mucosa is sensitive to the effects of several classes of inhaled carcinogens.

Although there was little evidence of an association between environmental tobacco smoke and nasal cancer for all dogs, effect modification by skull shape was pronounced. An increased risk of nasal cancer was found exclusively among long-nosed dogs, with odds ratios rising to approximately 2.5 for the highest tertile of exposure. Further, a dose-response relation was suggested by the monotonic increase in risk across strata of environmental tobacco smoke exposure.

The increased risk of nasal cancer among long-nosed breeds of dogs exposed to environmental tobacco smoke and the corollary, increased lung cancer risk among short-nosed dogs (7), suggests that ana-

TABLE 3. Adjusted odds ratios (ORs) for exposure to environmental tobacco smoke in canine nasal cancer, by skull shape, Colorado, 1986–1990

Risk factor	Brachy- and mesocephalic dogs				Dolichocephalic dogs			
	Cases exposed (n = 50)	Controls exposed (n = 143)	OR*	95% CI†	Cases exposed (n = 53)	Controls exposed (n = 235)	OR*	95% CI
Smoker								
None	33	68	1.0		21	138	1.0	
Smoker	17	75	0.5	0.3–0.9	32	97	2.0	1.0–4.1
Packs smoked								
None	33	68	1.0		21	138	1.0	
1 to <12	9	40	0.5	0.2–1.0	17	54	1.7	0.7–4.1
≥12	8	35	0.4	0.2–0.9	15	43	2.4	1.0–5.9
Exposure index								
None	34	73	1.0		22	141	1.0	
0 to ≤4.5	7	24	0.5	0.2–1.0	11	32	1.5	0.6–4.1
>4.5	9	46	0.5	0.3–1.1	20	62	2.5	1.1–5.7

* Adjusted for age, gender, and use of flea control products.
† CI, confidence interval.

tomic and physiologic features of the respiratory tract modify risk in dogs. Airflow patterns may also account for interspecies differences in the site of neoplasia associated with tobacco smoke exposure. The human nasopharyngeal region is short and not as effective a filter as that of the dog and rat (18, 19). Conversely, the complex maxilloturbinate region of the dog increases the turbulence of airflow and provides an abundant surface for inhaled particle deposition (19).

An increased risk of nasal cancer among long-nosed dogs may be explained by enhanced filtration and impaction of particles on the mucosa. Further, nasal airflow patterns may be altered by intraspecies anatomic variation. The basis for the apparent protective effect of environmental tobacco smoke on brachycephalic and mesocephalic dogs is unclear; however, an inverted dose-response pattern corresponding to that found among long-nosed dogs was not observed among short- and medium-length-nosed dogs.

We defined exposure to environmental tobacco smoke during the dog's lifetime by obtaining relevant smoking histories and behaviors for the period of interest. We accounted for periods when the owner was not at home and for time spent outdoors by the dog. Nonetheless, exposure misclassification may have occurred, since the data were collected up to 5 years after diagnosis. In a separate study, we validated the owner's report of current exposure to environmental tobacco smoke by using the concentration of cotinine in the dog's urine as a biomarker (unpublished data). Misclassification of skull shape undoubtedly occurred, especially in dogs which fell into the midrange of nasal length and in dogs of mixed ancestry. A morphometric validation of skull shape could not be performed retrospectively. These sources of misclassification would be expected to be nondifferential with respect to cancer diagnosis and would thus have biased the risk estimate toward the null. We used dogs with other forms of cancer as controls to minimize recall bias, as well as to control for selection bias in this hospital-based study. A series of demographic and environmental variables was screened as potential confounders. With the exception of the use of flea control products, which was included in all logistic regression models, these were not associated with nasal cancer.

The occurrence of canine nasal cancer in a household may provide an early "sentinel event" for human cancer risk. Since canine nasal cancer is a relatively common neoplasm, its diagnosis may provide further rationale for aggressive public health intervention to prevent human cancers associated with exposure to second-hand smoke.

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