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Mesothelioma in Pet Dogs Associated with Exposure of Their Owners to Asbestos[1,2]

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Pet dogs with spontaneous mesothelioma were used to identify environmental exposures that might increase their owner's risk of asbestos-related disease. These animals share man's domicile environment, yet do not indulge in activities (e.g., smoking, working) which confound interpretation of epidemiologic studies. Eighteen histologically confirmed canine mesotheliomas were diagnosed at the Veterinary Hospital of the University of Pennsylvania, Philadelphia, from April 1977 to December 1981. Sixteen owners of cases and 32 owners of age, breed, and sex-matched controls were interviewed to determine their occupation and medical history and their dog's medical history, life style, diet, and exposure to asbestos. An asbestos-related occupation or hobby of a household member and use of flea repellents on the dog were significantly associated with mesothelioma. In addition, there was a trend indicating an increased risk of mesothelioma with an urban residence. Lung tissue from three dogs with mesothelioma and one dog with squamous cell carcinoma of the lung had higher levels of chrysotile asbestos fibers than lung tissue from control dogs. These findings indicate that well-designed epidemiological studies of spontaneous tumors in pet animals may provide insight into the role of environmental factors in human cancers and serve as a valuable sentinel model to identify environmental health hazards for humans.

INTRODUCTION

Epidemiological evidence indicates that asbestos is a causal factor for human mesothelioma and lung cancer (1, 2). The risk of tumor development appears to be influenced by the fiber type and by personal habits such as smoking (3). The latent period for tumor development following occupational exposure usually exceeds 20 years with a marked increase in risk after 30 to 35 years (4). An increased risk of mesothelioma has also been reported for persons residing near industrial sources of asbestos and for spouses of workers in asbestos-related occupations (5, 6). However, up to 38% of individuals with mesothelioma have no documented history of exposure to asbestos (7).

Pet animals have been a neglected resource for identifying environmental car-

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cinogens. In the United States, an estimated 40 million pet dogs (8) share their owner's domestic environment yet do not indulge in activities that could confound interpretation of epidemiologic studies (e.g., smoking and working). Given the relatively short lifespan of these animals, the latent period for tumor development is decreased and accurate information regarding environmental history can be obtained. In this study we used pet dogs as sentinels to identify environmental exposures that might increase their owners risk of mesothelioma and other asbestos related pulmonary diseases.

PATIENT SELECTION AND METHODS

The study group consisted of 18 dogs with histologically confirmed mesothelioma that were diagnosed between April 1977 and December 1981 at the Veterinary Hospital of the University of Pennsylvania (VHUP). The VHUP is a major veterinary referral center for the Northeast and Middle-Atlantic regions of the United States. Each year there are approximately 17,000 admissions and visits to the VHUP and an additional 6000 submissions of biopsy specimens to the Pathology Department.

A cancer and noncancer control patient were selected from hospital records and matched to each mesothelioma case by age and date of diagnosis (± 1 year), sex, and breed. Excluded from the noncancer control group were dogs with any respiratory disease or suspected malignancy. Dogs with respiratory cancer were excluded from the cancer control group. Owners were interviewed by telephone, and questioned about their dog's medical history, residences, lifestyle (management factors), as well as the occupation and medical history of household members. Occupations and hobbies of household members were classified as definite, probable, possible, or unlikely according to the likelihood of asbestos exposure. This classification was adapted from data published by McDonald and McDonald (7, 9). Occupations and hobbies with definite or probable asbestos exposure were considered to be asbestos related. Residence was classified as urban (population 100,000 or greater) or rural, and analyzed by the first, longest, or residence at diagnosis. Only residences and occupations for the time period prior to the date of diagnosis of mesothelioma were considered. Lung tissue from three mesothelioma patients was analyzed using an electron microprobe for fiber content (10). For comparison, lung tissue was also obtained at necropsy from three dogs with lung cancer and six older dogs with no recognized respiratory or neoplastic disease. These comparison dogs were not included in the epidemiological study.

Because controls had been matched on age, sex, and breed, these characteristics for the cases were first compared to the entire canine hospital population. The odds ratio (OR), an estimate of the relative risk of disease for each category, was determined using the Mantel–Haenszel procedure (11). Age was controlled in sex comparisons, and sex was controlled in age comparisons.

Odds ratios for other risk factors were determined for matched pairs using the cancer and noncancer control groups separately. (12) The control groups were then combined and odds ratios calculated for matched triplets. Using a 95% confidence interval, the null hypothesis of an odds ratio equal to one was tested with computer programs developed by Rothman and Boice (13).

RESULTS

Eighteen dogs with mesothelioma were identified from hospital records. The diagnosis for each patient was confirmed histologically by a veterinary pathologist (R.R.D.) and by a physician pathologist (Dr. Jacob Churg, Barnert Memorial Hospital Center, Paterson, N.J.). Characteristics of the patients with mesothelioma and the sources of asbestos exposure of their owners are listed in Table 1. The distribution of mesotheliomas by site was six (33%) peritoneal, five (28%) pleural, five (28%) both peritoneal and pleural, and two (11%) pericardial.

The mean age (± 1 SD) of the mesothelioma dogs was 8.0 ± 1.9 years; 17 (94%) were male and 15 (83%) were purebreeds. When compared to the entire canine hospital population, males had a relative risk for mesothelioma of 16.6 ($CL_{95\%}$ 6.4–97.3). When dogs 1 to 4 years of age were assigned a relative risk of 1.0, the greatest risk was observed in dogs 5 to 9 years of age (OR = 25.0, $CL_{95\%}$ 6.4–97.3) and in dogs 10 years of age or older (OR = 16.9, $CL_{95\%}$ 3.4–84.3). The risk for purebreed dogs when compared to dogs of mixed breeding was 1.7, but this difference was not statistically significant ($CL_{95\%}$ 0.51–5.9). The relative risk for individual purebreeds represented by more than one dog with mesothelioma was Bouvier des Flandres (OR = 124.3, $CL_{95\%}$ 62.6–246.7), Irish Setter (OR = 5.3, $CL_{95\%}$ 1.4–9.6), and German Shepherd (OR = 3.3, $CL_{95\%}$ 1.3–8.2).

The cancer and noncancer control patients represented a wide variety of diseases and conditions; not more than two dogs had the same diagnosis. Owners of 16 of the 18 mesothelioma patients were contacted and interviewed. The OR for suspected risk factors for canine mesothelioma are shown in Table 2. The findings were similar when mesothelioma patients were compared to either the cancer or noncancer control group. However, for 11 of the 14 risk factors studied, a stronger association with mesothelioma was noted in the analysis using the noncancer controls. Exposure of the owner to asbestos at work or through a hobby was found to be significantly associated with mesothelioma in the analysis using noncancer controls, (OR = 8.0, $CL_{95\%}$ 1.4–45.9); when cancer controls were used the odds ratio was 2.3, but was not significant ($CL_{95\%}$ 0.6–8.7). The relative risk for mesothelioma with both control groups combined was 3.5 ($CL_{95\%}$ 1.1–11.0). Two mesothelioma dog owners had worked in a shipyard during the time period they owned the pet and another who regularly took his dog to work with him was employed by a trucking company that was located adjacent to a shipyard. No owners of control dogs reported working in a shipyard during the dog's lifetime. Epidemiological studies in humans have shown that shipyard workers are likely to be exposed to asbestos and have an increased risk for mesothelioma(9).

Location of residence (urban versus rural) was not significantly associated with mesothelioma in the analysis with cancer or noncancer controls. However, for first, longest, and last residence, living in an urban environment appeared to increase the risk for mesothelioma; this was most evident for the first residence (Table 2). No other residential or neighborhood source of asbestos exposure for the dog was found to be associated with mesothelioma.

Management factors that might have increased the likelihood of a dog being exposed to environmental sources of asbestos without the knowledge of its owner

TABLE 1

CHARACTERISTICS OF 18 CANINE PATIENTS DIAGNOSED WITH MESOTHELIOMA AT VHUP BETWEEN 1977 AND 1981, AND THEIR EXPOSURE TO ASBESTOS

Patient	Breed	Sex	Age at diagnosis (years)	Year of diagnosis	Site of meso-thelioma[a]	Type of asbestos exposure		
						Owner occupation (O)/ hobby (H)	Household/ neighborhood	Other possible
1.	Mixed	M	12	1978	P	Auto body repair (O)	Extensive home remodeling	None
2.	German Shepherd	M	7	1978	P	Auto mechanic (H)	Change of heating system	None
3.	German Shepherd	M	9	1978	P	Truck repair (O) adjacent to shipyard	None	Accompanied owner to job adjacent to shipyard
4.	Doberman Pinscher	M	8	1978	P&Pl	None	None	None
5.	Irish Setter	F-S[b]	8	1979	Pe	Plumbing, heating, sheet rock spackling (H)	Cement factory	None
6.	Bouvier des Flandres	M	8	1979	P	None	None	Flea powder
7.	Mixed[c]	M	10	1979	P&Pl	—	—	—
8.	Bouvier des Flandres	M	8	1979	Pl	None	None	None
9.	German Shepherd	M	7	1979	P&Pl	Sheet rock spackling at shipyard (O)	Demolition and construction site	Flea powder
10.	Boston Terrier	M	7	1979	P&Pl	None	None	None
11.	Irish Setter	M	5	1980	Pl	None	Home insulation, construction site	Flea powder
12.	German Shepherd	M	10	1981	P&Pl	Pipefitting at shipyard (O)	None	Flea powder
13.	Bernese Mtn. Dog	M	4	1977	Pl	None	None	None
14.	Old Eng. Sheepdog	M	6	1981	Pe	None	Demolition & con-	None

						sheet rock spackling (H)		
6.	Bouvier des Flandres	M	8	1979	P	None	None	Flea powder
7.	Mixed[c]	M	10	1979	P&Pl	—	—	—
8.	Bouvier des Flandres	M	8	1979	Pl	None	None	None
9.	German Shepherd	M	7	1979	P&Pl	Sheet rock spackling at shipyard (O)	Demolition and construction site	Flea powder
10.	Boston Terrier	M	7	1979	P&Pl	None	None	None
11.	Irish Setter	M	5	1980	Pl	None	Home insulation, construction site	Flea powder
12.	German Shepherd	M	10	1981	P&Pl	Pipefitting at shipyard (O)	None	Flea powder
13.	Bernese Mtn. Dog	M	4	1977	Pl	None	None	None
14.	Old Eng. Sheepdog	M	6	1981	Pe	None	Demolition & construction sites	None
15.	German Shepherd	M	8	1981	P	Auto mechanic (O)	Home insulation	None
16.	German Short Hair Pointer[c]	M	11	1981	Pl	—	—	—
17.	Mixed	M	8	1981	Pl	Oil burner and furnace installation (O)	None	Flea powder
18.	German Shepherd	M	6	1981	P	Auto body and used parts supply (O)	None	Accompanied owner to work

[a] P = peritoneal, Pl = pleural, Pe = pericardial.

[b] Female–spayed.

[c] Not included in case–control analysis. Unable to contact owner for interview.

TABLE 2
MATCHED PAIR ANALYSIS OF RISK FACTORS FOR CANINE MESOTHELIOMA

Risk factor	Noncancer controls			Cancer controls		
	Odds ratio	No. D.P.[a]	Confidence limits (95%)	Odds ratio	No. D.P.[a]	Confidence limits (95%)
Domestic and owner occupational exposures						
Home remodeling or construction	0.3	8	0.1–1.2	0.4	10	0.1–1.6
Addition of home insulation	0.5	6	0.1–2.6	0.8	7	0.2–3.3
Home in vicinity of asbestos-related industry	2.0	6	0.4–10.6	0.8	7	0.2–3.3
Occupation or hobby asbestos related	8.0	9	1.4–10.6	2.3	10	0.6–8.7
Urban (vs rural) residence of dog						
First residence	[c]	5	—	1.5	9	0.4–5.3
Longest residence	4.0	5	0.5–30.3	1.2	11	0.4–3.9
Residence at diagnosis	2.0	6	0.5–10.6	1.0	10	—
Management of dog						
Source: stray vs all other	2.0	3	0.2–21.0	[b]	4	—
Time outside: ≥50% vs <50%	5.0	6	0.7–34.5	2.5	7	0.5–12.2
Supervision: allowed to roam vs confined	2.0	9	0.5–7.8	3.0	8	0.7–13.8
Pesticides used on dog						
Flea powder	5.0	6	0.7–34.5	1.7	8	0.4–6.9
Flea spray	3.0	4	0.4–25.8	1.5	10	0.4–5.3
Flea dip	2.5	7	0.5–12.2	1.5	10	0.4–5.3
Flea collar	1.3	7	0.3–5.9	1.0	6	—
Any pesticide	11.0	5	1.5–82.1	5.0	6	0.7–35.5

[a] Number of Discordant Pairs.
[b] Not able to calculate; The cases were all strays while the controls were of known origin.
[c] Not able to calculate; The cases all had an urban residence while the controls had a rural residence.

are listed in Table 2. For example, if the dog was obtained as a stray, exposure to asbestos could have occurred prior to adoption. None of these management factors was significantly associated with mesothelioma when analyzing the control groups separately or combined as matched triplets.

The medical histories did not reveal an association between mesothelioma and other illnesses requiring hospitalization in the study dogs or in other household dogs. The number of other dogs in the household was similarly unrelated to development of mesothelioma. No asbestos-related tumors were identified among household members of the study dogs.

Information on the use of pesticides and insect repellents was obtained because talc may be contaminated with asbestos and other mineral fibers (14). The relative risk for all forms of pesticides was elevated and was significant when any pesticide use was considered in comparison to noncancer controls. (OR = 11.0, $CL_{95\%}$ 1.5–82.1). The risk associated with any pesticide use when the control groups were combined was also significant (OR = 7.6 $CL_{95\%}$ 1.2–49.0). Preliminary microscopic observations of seven commercially available pet flea powders and

sprays revealed large amounts of quartz, silicates, and silica, and small amounts of antigonite, a fiber closely related to chrysotile asbestos. While asbestos fibers were not specifically identified, exposure of humans to other mineral fibers has been associated with pulmonary disease (e.g., silicosis).

Results of the lung tissue fiber analysis are presented in Table 3. The three dogs with mesothelioma had the highest levels of chrysotile fibers. The amiphibole consisted of tremolite and actinolite, except in the case of control dog 1, where it was commercial amphibole in the form of amosite and crocidolite. The tremolite and actinolite were probably contaminants of the chrysotile. The probable source of asbestos exposure for the three mesothelioma patients (Numbers 12, 14, and 18) in whom asbestos content was determined is shown in Table 1.

DISCUSSION

As in epidemiological studies of humans with mesothelioma, we were able to identify possible sources of asbestos exposure for 12 of 16 (75%) dogs. These included a household member with an asbestos-related occupation or hobby for nine dogs, home remodeling or addition of home insulation for five dogs, residential proximity to an industrial source of asbestos for five dogs, and use of flea powder for five dogs. The asbestos levels in lung tissue of dogs with mesothelioma were higher than levels found in control dogs. Squamous cell carcinoma of the lung in humans has been associated with asbestos exposure (15). The dog with squamous cell carcinoma of the lung had asbestos fiber levels similar to levels in dogs with mesothelioma, and these were similar to levels reported in lung tissue of humans with mesothelioma who had had occupational exposure to asbestos (16).

TABLE 3
ASBESTOS FIBER CONTENT IN LUNG TISSUE OF DOGS

Patient	Category	Age at Diagnosis (Years)	Fiber type (No./g dry wt.)	
			Chrysotile	Amphibole
	Mesothelioma			
12		10	3,100,000	0
14		6	7,200,000	3,300,000
18		6	22,000,000	760,000
	Lung Cancer			
A	Squamous cell carcinoma	12	8,200,000	4,800,000
B	Bronchial–alveolar carcinoma	13	280,000	280,000
C	Bronchial–alveolar carcinoma	8	69,000	0
	Controls[a]			
D		5	325,000	81,000
E		9	700,000	0
F		6	300,000	200,000
G		6	2,900,000	720,000
H		8	1,100,000	0
I		8	0	340,000

[a] Non-respiratory disease and noncancer.

Significant associations with mesothelioma in pet dogs were found with an asbestos-related occupation or hobby of a household member and with pesticide use. The asbestos-related occupations and hobbies identified may indicate previously unrecognized sources of asbestos exposure for household members. These individuals may be at increased risk of subsequently developing asbestos-related diseases. Because of the short latent period for tumor development in dogs, their mesothelioma would often precede human disease by many years. Therefore, dogs serve as useful sentinels for human exposure to asbestos. Development of an animal mesothelioma registry would provide a mechanism for identifying those persons at high-risk of asbestos-related diseases. Efforts could be made to identify the source of asbestos for these individuals and to provide information about the health risks. These individuals could be screened for early signs of asbestos-related disease and then examined at regular intervals.

Contaminants in flea repellents may represent a previously unrecognized source of asbestos or they may be another risk factor for mesothelioma. Analysis by polarized light microscopy of a variety of flea powders and sprays revealed fibers of talc, quartz, and silica, and trace amounts of antigonite, a silicate similar to asbestos that is often found in association with chrysotile asbestos. These fibers or asbestos contaminants may present a health risk for dogs as well as humans. These results are consistent with the recent report of an association of ovarian cancer and use of cosmetic talc in women. (17) Further investigation should be made of the human cancer risk associated with exposure to flea repellents since they could explain some of the non-occupationally related cases of human mesothelioma. This could be examined by testing for an association of dog ownership and human mesothelioma. Also, when additional dogs with mesothelioma are identified, it will be possible to evaluate interactive effects of pesticide use and occupational asbestos exposure.

An urban residence was associated with an increased risk of canine mesothelioma. Although this association was not statistically significant, the greatest risk was seen with first residence and the lowest risk with residence at diagnosis. This suggests that early exposures may be important in the initiation of mesothelioma. The association with urban residences was consistently higher when mesothelioma cases were compared with noncancer controls as opposed to cancer controls. This trend was also seen for 11 of the 14 factors analyzed. One explanation is that many chemicals in the urban environment are also associated with an increased risk of tumors other than mesothelioma in the dog. This is also consistent with the finding that the amount of time spent outdoors, the amount of time spent outdoors unsupervised, and origin as a stray were all associated with increased risks of mesothelioma although they were not statistically significant. Dogs may have had exposure to asbestos of which their owner was unaware.

Using a method to equate dog to human years (18) the age of dogs with mesothelioma was found to be similar to human mesothelioma patients; the mean age of the dogs was 48 years and the range was equivalent to 32 to 64 years. Thus, as in humans, the latent period for canine mesothelioma is long in proportion to the dog's lifespan.

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We cannot explain why male dogs were at such a high risk for mesothelioma. Mesothelioma usually occurs in males in humans and this is consistent with occupational patterns of asbestos exposure. Further studies are needed to determine if the predominance of male dogs is related to genetic or hormonal factors, or to different exposure patterns than female dogs.

There appeared to be a breed related risk for mesothelioma. The Bouvier des Flandres may be a potentially valuable model for experimental studies of mesothelioma. This breed susceptibility, however, must be interpreted with caution until the findings are replicated elsewhere. Since there are over 125 recognized dog breeds, a chance association with any given breed is not unlikely.

Pet animals with spontaneous tumors provide a valuable resource for epidemiological studies of environmental and dietary risk factors for cancer. They have been used previously to evaluate risk factors for breast cancer (19, 20) and osteosarcoma (21, 22) that are difficult to study in humans. Provided that only histologically verified tumors are included and accepted epidemiological techniques are used, pet animals may provide insight into the role of environmental and dietary factors in human cancers.

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