REPORTS

Case-Control Study of Canine Malignant Lymphoma: Positive Association With Dog Owner's Use of 2,4-Dichlorophenoxyacetic Acid Herbicides

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A hospital-based case-control study of companion dogs examined the risk of developing canine malignant lymphoma associated with the use of chemicals in and about the home. Information from a self-administered owner questionnaire and/or a telephone interview of about 491 cases, 466 nontumor controls, and 479 tumor controls indicated that owners in households with dogs that developed malignant lymphoma applied 2,4-dichlorophenoxyacetic acid (2,4-D) herbicides to their lawn and/or employed commercial lawn care companies to treat their yard significantly more frequently than control owners (odds ratio = 1.3). In addition, the risk of canine malignant lymphoma rose to a twofold excess with four or more yearly owner applications of 2,4-D. The findings in this study are consistent with occupational studies in humans, which have reported modest associations between agricultural exposure to 2,4-D and increased risk of non-Hodgkin's lymphoma, the histology and epidemiology of which are similar to those of canine malignant lymphoma. The present study suggests that human health implications of 2,4-D exposure in the home environment should receive further investigation.
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Non-Hodgkin's lymphoma has had the second fastest increase in cancer incidence rates of all human cancers in the United States over the last 15 years (*1*). The etiology of non-Hodgkin's lymphoma is unclear, although there are several well-established risk factors. Known risk factors include age, male gender (*2*), congenital immunodeficiency states, infection with the human immunodeficiency virus (*3*), other immune-altering conditions [e.g., transplant recipients (*4*)], chemotherapy for Hodgkin's disease (*5*), and being a member of a lymphoma-prone family (*6*).

Evidence continues to accumulate implicating phenoxyacetic acid herbicides, in particular 2,4-dichlorophenoxyacetic acid (2,4-D), with risk of non-Hodgkin's lymphoma in farmers (*7*). A population-based case-control study of non-Hodgkin's lymphoma in Kansas farmers reported a 2.2-fold excess risk for those who frequently mixed or applied herbicides (specifically 2,4-D) that rose to over sixfold among frequent users (*8*). A mortality study of 70 000 Saskatchewan farmers, age 35 years and older, showed a significant positive association between non-Hodgkin's lymphoma and the number of acres sprayed with herbicides, predominantly (i.e., 75%-90% by weight) 2,4-D (*9*). A recent case-control study of non-Hodgkin's lymphoma in Nebraska found a significant threefold excess in farmers who mixed or applied 2,4-D more than 20 days per year (*10*). With the extensive use of phenoxyacetic acid herbicides in the United States since the mid-1960s (*11*) and the frequent use of 2,4-D on public park lands, golf courses, and private lawns (*12*), particularly by commercial lawn care companies (*13*), the potential exposure opportunities to people and farm and companion animals continue to be substantial.

Malignant lymphoma, the canine equivalent of non-Hodgkin's lymphoma, is the most frequently diagnosed hematolymphopoietic cancer in dogs (*14*). Approximately one in seven companion dogs brought to medical attention at U.S. university veterinary teaching facilities and diagnosed with any type of malignancy will have malignant lymphoma. Presently, seven new cases of malignant lymphoma are diagnosed per 1000 canine patient years-at-risk at U.S. university veterinary medical teaching hospitals (Hayes HM: unpublished results).

Although canine malignant lymphoma has been extensively studied, its etiology is obscure. The disease occurs at all ages, but it is more frequently diagnosed as the dog grows older (*15*); as in humans, there is a male excess. Several breeds have been identified at increased risk (*14*), including the boxer (*16*), bull mastiff (*17*), and Scottish terrier (*18*). Unlike malignant lymphoma in other laboratory and domestic animal species, no canine retrovirus has been associated unequivocally with the disease, although virus-like

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particles in affected tissue have been reported (*19-21*). Naturally occurring canine malignant lymphomas are similar to human non-Hodgkin's lymphoma in histologic type, biological behavior, and cell responses to the same chemotherapeutic agents (*22-24*). These malignancies have occurred in companion pets and their owners in the same household (*25,26*).

The pet dog is normally fastidious about its grooming habits. It is common for a dog to clean itself by licking its paws, thereby ingesting any substances it has walked in or that have been applied to its body accidentally or intentionally as therapy or prevention. The companion dog is not generally subjected to direct occupational exposures experienced by its owners, although it may have contact with particulate matter or residues brought into the home on its owner's clothing and shoes (*27*). Thus, environmentally related cancer in the pet dog may be considered primarily the result of local exposures in and around the owner's home.

To investigate canine malignant lymphoma and its relationship to chemical exposures, particularly the herbicide 2,4-D, we conducted a case-control study of dogs diagnosed with malignant lymphoma at three university veterinary medical teaching hospitals. We used a questionnaire to obtain information from dog owners on demographics, lifestyle, and household and lawn chemical exposure.

Materials and Methods

Subjects

Dogs with histopathologically confirmed malignant lymphoma, newly diagnosed from January 1984 through February 1988, were identified using computerized medical record abstracts from three veterinary medical teaching hospitals that participate in the Veterinary Medical Data Program (*28*). The collaborating veterinary medical teaching hospitals were the University of Minnesota at St. Paul, Purdue University at West Lafayette, Ind., and Colorado State University at Ft. Collins.

Two comparison groups of hospital-based control animals, matched by age group, but not by sex, were chosen from dogs seen at the same veterinary medical teaching hospital in the same year as the identified case, with one-to-one matching for each control group. Age was reported in range values on the Veterinary Medical Data Program medical record abstract (i.e., 1, 2-3, 4-6, 7-9, 10-14, and 15+ years). The first control group was selected from all other tumor cases diagnosed at the veterinary medical teaching hospital, excluding transitional cell carcinomas of the lower urinary tract because of a potential etiology related to chemical exposures. Twenty percent of these tumor controls had bone cancer, 19% skin tumors (excluding melanoma), 13% oral and/or nasal tumors, 7% mast cell tumors, and 41% other neoplasms. The second control group was selected from dogs seen for any other diagnostic reason, excluding those with conditions possibly related to chemical exposures (e.g., nonspecific dermatitis, neuropathies). Twenty-six percent had degenerative diseases, 18% broken bones or soft tissue trauma, 14% diagnostic examinations or elective surgery, 14% infections, and 28% other conditions.

Written Questionnaire/Telephone Interview

Owners of selected case and control animals were identified by the participating veterinary medical teaching hospital. A standardized questionnaire was sent to the last known address of each owner. The cover letter to the questionnaire noted that the dog in question had been seen at the veterinary medical teaching hospital on a particular date and was selected to be part of a study being conducted by the National Institutes of Health. No mention was made of the animal's diagnosis at that time or of the disease of interest in the study. The questionnaire requested information about demographic characteristics of all people living in their home, basic information about the pet's life history, household use of chemicals (in and about the home) including those directly applied to the pet, and personal use of and/or the employment of commercial companies applying chemicals of whatever kind on the lawn and garden. In addition, owners were asked about opportunities for exposure of their pets to lawn and garden chemicals, including frequency and seasonality of access to the yard. The questionnaire did not provide a list of chemicals which the owner could consult in responding to the various questions regarding home, lawn, and gardening chemicals.

After 2 weeks, owners who did not respond were sent another letter requesting participation. U.S. Postal Service forwarding addresses were used when available. If there was no subsequent response, an attempt was made to conduct a telephone interview using the standardized questionnaire. Trained interviewers were not told the name of the disease or exposures of interest or which households had case subjects.

Data Analysis

The relative risk, as estimated by the maximum likelihood estimate of the odds ratio (OR) (*29*), was used as the measure of association between malignant lymphoma and the variables of interest. Summary ORs and 95% confidence intervals (CIs) were calculated, stratifying to control for potential confounding factors as judged by a change in the effect estimate. The Haldane-Smith-Mantel procedure was used to test for trends in proportions (*30*). Logistic regressions evaluated the effects of several factors simultaneously (*31*).

Results

Malignant lymphoma was diagnosed in 588 canine patients that met eligibility criteria. Questionnaires were returned or telephone interviews were completed by 491 (84%) households with dogs having malignant lymphoma (case households). Of the 583 nontumor control households, 466 (80%) responded; of the 586 tumor control households, 479 (82%) responded. Forty-five percent of the total completed responses came from telephone interviews. Most nonresponses were due to the inability to contact the owner. Only four owners (owners of one case animal and three tumor controls) who were contacted refused to participate.

There were no discernible differences between study groups in demographic variables, although median income was slightly higher for case households versus control households, as was the number of household members supported by that income (Table 1). Slightly fewer case than

Table 1. Demographics: Lifestyle and environmental characteristics of reporting households expressed as a percentage of the eligible study group

Characteristic	Malignant lymphoma (n = 491)	Nontumor control (n = 466)	Tumor control (n = 479)
Median income*	$43 500	$40 500	$39 500
Mean household members supported by income†	2.77	2.67	2.68
Mean No. of years dog lived with owner	9.32	9.05	9.75
Home location			
In rural area	29.5	32.8	32.6
Within 2 miles of factory of plant that emitted gases, fumes, or particles of some kind	12.4	13.5	16.9
Pet's diet			
Commercial dog food	97.6	97.0	97.7
Drinking water from community source	69.2	72.5	70.4
Potential for in-home chemical exposures			
Dog allowed inside home	95.7	95.3	93.3
Home had carpet/area rugs	93.9	93.3	92.5
Carpets or rugs ever commercially cleaned	12.1	12.6	11.1
Drapes present in home	88.8	86.7	87.5
Drapes ever commercially cleaned	45.9	46.3	48.0
Cigarettes smoked in home	47.5	46.4	48.2
Insecticides used in home	37.9	38.0	42.2
Ever applied flea and tick preparations	6.3	7.1	7.6
Potential for exposures outside of home			
Owner had yard used by dog	95.7	94.9	94.8
Chemicals ever used on yard during dog's lifetime	67.2	67.6	64.9
Dog ever in American Kennel Club show or hunting trial	10.6	11.6	10.6
Dog ever commercially groomed	2.2	3.9	2.5

*Percent not answering question was 8.1% of case households, 8.4% of nontumor control households, and 9.8% of tumor control households.

†Percent not answering question was 3.5% of case households, 4.3% of nontumor control households, and 5.2% of tumor control households.

control households were located in rural areas. However, case households were less frequently located within 2 miles of industrial plants or facilities reported as emitting into the atmosphere.

Dogs studied in this investigation usually ate commercial dog food, and most were provided drinking water from a community source. They were usually allowed inside their owner's home, and most of these homes had carpet and/or area rugs and window drapes. Most dogs were allowed access to their owner's yard. Lifestyle experiences and exposures inside and outside the home were quite similar between the two control groups. Because of a lack of discernible differences between tumor and nontumor control households, subsequent analyses utilized pooled controls (Table 1). Using mixed breed dogs as the standard (OR = 1), canine breeds previously identified as having a low risk of malignant lymphoma (*14*) were found to be underrepresented in the case series (OR = 0.3); breeds expected to be at high risk had a twofold excess representation (Table 2). Approximately two thirds of all households surveyed had used lawn chemicals of some type on their yards (OR = 1.1). When all dogs who did not have access to their owner's yard were classified as unexposed, the OR for owner application of 2,4-D and/or the employment of commercial lawn care service was 1.3 (95% CI = 1.04-1.67). No difference in OR was detected for owner application of 2,4-D only (OR = 1.3) and sole use of commercial lawn treatments (OR = 1.3); however, the OR for owner application plus the employment of commercial lawn service was 1.9 (95% CI = 0.88-4.14) (Table 3). Adjustment for age in these analyses did not change the ORs. Liquid 2,4-D was sprayed by fewer owners of case animals than owners of control animals applying 2,4-D, a difference that was not significant.

A positive trend ($P<.02$) was evident for the yearly number of owner applications of 2,4-D. This trend was significant ($P<.05$) for both long-term use (≥5 years' duration prior to diagnosis) and short-term use (<5 years' duration). No significant association was observed between malignant lymphoma risk and duration of owner application of 2,4-D (OR = 1.5 for ≥5 years of use; OR = 1.3 for <5 years of use). We could not distinguish possible latency effects from duration effects, as the questionnaire did not ask for the date on which the owner began 2,4-D use or the employment of professional lawn care services. No discernible trend was observed for yearly number of commercial lawn treatments (Table 3).

Multivariate analyses considered the ever-never variables of flea and tick control exposures (i.e., collars, powder, spray, dip), in-home use of insecticides, cigarette smoking, the presence of carpet and window drapes (and whether they were commercially cleaned), use of yard insecticides and/or fertilizers, dog breed risk group and sex, and application of 2,4-D by owner and/or commercial lawn care service. Separate analyses considered 1) number of applications per year of flea- and tick-control products, 2) number of applications of household insecticides per year, number of cigarette packs smoked per year by household members, and the number of times carpets and drapes were commercially cleaned per year for dogs allowed inside the owner's home, and 3) number of applications per year of yard insecticides and fertilizers for those yards available to the dog. The only factors related to case households in the multivariate analyses were breed risk group and owner application of 2,4-D and/or use of a commercial lawn care service.

When the OR for owner application of 2,4-D and/or commercial lawn treatments was evaluated for each breed risk group, an inverse relationship with breed risk

Table 2. ORs of canine malignant lymphoma by host

Characteristic	No. of cases	No. of controls	OR	95% CI
Breed*				
Mixed breed	128	243	1.0	
Low-risk breeds combined	16	94	0.3	0.17-0.59
Average-risk breeds combined	228	496	0.9	0.66-1.14
High-risk breeds combined	119	112	2.0	1.40-2.83
Sex*				
Female	237	508	1.0	
Male	254	437	1.2	0.97-1.54

*Adjusted for sex in calculating breed risk group ORs and breed risk group in calculating the effect of sex.

Table 3. ORs of canine malignant lymphoma by exposure

Characteristic	No. of cases	No. of controls	OR	95% CI
Owner application of any yard chemical and/or commercial lawn treatment*				
No	161	319	1.0	
Yes	330	626	1.1	0.84-1.37
Owner application of 2,4-D and/or commercial lawn treatment*				
None or dog never allowed in yard	300	641	1.0	
Yes	191	304	1.3	1.04-1.67
Commercial lawn treatment only*	115	189	1.3	0.96-1.70
Owner application of 2,4-D only*	60	99	1.3	0.90-1.90
Owner application of 2,4-D and commercial lawn treatments*	16	16	1.9	0.88-4.14
No. of commercial lawn chemical treatments/y†				
0	300	641	1.0	
1	16	25	1.4	0.70-2.84
2	20	25	1.5	0.75-2.86
3	19	33	1.1	0.60-2.14
≥4	76	122	1.3	0.95-1.87
No. of owner applications of 2,4-D/y†				
0 or dog never allowed in yard	300	641	1.0	
1	20	34	1.3	0.72-2.50
2	28	47	1.3	0.74-2.13
3	11	17	1.3	0.57-3.13
≥4	17	17	2.0	0.92-4.15
			Trend test	$P<.02$

*Adjusted for sex and breed risk group.
†Adjusted for sex and breed risk group; includes 16 cases and 16 control households where the owner applied 2,4-D and also had commercial lawn treatments.

level was found, the OR being highest for low-risk breeds (Table 4). Male dogs, known to be at elevated risk for malignant lymphoma, exhibited the same OR (1.3) as females for owner application of 2,4-D and/or commercial lawn treatment (Table 4).

To test recall, owners were asked if their dog had died; if so, they were asked if it had cancer and the cancer type was requested. Among the owners of case animals who reported never using 2,4-D and/or commercial lawn care services or never allowing their pet access to their yard, slightly more knew that their pet died of malignant lymphoma compared with the case households that applied 2,4-D or employed commercial lawn services (Table 5).

Discussion

We found a modest association (OR = 1.3; 95% CI = 1.04-1.67) between malignant lymphoma in companion dogs and their owners' applying 2,4-D on their lawn and/or using commercial lawn care services, with the risk rising with increasing number of owner applications per year. These findings are consistent with studies suggesting that agricultural 2,4-D use increases the risk of non-Hodgkin's lymphoma among farmers (*8-10*). Also consistent with human studies was the lack of a significant association with duration of 2,4-D application by the owner.

Findings of case-control interview studies may be biased because of differential recall of cases and referents. In the last several years, results from several studies of this design have suggested links between use of phenoxyacetic acid herbicides and development of non-Hodgkin's lymphoma in humans. Some have suggested problems in recalling may explain these associations (*13*). In the current study, recall bias could have occurred if owners of case animals were more likely to remember using such herbicides on their yards and, therefore, exposing their pets. The lack of any association, among cases, of owner's knowledge of their pet's type of cancer at death and opportunity for exposure to 2,4-D strongly argues against such a bias in this study (Table 5).

Any recall bias related to socioeconomic status probably did not affect this study because case and control households were strikingly similar in median income, number of household members supported by such income, use of commercial dog food, home lifestyle (service by municipal water supply, presence of carpet/area rugs and drapes, access inside the home by the dog), or the presence of yards. Bias may also arise from an unwillingness of certain selected subjects to participate. The percentages of responses from case and control household groups, however, were nearly the same. The major limiting factor was the ability to locate owners, not an unwillingness to participate. Only four of 1440 successfully contacted owners refused to participate.

Recall may be hampered by the lapsed time between the time period of interest and the questionnaire/interview date. The response data analyzed in this study were acquired 10-58 months after the selected animals were seen at the veterinary medical teaching hospital; however, control dogs were matched to case dogs by age and year of medical attention. Therefore, the lapsed time between the period of interest (the years the dog lived with its owner until the date of university treat-

Table 4. ORs for exposure to owner-applied 2,4-D and/or commercial lawn treatments for malignant lymphoma by canine breed risk groups and by sex

Characteristic	No. of cases		No. of controls		OR*	95% CI
	Exposed	Unexposed	Exposed	Unexposed		
Risk group						
Mixed breed	45	83	80	163	1.1	0.69-1.78
Low-risk breeds	8	8	29	65	2.0	0.60-6.89
Average-risk breeds	91	137	155	341	1.4	1.03-2.03
High-risk breeds	47	72	40	72	1.2	0.67-2.10
Sex						
Female	88	149	152	356	1.3	0.94-1.87
Male	103	151	152	285	1.3	0.93-1.84

*Adjusted for sex in calculating breed risk group ORs and breed risk group in calculating the effect of sex.

Table 5. Owner's recall of pet's malignancy at death by yard chemical use among malignant lymphoma case households

Yard chemical use	No.	Owner's knowledge of malignant lymphoma, %
Owner applied 2,4-D only	60	61.3
Commercial lawn treatment only	115	60.8
Owner applied 2,4-D and also used commercial lawn care treatments	16	58.8
Owner neither applied 2,4-D nor used a commercial lawn care company or the pet was not allowed in the yard	300	64.8

ment) and the date of the questionnaire or interview was approximately the same for owners of case and control dogs.

It is possible that unmeasured confounders could explain the risk, but we collected data on the most likely concomitant exposures in the household environment. Household insecticides, contact insecticides for flea and tick control, and outdoor insecticides played no discernible role in the association between 2,4-D exposure and development of malignant lymphoma. We controlled for sex and breed association in all analyses; these two factors play a role in the occurrence of the disease, but they did not strongly affect the risk from 2,4-D exposure. Although viruses have been associated with lymphoma development in many animal species (*32*), they have not been linked to lymphoma development in the dog. While viral infection of some type may be an important factor, it is unlikely to be responsible for the significant association between canine malignant lymphoma development and owner use of 2,4-D and/or commercial lawn care services.

The type of 2,4-D applied by the owner, liquid spray or granular, had little influence on risk. The consistency between the ORs for male and female case animals with 2,4-D exposure also argues against inhalation of herbicide spray as a likely route of exposure, because the male dog's sniff-scent marking tendencies might place males at greater risk than females (*33*). Occupational studies of herbicide exposures by agricultural workers generally agree that inhalation is a minor source of human exposure (*34*).

A major weakness of the current study is the lack of precise exposure data for herbicides. Frequency of application was the primary measure of exposure used in this study. The lack of a clear pattern of association with total number of yearly commercial lawn treatments contrasts with the consistent application-response relationship ($P<.02$ for trend) exhibited for owner application of 2,4-D (Table 3). The yearly number of applications of 2,4-D by the owner is more likely to reflect the actual 2,4-D exposure opportunity for pet dogs than the number of lawn treatments by commercial lawn care companies because some commercial treatments during each year may contain only fertilizer and/or insecticides and, thus, not lead to herbicide exposure.

In a laboratory carcinogenicity study, 12 male and 12 female beagles were exposed to 2,4-D in their diet for 2 years (*35*). No malignant tumors were reported in any of the exposed dogs or in the three male or three female control dogs. A related 2-year feeding study of 2,4-D in Osborne-Mendel rats (*35*) resulted in an increased incidence of lymphosarcomas in exposed male rats (10 of 125 exposed male rats developed lymphosarcomas compared with 0 of 25 control rats; Fisher's exact test yields $P = .15$) but no evidence of increased tumors in female rats (1 of 125 exposed female rats compared with 0 of 25 control rats).

Studies involving 18 male and 18 female mice from each of two strains gave no evidence of carcinogenicity for 2,4-D fed for 18 months (*36*). The isopropyl, butyl, and isooctyl esters of 2,4-D were also tested, and no significant increases in tumor incidence were observed (*36*). In companion studies, 2,4-D and its esters were administered by subcutaneous injection in 18-month carcinogenicity experiments. Although the results of the injection studies were not given in the initial report (*36*), a significant increase in reticulum cell sarcomas was reported for the isooctyl ester of 2,4-D in one female mouse strain (*37*). No reticulum cell sarcomas were observed in the 18 male mice of the same strain similarly exposed. Thus, although lymphoreticular tumors have been found in excess in two rodent studies, laboratory animal experiments provide only weak support for a role of 2,4-D in lymphoreticular carcinogenicity.

The current investigation began with an a priori hypothesis that exposure to 2,4-D might be associated with development of malignant lymphoma in the pet dog. Our findings support this proposition, with a modest statistically significant OR of 1.3 for owner application of 2,4-D and/or commercial lawn treatments. Further support derives from the higher risk observed for pets of owners who applied their own 2,4-D in addition to exposure to commercial applications (OR = 1.9; 95% CI = 0.88-4.14) and the increase in risk to a twofold excess with four or more owner applications per year. In view of a suggested link between non-Hodgkin's lymphoma in humans and farm exposures to 2,4-D, and because malignant lymphoma

in the dog is considered the equivalent of non-Hodgkin's lymphoma in humans, our finding of an association between 2,4-D exposure and development of malignant lymphoma in companion dogs suggests that the human health implications of 2,4-D exposure in the home environment warrant further investigation.

References

(1) National Center for Health Statistics: Cancer Statistics Review 1973-87 DHHS Publ No. (NIH)90-2789. Bethesda, Md: National Center for Health Statistics, 1990

(2) Surveillance, Epidemiology, and End Results: Incidence and Mortality Data, 1973-77. Natl Cancer Inst Monogr 57:1–1082, 1981

(3) Freter CE: Acquired immunodeficiency syndrome-associated lymphomas. *In* The Lymphomas: Current Concepts in Patho-genesis and Management. J Natl Cancer Inst Monogr 10:45–54, 1990

(4) Hoover R, Fraumeni JF Jr: Risk of cancer in renal-transplant recipients. Lancet 2:55–57, 1973

(5) Tucker MA, Coleman CN, Cox RS, et al: Risk of second cancers after treatment for Hodgkin's disease. N Engl J Med 318:76–81, 1988

(6) Greene MH: Non-Hodgkin's lymphoma and mycosis fungoides. *In* Cancer Epidemiology and Prevention (Schottenfeld D, Fraumeni JF Jr, eds). Philadelphia: Saunders 1982, pp 754–778

(7) Blair A: Herbicides and non-Hodgkin's lymphoma: New evidence from a study of Saskatchewan farmers. J Natl Cancer Inst 82:544–545, 1990

(8) Hoar SK, Blair A, Holmes FF, et al: Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. JAMA 256:1141–1147, 1986

(9) Wigle DT, Semenciw RM, Wilkins K, et al: Mortality study of Canadian male farm operators: Non-Hodgkin's lymphoma mortality and agricultural practices in Saskatchewan. J Natl Cancer Inst 82:575–582, 1990

(10) Zahm SH, Weisenburger DD, Babbitt PA, et al: A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. Epidemiology 1:349–356, 1990

(11) Eichers TR, Andrilenas PA, Anderson TW: Farmers' Use of Pesticides in 1976, Agricultural Economic Report 418. Economics, Statistics, and Cooperatives Service. Washington, DC: USDA, 1978

(12) International Agency for Research on Cancer: Some fumigants, the herbicides 2,4-D and 2,4,5-T, chlorinated dibenzodioxins and miscellaneous industrial chemicals. IARC Monogr Eval Carcinog Risk Chem Man 15:1–354, 1977

(13) Council for Agricultural Science and Technology: Comments from CAST. Perspectives on the safety of 2,4-D. Ames, Iowa: CAST, December 1987

(14) Priester WA, McKay FW: The occurrence of tumors in domestic animals. Natl Cancer Inst Monogr 54:1–210, 1980

(15) Schneider R: Comparison of age- and sex-specific incidence rate patterns of the leukemia complex in the cat and the dog. JNCI 70:971–977, 1983

(16) Priester WA: Canine lymphoma: Relative risk in the boxer breed. JNCI 39:833–845, 1967

(17) Onions DE: A prospective survey of familial canine lymphosarcoma. J Natl Cancer Inst 72:909–912, 1984

(18) Hayes HM: Hospital prevalence of cancer in the Scottish terrier. *In* Scottish Terrier Club of America Handbook (Cooke CM, Hach S, eds), 3rd ed. Lynchburg, Va: Scottish Terrier Club of America, 1986, pp 158–167

(19) Chapman AL, Bopp WJ, Brightwell AS, et al: Preliminary report on virus-like particles in canine leukemia and derived cell cultures. Cancer Res 27:18–25, 1967

(20) Cohen H, Chapman AL, Ebert JW, et al: Cellular transmission of canine lymphoma and leukemia in beagles. J Natl Cancer Inst 45:1013–1023, 1970

(21) Rudolph R: Virus-like structures in canine lymphatic leukosis tumor cells. Berl Munch Tierarztl Wochenschr 84:68–70, 1971

(22) MacEwen EG, Brown NO, Patnaik AK, et al: Cyclic combination chemotherapy of canine lymphosarcoma. J Am Vet Med Assoc 178:1178–1181, 1981

(23) Weller RE, Theilen GH, Madewell BR: Chemotherapeutic responses in dogs with lymphosarcoma and hypercalcemia. J Am Vet Med Assoc 181:891–893, 1982

(24) MacEwen EG: Spontaneous tumors in dogs and cats: Models for the study of cancer biology and treatment. Cancer Metastasis Rev 9:125–136, 1990

(25) Squire RA, Melby EC: Naturally occurring canine and feline lymphomas as biomedical models. *In* Animal Models for Biomedical Research. National Academy of Sciences Report. Publ No. 1594. Washington, DC: NAS, 1968

(26) Holmberg CA, Wilson FD: Lymphoid neoplasia in the canine. *In* The Canine as a Biomedical Research Model. Immunological, Hematological and Oncological Aspects (Shifrine M, Wilson FD, eds). Washington, DC: Technical Information Center, US Department of Energy, 1980, pp 296–313

(27) Glickman LT, Domanski LM, Maguire TG, et al: Mesothelioma in pet dogs associated with exposure of their owners to asbestos. Environ Res 32:305–313, 1983

(28) Hayes HM, Wilson GP, Moraff H: The veterinary medical data program (VMDP): Past, present, and future. *In* Proceedings of International Symposium on Animal Health and Disease Data Banks, December 4-6, 1978. APHIS Misc Publ No. 1381. Washington, DC: USDA, 1979, pp 127–132

(29) Gart JJ: Point and interval estimation of the common odds ratio in the combination of 2×2 tables with fixed marginals. Biometrika 57:471–475, 1970

(30) Thomas DG, Gart JJ: Stratified trend and homogeneity analyses of proportions and life table data. Comput Biomed Res 16:116–126, 1983

(31) Engelman L: Stepwise logistic regression. *In* BMDP Statistical Software (Dixon WJ, ed). Berkeley: Univ Calif Press, 1983, pp 330–344

(32) Theilen GH, Madewell BR: Leukemia-sarcoma disease complex. *In* Veterinary Cancer Medicine (Theilen GH, Madewell BR, eds). Philadelphia: Lea & Febiger, 1979, pp 204–208

(33) Sprague RH, Anisko JJ: Elimination patterns in the laboratory beagle. Behaviour 47:257–267, 1973

(34) Yeary RA: Urinary excretion of 2,4-D in commercial lawn specialists. Appl Ind Hyg 1:119–121, 1986

(35) Hansen WH, Quaife ML, Habermann RT, et al: Chronic toxicity of 2,4-dichlorophenoxyacetic acid in rats and dogs. Toxicol Appl Pharmacol 20:122–129, 1971

(36) Innes JRM, Ulland BM, Valerio MG, et al: Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note. J Natl Cancer Inst 42:1101–1114, 1969

(37) Reuber MD: Carcinogenicity and toxicity of 2,4-dichlorophenoxyacetic acid. Sci Total Environ 31:203–218, 1983

Low-Grade, Latent Prostate Cancer Volume: Predictor of Clinical Cancer Incidence?

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We hypothesize that each cell in low-grade (Gleason grade 1-3) prostate cancer tissue is at risk of transformation into a cell which produces a high-grade (Gleason grade 4-5) clinical cancer after a short period of growth. As a consequence, the volume of low-grade, latent cancer tissue in the prostate glands of men at any age determines their incidence rate for high-grade, clinical cancer a few years later. Autopsy and incidence data for both white men and black men support this conclusion, with a tumor growth period of about 7 years. The transformation rate is similar for black men

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