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Epidemiologic Studies of Risk Factors for Cancer in Pet Dogs

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INTRODUCTION

In 1996, an estimated 52.9 million dogs were living in 31.6 percent of all households in the United States (1). Several epidemiologic studies have been undertaken to identify risk factors for cancer in pet dogs. This presentation reviews the literature on canine cancer epidemiology with a view towards exploring how these studies inform us about cancer causation in dogs and in humans. It focuses on observational studies of dogs living in their usual environments, and considers experimental studies in laboratory settings only to the extent that such studies shed light on the observational studies. It begins with a discussion of some methodological issues that make epidemiologic studies of cancer in dogs somewhat different from those in humans.

METHODOLOGICAL CONSIDERATIONS

Most of the recent studies to identify risk factors for cancer in dogs have used the case-control approach. Thus, we will focus on issues that arise in case-control studies.

Cases

No population-based cancer registry for dogs currently exists. The Veterinary Medical Data Program (VMDP), begun in 1964 by the National Cancer Institute and now housed at the School of Veterinary Medicine at Purdue University, collects and stores data in an electronically retrievable form on all domestic animals seen at 24 participating veterinary hospitals in the United States and Canada (2); these data have been used for several case-control studies. Since all the VMDP data come from teaching hospitals, cases seen only by primary care veterinarians are not represented.

Eighty-five percent of dog-owning households reported taking their dog to a veterinarian in 1996, for an average of 1.8 visits per dog. The average expenditure per visit was $73.60 (1). The vast majority of pet owners do not have health insurance for their animals, and costs for diagnostic procedures and treatment are an important consideration for many pet owners. A few pet owners may not seek veterinary care at all for a dog that may have cancer, and among the dogs that are seen by a veterinarian, many are euthanized without a biopsy or definitive diagnosis. Also, dogs may be treated on the basis of a presumptive diagnosis without a biopsy being done. Thus, applying the same standards used for human epidemiologic studies to case-control studies in dogs may be inappropriate and impractical.

All of the case-control studies included in this review identified cases from the VMDP or from other selected animal hospitals. All of the recent studies required that the diagnosis of a malignant neoplasm be confirmed by biopsy, while some of the older studies did not. Some of the older studies, and one recent study (3), in fact, included both benign and malignant cases of cancer of a given site. Clearly, it would be easier to identify risk factors for cancer if cases were selected on the basis of histopathologic diagnosis rather than anatomic site of the tumor, and if cases of cancer were not combined with other lesions of a possibly different etiology.

Controls

A good working concept of a control group (4) is that the controls should be selected in an unbiased manner from those individuals who would have been included in the case series had they developed the disease under study. For case-control studies in dogs, then, selecting controls from the general population of dogs in a community does not make sense because a

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Abbreviations: PIN, prostatic intraepithelial neoplasia; VMDP, Veterinary Medical Data Program; 2,4-D, 2,4-dichlorophenoxyacetic acid.

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certain proportion of dogs in the general population would not be brought to veterinary attention and have their cancer diagnosed. Fewer still would be seen at veterinary teaching hospitals. Diagnosed cases tend to come from upper- and middle-income families who regard the dog as an important family member (5). Accordingly, in all of the case-control studies reviewed here, controls were patients with other cancers or patients seen for problems other than cancer at the referral veterinary hospitals. Perhaps dogs who are neighbors of the cases would also be appropriate controls for the study of some exposures that are not associated with specific neighborhoods.

Measurement of exposure

If questionnaires are used to determine exposures, a number of issues arise in studies of dogs that are somewhat different from most studies in humans. Of primary importance, proxy respondents (i.e., the human owners) must be used for information obtained by questionnaire, since the dogs cannot answer for themselves. Many people have owned their dogs since early puppyhood, have close relationships with them, have fed and exercised them in a routine manner for many years, and have kept them in the same environment most of the time. Under such circumstances, reports of exposures by the current owner may be quite accurate. In fact, because of the short life-span of dogs, many dogs will have spent their entire life in the same environment, thus facilitating measurement of their lifetime exposures. On the other hand, a certain proportion of dogs have had several owners, may roam freely, and little may be known about their past exposures. The non-informative data about such dogs will dilute out the meaningful data, and associations between many exposures and diseases will be more difficult to detect. We recommend including questions for owners of all case and control dogs about how well the history of the dog is known, and stratifying in the analysis according to the likely quality of information regarding exposure. If there is a relation between exposure and disease, one would expect stronger odds ratios with increasing quality of information.

In only a few instances have blood and urine samples been used to measure exposures (for instance, Perez Alenza et al. (3), Schilling et al. (6), and Reynolds et al. (7)), and only once in a case-control study concerned in part with cancer (3). However, in a small case-control study of asbestos as a risk factor for mesothelioma, asbestos particles in the lungs were measured (8). It is likely that future studies of cancer etiology in dogs will employ more examples of biomarkers of exposure.

Confounding and bias

It has been pointed out (8) that one advantage to case-control studies in dogs is that confounding by certain variables, such as personal smoking and alcohol consumption, is minimal compared with confounding by these factors in epidemiologic studies in humans. Although this is indeed an advantage, so little is known about cancer etiology in dogs that confounding by other unmeasured variables is a distinct possibility. Also, this advantage may be offset by the potential for selection bias; that is, cases and controls may be selected in such a way that the cases are more or less likely than controls to have the exposure of interest even if no association exists. Recall bias is a potential problem for people reporting for their dogs much as it is for people reporting for themselves. In addition, the quality of exposure measurement in these studies has varied a great deal. Thus, while compared with human studies, case-control studies in dogs may reduce bias in some ways, they may increase it in others. All of these possibilities must be considered in both planning and interpreting the results of epidemiologic studies in dogs.

Statistical analysis

The statistical analysis of case-control studies in humans and dogs is usually similar. In general, descriptive statistics are presented, odds ratios are used to estimate relative risks, and potential confounders are controlled by the Mantel-Haenszel procedure and logistic regression. Subgroup analyses are also important and have been put to good advantage in studies of dogs. For instance, exposure-disease associations may be seen only in certain breeds. Male and female dogs may show different associations. Examples will be presented where such observations have led to the formulation of hypotheses and to an enhanced understanding of disease pathogenesis.

Some complications in the statistical analysis can arise. Biopsies are not performed on all cases, yet for some tumors in some sites there can be a high degree of certainty that the tumor is malignant on clinical and cytologic evidence alone. In such instances, we recommend that criteria for inclusion of such cases be established in advance of data collection and that these cases be retained as a separate group in the analysis. Results can be presented with and without the inclusion of these cases. Dogs that are euthanized without a thorough workup, however, would still have to be excluded. Another issue is that 143 breeds of dog are recognized by the American Kennel Club. In many studies it would be desirable to control in the analysis on breed of dog and to consider breed as a possible

effect modifier. Unfortunately, in most studies there are almost as many breeds as study subjects, so this is not feasible. In smaller studies, breeds of dogs can be grouped according to some criterion such as size or other characteristic. In the large case-control studies, the more common breeds of dogs can be considered separately. An example of how this was done to good advantage is presented in the section on osteosarcoma (below). A related issue is that the lifespan of small dogs is generally much longer than that of large dogs, so that data often need to be adjusted not just for age, but also for body size.

FREQUENCY OF CANCER IN DOGS BY SITE

From July 1963 to June 1966, Dorn et al. (9, 10) attempted to identify all cases of neoplasms diagnosed in companion animals in Alameda and Contra Costa Counties, California, so as to provide an idea of the frequency of occurrence of neoplasms of various sites in an unselected population. Cases were identified from all 65 veterinary practices in the two counties and from 11 practices in surrounding counties that treated animals from Alameda and Contra Costa Counties. A pathologist read biopsy specimens sent to the registry. Incidence rates were calculated for Alameda County. The denominators for the incidence rates were estimated from interviews conducted in a probability sample of households in Alameda County by the Human Population Laboratory in 1965. Data on age, sex, breed, and whether the household used veterinary services were collected. Households that had not used veterinary services in the past 5 years were excluded from estimates of the denominators for the incidence rates.

The estimated annual incidence rate in dogs of 3.8 per 1,000 for cancers of all sites calculated in this study indicates that for each 1,000 dogs living in households that used veterinary services, almost four per 1,000 have cancer newly diagnosed each year. The current incidence rate is undoubtedly considerably higher, not only because some dogs with cancer do not have it diagnosed, but also because of the greater life expectancy of dogs in the 1990s compared with the 1960s. Furthermore, it is likely that the incidence of some of these cancers has changed since the 1960s, but no more recent data are available on a representative series of cases. The more recently reported case series seen at referral hospitals tend to be weighted toward cancers that are to some extent treatable (e.g., lymphoma). Thus, such series do not give a good idea of the distribution of cancers seen in the general population of dogs.

The major cancers (excluding non-melanoma skin cancers) in female and male dogs in the 1960s (9), and in humans around the same time period (11) and in a recent year (12), are shown in tables 1 and 2. Among female dogs, the most common cancers were breast, connective tissue, malignant melanoma, and lymphoma, while in male dogs the leading cancers were of connective tissue, testis, malignant melanoma, and mouth and pharynx.

Breast cancer is common in both women and female dogs. Cancers of the uterus and ovary are rare in dogs because a relatively small proportion of dogs reach the ages at highest risk with intact ovaries and uteri. Lung cancer is much less common in dogs than in humans, probably, at least in part, because dogs do not smoke cigarettes themselves and do not usually have occupational exposures that would put them at higher risk. It is not known why colon and rectal cancers are rare in dogs, although diet, physical activity, more rapid transit time through the shorter intestine, and a lower genetic predisposition may play a role. Lymphoma is relatively common in both people and dogs. Although prostate cancer is not among the most frequent cancers in dogs, they are the only species other than humans in whom prostate cancer is known to occur spontaneously to any appreciable extent.

In dogs, as in humans, skin tumors are relatively common. Localized tumors, such as squamous cell

TABLE 1. Most common incident cancers in female dogs and humans

Dogs* (1963–1966)		Women† (1969–1971)		Women‡ (1998)	
Cancer	% of total	Cancer	% of total	Cancer	% of total
Breast	51	Breast	27	Breast	30
Connective tissue	9	Colon and rectum	15	Lung and bronchus	13
Malignant melanoma of skin	8	Corpus uteri	7	Colon and rectum	11
Lymphoma	6	Cervix	6	Corpus uteri	6
Mouth and pharynx	5	Lung	5	Ovary	4
Biliary passages and liver	2	Ovary	5	Non-Hodgkin's lymphoma	4
Bone	2	Leukemias	3	Melanoma of skin	3

* Adapted from Dorn et al. (9).
† From Cutler and Young (11).
‡ From Landis et al. (12).

TABLE 2. Most common incident cancers in male dogs and humans

Dogs* (1963–1966)		Men† (1969–1971)		Men‡ (1998)	
Cancer	% of total	Cancer	% of total	Cancer	% of total
Connective tissue	17	Lung and bronchus	21	Prostate	29
Testis	16	Prostate	16	Lung and bronchus	15
Malignant melanoma of skin	14	Colon and rectum	14	Colon and rectum	10
Mouth and pharynx	10	Urinary bladder	6	Urinary bladder	6
Lymphoma	10	Bucca cavity and pharynx	5	Non-Hodgkin's lymphoma	5
Bone	4	Stomach	4	Malignant melanoma of skin	4
Stomach and intestines	3	Leukemias	4	Oral cavity and pharynx	3

* Adapted from Dorn et al. (9).
† From Cutler and Young (11).
‡ From Landis et al. (12).

carcinoma, are associated with sunlight exposure in both species. The usual ease of treatment, which is often carried out on an outpatient basis in humans, means that such tumors are not included in routinely published incidence statistics for humans. Therefore, we are not including non-melanoma skin cancers in humans or in dogs in tables 1 and 2. Other skin tumors in dogs, such as melanoma, have a very different biologic behavior from those in humans, and little is known of the epidemiology of connective tissue tumors (13). For these reasons, we will not discuss these tumors further.

EPIDEMIOLOGY OF CANCER OF SELECTED SITES IN DOGS

In this section we review what is known of the epidemiology of nine canine cancers that we consider to be of greatest interest at this time. These cancers were selected both because at least some analytic epidemiologic studies have been undertaken of their etiology and because some of the risk factors that have been identified in dogs are potentially relevant to humans.

Female breast cancer

In the Alameda/Contra Costa Counties survey of cancer incidence in pet dogs, about 97 percent of breast cancer cases were in females. As indicated above, breast cancer is the most common malignant neoplasm in female dogs (9), accounting for 51 percent of cancer cases in this survey, if non-melanoma skin cancers are excluded. This percentage may be lower now because dogs are more frequently spayed (i.e., have had their ovaries and uterus surgically removed), and, as will be discussed below, spaying at an early age protects against breast cancer. About 76 percent of breast cancers in dogs are adenocarcinomas. In humans, adenocarcinomas also predominate. Both benign and malignant lesions in dogs increase in frequency from anterior to posterior breasts; this gradient may relate to the greater growth rate, weight, lobularity, and secretion in the posterior breasts compared with the anterior (14, 15). Breast cancer incidence rates increase steeply with age in dogs. Purebred dogs have about a twofold higher rate of breast cancer than crossbred dogs of the same age (10).

One of the first pieces of information to be learned about cancer etiology in dogs was that spaying protects against breast cancer (10, 16). Table 3 shows the odds ratios reported by Schneider et al. (16) to be associated with spaying, using dogs with intact ovaries as the referent group. The protective effect was present only if the dog was younger than 2½ years at the time of spaying. In general, female dogs are considered to have reached maturity around 2–2½ years of age (17, 18). Another study (19) found some protection from spaying up to 5 years of age. It is well known that premenopausal oophorectomy protects against breast cancer in humans (20). However, in humans, oophorectomy before puberty is practically unheard of, so that the studies in dogs provide information that cannot be obtained from humans; that is, the risk is essentially zero if oophorectomy is performed before puberty. This, in turn, provides very strong evidence

TABLE 3. Odds ratios for breast cancer according to timing of spaying, Alameda County, California, 1963–1965*†

Time of spaying	Odds ratio‡
Before first estrous cycle	0.005
Between first and second estrous cycles	0.080
After two or more estrous cycles	0.260

* Includes female dogs of all breeds resident in Alameda County reported to the Alameda-Contra Costa Counties Animal Neoplasm Registry. Cases had histologically confirmed adenocarcinoma (n = 61) or malignant mixed mammary tumors (n = 22). Controls, matched to cases on age and breed (purebred versus crossbred), had non-neoplastic lesions of sites other than the breast.
† From Schneider et al. (16).
‡ Relative to never spayed.

that ovarian hormones are essential for the development of most cases of breast cancer.

The presence of both estrogen and progesterone receptors in mammary tumors in dogs (21, 22) also strongly suggests hormonal involvement. It has been found (23) that poorly differentiated malignant tumors have lower concentrations of estrogen and progesterone receptors than do benign or well-differentiated malignant tumors. The estrogen-receptor and progesterone-receptor concentrations decreased with increasing size of the tumor as well.

The sex hormone cycle in female dogs differs from that in humans. The dog's first estrous cycle generally begins between 6 and 13 months of age. Both average age at first estrous cycle and cycle length vary a great deal by size of dog, but on average a dog has about one cycle every 7 months, and it is only for a short period of time during each cycle (usually 5–9 days) that a dog can become pregnant. During much of the estrous cycle (typically 4½ months), the levels of estrogen and progesterone are low. Estrogen levels, and then progesterone levels, rise in conjunction with the dog's short period of ovulation and receptivity to the male, and progesterone levels remain high for several weeks after ovulation whether or not the dog is pregnant (24). Because estrous cycles in dogs are so different from menstrual cycles in humans, one would not necessarily expect the reproductive risk factors for women to pertain to dogs. In fact, studies concerned with such characteristics as age at first birth and number of pregnancies have been inconclusive (15, 16, 25–27), with most studies showing no relation. The small number of pregnancies experienced by most pet dogs, and the small amount of variation in age at first pregnancy, make these results difficult to interpret, in any event. Individual studies have found no association of breast cancer risk with irregularity of estrous cycle length (regular cycles being defined as every 6 months ± 1 month) (26) and owner-reported "abnormal" estrous cycles, still births, and litter size (16). However, given the likely amount of measurement error for some of these variables, it is difficult to reach any firm conclusions. One author (28) reported that beagles who become pregnant at every estrous cycle do not develop breast cancer.

A report that non-malignant proliferative lesions with moderate to marked atypia are associated with a high risk of subsequent breast carcinoma (29) needs to be evaluated in other studies. One study (30) suggests that overexpression of the oncogene c-*erb*B-2 plays a role in the development of malignancy. Overexpression of c-*erb*B-2 has been associated with a poor prognosis in human breast cancer.

Experimental studies have suggested that high doses of oral contraceptives can induce breast cancer in beagles (31). It would be of interest to see whether oral contraceptives at lower doses are associated with breast cancer in a more general population of dogs in a country such as Israel where they are widely used for contraception in dogs.

An observational study found that the amount of fat in the diet was not associated with an increased risk for the development of breast cancer (19), but that a high protein diet in conjunction with a low fat intake was associated with increased survival with breast cancer (32). Unspayed dogs reported to have been underweight as puppies had about half the risk for developing breast cancer as unspayed dogs who were not reported to have been thin as puppies. Among the spayed dogs the odds ratio for thinness as a puppy was 0.04 compared with spayed dogs who had not been thin as puppies (19). In a case-control study in which cases included dogs with either benign or malignant breast lesions (3), cases were more than four times as likely as controls to be reported as obese at 1 year of age. These findings needs to be evaluated in other studies.

Thus, other than the protective effect of spaying at an early age, little is known with certainty of risk factors for breast cancer in dogs. Most of the studies reported to date have included relatively small numbers of breast cancer cases. Often, lack of statistical significance has been interpreted as lack of association when the small sample size has rendered the power to detect an association very low. It would also be desirable to consider the adenocarcinomas separately, in the event that their etiology differs from the less common types.

Testicular cancer

Whereas in men seminomas are most frequent, in dogs Sertoli cell tumors, seminomas, and interstitial cell tumors are all commonly seen (13). Incidence rates in dogs increase with age for all three cell types, although Sertoli cell tumors on average occur at a younger age than the other cell types (33). In dogs there is no peak incidence in early adulthood as there is in men.

Several case-control studies (33–36) and one prospective cohort study (37) have reported that dogs with cryptorchidism have a markedly elevated risk for testicular seminomas and Sertoli cell tumors. The tumors tend to develop at a younger age in the cryptorchid dogs than in other dogs (37). In humans, estimated relative risks for testicular cancer among men with cryptorchidism have ranged from 2.5 to 11.4 (38). Dogs with inguinal hernia are also at increased risk for testicular cancer, independent of the association between cryptorchidism and testicular cancer (34).

An excess risk for seminomas was found among military working dogs who had served in the Vietnam War (39). These dogs were exposed to zoonotic and other parasitic infections, extensive treatment with drugs (especially tetracycline), and man-made chemicals such as phenoxy herbicides and malathion. Which specific exposure(s) account for the excess risk is not known. In human Vietnam veterans, an increased risk of testicular cancer has also been suspected, but a specific environmental agent has not been implicated (40, 41).

Lymphoma

Lymphoma in dogs shows biologic, pathologic, and clinical similarities to non-Hodgkin's lymphoma in humans (42). The most common histologic characteristic is either a diffuse large cell or immunoblastic tumor of B-cell origin (42–44). Incidence rates increase with age. With some variation from one study to another, males and females have similar incidence rates, and age-adjusted rates are approximately the same in neutered and intact dogs of both sexes. Age-adjusted rates are slightly higher in purebred than in crossbred dogs (45).

Chaganti et al. (46) found that the canine *MYC* gene has the same structural organization as the human *MYC* gene, and the *IGH*, *TCRB*, and *BCL2* genes also showed organizational similarities in dogs and humans. Since activation of *MYC* and *BCL2* protooncogenes from chromosome translocation has been shown to be a major pathway in the development of non-Hodgkin's lymphoma in humans, one might expect similarities in the etiologies of canine and human lymphomas. Another study (47) reported that, similar to humans, c-N-*ras* mutations are uncommon in dogs with malignant lymphoma.

A modest association (odds ratio = 1.3) has been reported with the use of 2,4-dichlorophenoxyacetic acid (2,4-D) herbicides on lawns or the use of a commercial lawn care company to treat the lawn (48). The risk increased with greater numbers of annual owner applications, but not with increasing number of commercial applications. This study has been criticized (49) because of poor measurement of exposure, methods of statistical analysis, possible uncontrolled confounding by other unmeasured characteristics of the dogs, and other problems. Nevertheless, dogs living in areas recently treated with 2,4-D do absorb measurable amounts for several days after the application (7). This, together with reports of increasing risk for non-Hodgkin's lymphoma among human farmers (50–52), gives some credence to the finding of a weak association in dogs. It is possible that without what appears to be a great deal of measurement error, the observed association might have been higher. Further study is warranted.

An association between exposure to electromagnetic fields and canine lymphoma was found in one study (53). Dogs that lived in homes with very high current codes had an odds ratio of 6.8 for developing lymphoma. Smaller increases in risk were found for dogs residing in homes with magnetic fields of 2.0 mG or greater around sidewalks, backyards, or front yards, but not for indoor measurements. Whether exposure to electromagnetic fields increases the risk for cancers of certain sites in humans is controversial (54). Dogs may offer some advantage in measuring exposure because of the amount of time that many spend year after year in a relatively circumscribed environment at their residence.

Osteosarcoma

Osteosarcoma in dogs is similar in many respects to osteosarcoma in humans, in that the metaphyseal region of long bones is frequently affected, malignancies are high-grade, metastasis is frequent, and the lung is the most common site of metastasis (55). However, there is no adolescent peak in incidence in dogs as there is in humans.

The incidence rate increases only slightly with age, but the tendency of this cancer to affect large breeds with short life expectancy must be taken into account when interpreting the age distribution. In fact, when breed and body weight are taken into account, the odds ratio increases monotonically with age (56). Males are affected slightly more often than females (56–59). One large study (56) found that both male and female dogs who have been neutered have twice the risk of intact dogs, although the age at neutering was not known in this study. Long bones are involved in about three quarters of cases and flat bones in about one quarter. Four weight-bearing bones (radius, tibia, humerus, and femur) are affected in about 90 percent of cases (58). The metaphyses of these bones, especially the distal radius, are the most common sites of occurrence (59, 60).

Large breeds are at particularly high risk (56–61), including Irish wolfhounds, Saint Bernards, great danes, rottweilers, and Irish setters (56). The risk in dogs weighing over 80 pounds has been estimated to be at least 61 times the risk in dogs weighing less than 20 pounds, and may be as much as 185 times greater (57). The excess risk in large dogs is characteristic of large dogs in general rather than of certain breeds (57). In fact, within a given breed, heavier dogs are at higher risk (56). The standard height (distance from the floor to a point on the shoulder called the withers) of the breed is associated with risk independent of standard

weight (56) (table 4). The associations with height and weight are especially strong for the long weight-bearing bones of the front and hind limbs.

The findings in dogs are consistent with the hypothesis proposed by Johnson (62) and Fraumeni (63) that osteosarcoma in children is related to rapid bone growth and occurs preferentially at sites of bone growth, that is, the metaepiphyses of long bones. It is also consistent with the observation in dogs that height is a much stronger risk factor for osteosarcoma in the appendicular skeleton than in the axial skeleton. It is possible that external force applied to bones, such as that associated with strenuous physical activity during growth, causes microfractures leading to cancer induction in rapidly dividing cells in the long bones of the tallest and heaviest dogs. This hypothesis would be consistent with the higher frequency of osteosarcoma in the front limbs than in the hind limbs, given that dogs bear more weight on their front compared with their hind limbs, particularly during exercise. Also, small dogs may be at lower risk because their epiphyseal plates are closed in a much shorter time than the plates of large dogs, and are therefore not at risk for tumorigenesis for as long a time (55). The reduced risk associated with neutering in both male and female dogs suggests that hormonal factors are involved in the promotional phase.

It has been found in experimental studies, in dogs receiving irradiation for soft-tissue sarcomas and in dogs exposed to intraoperative irradiation of the lumbar spine, that, as in humans, ionizing radiation increases the risk for osteosarcoma (64–66). In Saint Bernards, a clustering of cases among first degree relatives has been noted, suggesting an hereditary component in some cases (67). Osteosarcomas developing at the site of previous fractures, particularly if the fracture had been repaired with a metallic implant, have been noted (68–70). The tumors are biologically as malignant as other osteosarcomas (55). The latent period between fracture and tumor diagnosis has ranged from a few months to 15 years, with an average of about 6 years (55, 71), suggesting that in most instances the fracture preceded the tumor. It is believed that either the bone remodeling following the fracture or metallic particles or corrosion products from the implants could increase the risk for cancer (55). On the other hand, a recent study (71), based on only eight cases of osteosarcoma, reported that osteosarcoma cases were no more likely than comparison patients to have had internal (as opposed to external) fixation of fractures. Thus, more research is needed before conclusions are reached about the relation among fractures, metallic implants, and osteosarcoma. In any event, if there were a causal association, only a small proportion of osteosarcomas in dogs would be attributable to metallic implants or fractures.

Bladder and urethral cancer

Similar to humans, most bladder cancers in dogs are carcinomas of the urothelium, most frequently transitional cell carcinomas (72, 73). Older dogs are most often affected. In two studies (72, 74) females had 1.5- to threefold higher risk than males. Norris et al. (73) found no sex predilection, but neutered dogs of both sexes seemed to be at higher risk. It has been suggested that the higher risk in female dogs is a result of less frequent urination, so that urine-borne carcinogens have a longer exposure in the bladder epithelium in female than in male dogs (72, 75). Another explanation for the higher risk in female dogs is offered below.

Experimental bladder tumors in dogs may be produced by aromatic hydrocarbons such as para-aminobiphenyl and paranitroliphenyl (76), beta-napthylamine (77), and others (78). These findings, together with the apparent correlation between degree of industrial activity and spontaneous canine bladder cancer frequency in various parts of the United States (79), suggest that chemical exposures are likely to be involved in the etiology.

In a case-control study of bladder cancer in dogs

TABLE 4. Adjusted odds ratios (OR) and 95% confidence intervals (CI) for osteosarcoma in dogs by standard height and standard weight*

Adjusted for standard weight and age			Adjusted for standard height and age		
Standard height (cm)	OR†	95% CI	Standard weight (kg)	OR†	95% CI
<35.5	1.0		<23	1.0	
35.5–54	2.2	1.7–2.9	23–33	1.4	1.1–1.8
54.5–60.5	8.7	4.6–16.8	34–44	1.1	0.5–2.2
≥61	4.8	1.6–14.8	≥45	5.4	1.7–17.7
	$p < 0.001$‡			$p < 0.001$‡	

* From Hu et al. (56).
† Odds ratios adjusted using the Mantel-Haenszel procedure.
‡ *p*-value of test of linear trend.

TABLE 5. Odds ratios (OR) and 95% confidence intervals (CI) for bladder cancer associated with sex, body condition, and history of flea and tick dip exposures, University of Pennsylvania Veterinary Hospital, 1982–1985

Sex	Body condition	History of flea and tick dips			
		No		Yes	
		OR	95% CI	OR	95% CI
Male	Thin or average	1.0		0.7	0.3–2.6
	Overweight or obese	2.2	0.5–10.0	3.5	0.4–32.9
Female	Thin or average	1.0		1.0	0.3–3.0
	Overweight or obese	1.6	0.5–4.8	27.2	3.1–237.2

* From Glickman, Purdue University, unpublished data, 1997, from the study described in Glickman et al. (74).

(74), flea and tick dips and possibly flea and tick shampoos, obesity a year before diagnosis, and residential proximity to a marsh were identified as risk factors. The risk associated with insecticides was especially high in obese animals, probably because many of the insecticides, when placed in organic solvent carriers, are highly lipophilic. Since female dogs, like female humans, have a higher body fat concentration than males, the risk would be expected to be enhanced in females. Although based on relatively small numbers in individual subgroups, table 5 in fact shows a very high odds ratio of 27.2 among obese females who had had flea and tick dips. No one chemical type of flea and tick dip accounted for the increased risk. However, the active ingredients generally account for less than 5 percent of the total product. The remaining ingredients were labeled as "inert" and consisted of solvents such as benzene, toluene, xylene, and petroleum distillates, many of which are themselves known carcinogens. Such epidemiologic findings in dogs point to the need to measure the concentration of these "inert" substances in the fatty tissue of people with bladder cancer, particularly non-occupationally exposed nonsmoking females.

Cancers of the nasal cavity and paranasal sinuses

In one large series (80), carcinomas of the nasal cavity alone accounted for 88 percent of tumors in the region of the nasal cavity and paranasal sinuses. Whereas in humans squamous cell carcinomas are most common, in dogs adenocarcinomas are the most frequently occurring cell type in the nasal cavity. Incidence rates increase with age (81, 82). Most studies have noted that males are affected somewhat more frequently than females (80, 83, 84), with a male to female ratio of around 1.3 to 1 (80). No urban-rural gradient has been found (85).

Breeds at particularly high risk in one study were airedales, basset hounds, old English sheepdogs, Scottish terriers, collies, Shetland sheepdogs, and German shorthair pointers, while cocker spaniels and dachshunds are probably at low risk (80). When breeds were classified by skull type, long-nosed breeds had the highest risk, breeds with medium length noses and dogs of mixed breed an intermediate risk, and short-nosed breeds the lowest risk. It has been suggested that the efficient mechanism for filtration of particulates in long-nosed dogs may lead to the deposition of airborne particulate carcinogens in the nasal area (85). A recent case-control study (86) in fact found that long-nosed breeds living with a smoker in the house had a relative risk of 2.0 for nasal cancer, while the relative risk in short and medium nosed breeds living with a smoker was less than 1.0 (table 6). In the long-nosed breeds, the greater the number of total packs smoked in the household, the greater the risk for nasal cancer. Whether there are anatomic differences in humans that affect risk for these cancers should be examined.

Lung cancer

Primary neoplasms of the lung are rare in dogs. Most of these cancers are adenocarcinomas arising in the peripheral portions of the lungs. In humans, squamous cell carcinomas, adenocarcinomas, and oat cell carcinomas are all common. Although the number of cases diagnosed in dogs has been increasing over time, it is unclear whether this increase is real or attributable to improved diagnostic techniques (84). Male and female dogs are affected with approximately equal frequency.

The two published case-control studies of lung cancer in dogs have been based on relatively small numbers of dogs. One study found no elevation in risk associated with urban residence (85), while another (87) found a weak association (odds ratio = 1.6), but no dose-response relation, with exposure to tobacco in the home. The magnitude of the elevation in risk, however, is fairly similar to that noted in most studies of lung cancer in humans, in whom the odds ratio is about 1.3 for passive smoking (88). In dogs, the asso-

TABLE 6. Adjusted* odds ratios (OR) and 95% confidence intervals (CI) for association between total pack years of exposure to environmental tobacco smoke in the home and canine nasal cancer, by skull shape, Colorado, 1986–1990†

Total pack years of exposure	Brachy/mesocephalic (short- and medium-nosed) dogs		Dolichocephalic (long-nosed) dogs	
	OR	95% CI	OR	95% CI
None	1.0		1.0	
1–11	0.5	0.2–1.0	1.7	0.7–4.1
≥12	0.4	0.2–0.9	2.4	1.0–5.9

* Adjusted for age, sex, and use of flea control products.
† From Reif et al. (86).

ciation would not be confounded by occupational exposures or personal smoking. Furthermore, when breeds were divided into those with short and medium length noses and those with long noses, the short-nosed breeds had more than a twofold increase in risk if they were exposed to tobacco smoke in the home, while the breeds with long noses had no increased risk. This observation suggests that the efficient air filtration system of long-nosed dogs may be protective against lung cancer (87). J. S. Reif and colleagues (Colorado State University, personal communication, 1995) found a strong association of both the number of smokers in a household and the total of number of packs smoked per day in the home with the mean cotinine level in the urine of the dogs living there. Further study of these issues with larger numbers of cases and controls would be desirable.

Mesothelioma

Mesothelioma is rare in dogs. In the only epidemiologic study in dogs (8), which was based on 18 cases with histologically confirmed mesothelioma, 33 percent were in the peritoneum, 28 percent in the pleura, and 28 percent in the peritoneum and pleura, and 11 percent in the pericardium. Of the 18 dogs with mesothelioma, 17 were male. The reasons for the male excess are not known. Only one case occurred in a dog younger than 5 years of age.

In a case-control comparison done as part of this study (8), owners of dogs with mesothelioma were more likely than owners of control dogs to have been exposed to asbestos at work or through a hobby. Lung tissue from three dogs with mesothelioma and from one dog with squamous cell carcinoma of the lung had higher levels of chrysolite asbestos fibers than lung tissue from control dogs and two dogs with bronchial-alveolar carcinoma. These results suggest that findings in dogs may provide a warning of possible carcinogenic effects in humans with similar exposures.

Prostate cancer

The dog is the only nonhuman species in which spontaneous prostate cancer occurs with appreciable frequency. At the Purdue University veterinary teaching hospital, one of every 150 male dogs 8 years or older who was examined at necropsy for any reason or at surgical biopsy was found to have prostate cancer (L. T. Glickman, unpublished data, 1997). Clinically apparent prostate cancer in dogs is an aggressive malignancy with a high propensity to metastasize to regional lymph nodes, lung, and bone. When one compares the age at diagnosis of prostate cancer in men who were diagnosed with the disease without use of screening to the age in dogs with prostate cancer, there is a remarkable similarity, provided one first converts the dogs' chronologic age into human physiologic equivalents. (The conversion factor differs by breed of dog. See Waters et al. (89) for breed-specific conversion factors.)

Serial sectioning of human radical prostatectomy specimens has revealed that multiple independent foci of prostatic intraepithelial neoplasia (PIN) and cancer frequently are present together. Because dogs diagnosed with prostate cancer typically have advanced disease in which the cancer has totally replaced the prostate gland, it is unclear whether multifocal lesions are a feature of prostate cancer. Recent studies comparing the prevalence of high-grade PIN in human prostates with prostates obtained from dogs at autopsy revealed a high prevalence of high-grade PIN in elderly males of both species and many common histologic features that are influenced by age and testicular androgens (90). Taken together, these observations suggest that canine PIN, like human PIN, represents a precancerous stage in the morphologic continuum of progression from benign epithelium to carcinoma. The dog prostate, therefore, may serve as a useful subject for epidemiologic studies to determine the factors that regulate carcinogenesis and malignant progression in both dogs and humans.

DISCUSSION AND CONCLUSIONS

The studies reviewed here have covered a wide range of issues and have been of varying quality. Many have had relatively small numbers of study subjects, and the amount of error in measuring some of the exposures has been rather large. Nevertheless, several of these studies have been quite informative.

For those concerned with cancer prevention in dogs, several preventive measures are suggested. For many years veterinarians have strongly recommended spaying before the first estrous cycle for females and castration at an early age for males with undescended testicles. These recommendations have, in all likelihood, had some impact on the frequency of breast and testicular cancers. Although the evidence is not definitive on the associations between certain environmental exposures and cancers, the prudent owner would do well to limit the exposure of dogs to certain substances, such as flea and tick dips, asbestos, and tobacco smoke. Dogs should be exposed to radiation only when the expected benefits will outweigh the risks. The associations between herbicides and lymphoma and between electromagnetic fields and lymphoma are far from established at this time. Nevertheless, in the event that upon further study these associations are found to hold, it would seem that

when feasible, dogs should be kept away from lawns that have been recently sprayed with herbicides and should not spend a great deal of time in areas exposed to high levels of electromagnetic fields. Future well designed epidemiologic studies can identify other carcinogens to which dogs are exposed and which can be avoided.

For those concerned with cancer etiology in humans, observational epidemiologic studies in dogs can also be useful. Since many dogs share environments and some aspects of lifestyle with humans, and since some cancers are clinically and histologically similar in dogs and humans, the potential for relevance to humans is present. The shorter life expectancy in dogs may allow the detection of hazards earlier in dogs than in humans. Other specific ways in which epidemiologic studies in dogs can enhance understanding of etiology in humans are listed below.

1. Studies in dogs can clarify observations made in human studies. For instance, ovarian hormones have long been believed to be important in breast cancer etiology (91), but definitive evidence is lacking. The observation that the incidence of canine breast cancer is reduced almost to zero in female dogs oophorectomized before their first estrous cycle provides strong evidence that ovarian hormones are necessary for most breast cancers to develop. As mentioned above, the effect of oophorectomy before a first menstrual cycle cannot be examined in human females, so the data from dogs add a piece of knowledge that cannot be obtained from humans.

2. Studies in dogs can suggest leads for study in humans. The high risk for bladder cancer in obese female dogs exposed to insecticides suggests the possibility of such an association in humans. The people who apply insecticides to dogs are themselves heavily exposed in the process. A separate survey (L. T. Glickman, unpublished data, 1997) found that some groomers and veterinary technicians reported doing more than 100 dips per week over many years with little or no protective clothing. Study of cancer risk in such occupationally exposed individuals would seem warranted.

3. Studies in dogs can confirm suspicions raised in studies of humans. The observations that both dogs and humans who served in Vietnam have elevated risks for testicular cancer raises the level of concern over what it would be if the elevated risk were found only in humans.

4. Occasionally, strong confounding that cannot be entirely controlled in human studies may not be as great a problem in studies of dogs. In studies of the association between environmental tobacco smoke and lung cancer in humans, for instance, there is concern that the relatively small reported elevation in risk can be explained by confounding from occupational exposures or personal smoking. In studies of canine lung cancer these problems are greatly reduced even if not completely eliminated.

5. In some instances dogs may be divided into subgroups for which there is a biologic basis for expecting an increased risk in one group and not another. If environmental tobacco smoke is increasing the risk for cancer, one would expect the risk for lung cancer to be higher in short-nosed dogs than in long-nosed dogs because of the more efficient air filtration system of long-nosed dogs. One would also expect the risk for nasal cancer to be greater in long-nosed dogs than in short-nosed dogs because carcinogens are deposited in that area rather than in the lungs. These expectations were borne out in case-control studies, thus increasing the strength of the evidence that environmental tobacco smoke can cause cancer. The finding by L. T. Glickman (unpublished data, 1997) of a strikingly high relative risk for the association between use of flea and tick dips and bladder cancer among obese female dogs provides another example of how identification of effect modification may shed light on mechanisms of carcinogenesis.

6. Measurement of exposures may sometimes be better for dogs than humans. Measuring household exposure to electromagnetic fields in humans, for instance, is difficult because the household is only one of several sources of exposure to electromagnetic fields and because there is a great deal of variation in exposure from one part of the house and yard to another. Measurement may be much more reliable in dogs who spend almost all of their time in one part of the house or yard and have lived in the same household for most of their lives.

7. Potential risk factors may be much more variable in dogs than in humans, making it easier to detect associations in dogs. The enormous variation in the size of dogs, for instance, greatly facilitates the ability to relate height and weight to risk of osteosarcoma.

8. Cancer in dogs may serve as a sentinel of human health risk long before it might otherwise be recognized in human epidemiologic studies. The use of animals to detect the presence of potential environmental hazards dates back to the canary in the mine for monitoring toxic concentrations of carbon monoxide (92). Before cancer in dogs becomes a reliable basis for detecting human carcinogen exposures, the following criteria should be met: 1) the histology and biology of the cancer should be similar in dogs and humans; 2) the latency period should be considerably shorter for dogs than humans; 3) there should be a high probability that the relation between the agent and the cancer

is causal; and 4) a system should be in place for identifying and reporting cancers in dogs to the appropriate public health authorities.

Epidemiologic studies of cancer in dogs, particularly using the case-control approach, will be the primary means for determining the environmental causes of disease in dogs and estimating dose-response relations and latency periods. Two conditions in dogs for which this has been effective are lead poisoning (93) and asbestos-related mesothelioma (8). A National Research Council Committee on Animals as Monitors of Environmental Hazards noted that animal sentinel systems are particularly well suited for monitoring the complex array of environmental insults to human health and recommended that "Animal diseases that serve as sentinel events should be legally reportable to appropriate state or federal authorities and when animal reporting systems are established for environmental diseases of animals in a defined geographic area, every appropriate effort should be made to compare the frequency and pattern of these diseases with those of corresponding disease in humans. Research should be emphasized for development of correlative relationships that reduce the uncertainty in animal to human extrapolation and how animal sentinels should be used in the risk assessment process" (94, pp. 132–133). A recent paper by Bukowski and Wartenberg (95) provides a further discussion of the potential usefulness of pets as sentinels of environmental cancer risk and as a source of additional evidence regarding the likely carcinogenesis of a given exposure.

9. Genetic studies in dogs offer many advantages. The dog's unique combination of interbreed diversity combined with intrabreed uniformity make it an ideal species for studying complex mammalian traits (96). Genetic diseases are predicted to occur with high frequency in populations with closed gene pools and in which breeding of close relatives is used to propagate desired traits. Breeds established from a small number of founders and expanded rapidly to meet breeders' and consumers' demands are most affected. This tendency to inbreed provides a valuable resource for genetic studies. Genetic pathways of disease pathogenesis can be elucidated in high risk families of dogs. For instance, L. T. Glickman (unpublished data, 1997) found an odds ratio of 19 for bladder cancer in Scottish terriers relative to mixed breeds. No other breed had nearly so high an odds ratio. This suggests both a strong hereditary predisposition to bladder cancer in dogs, and that Scottish terriers would be a good model in which to identify metabolic pathways for susceptibility to bladder cancer.

Because of the much shorter lifespan of dogs than humans, it may be easier to study the genetics of adult-onset diseases such as most cancers. Pedigrees of several generations are available through breeders and the American Kennel Club. Since litter size is typically five puppies or more, it is possible to conduct genetic analyses to determine the patterns of inheritance. For example, Bech-Nielsen et al. (67) demonstrated a familial aggregation of osteosarcoma in Saint Bernards. These investigators found that dogs with osteosarcoma had a higher coefficient of relatedness than did unaffected dogs in the same pedigrees.

A number of canine disease genes have already been identified, largely because of their similarity to human disease genes. The canine genome is currently being mapped. As the mapping progresses, there will be numerous opportunities for comparative studies of cancer in dogs and humans (96).

Finally, assuming that adequate study designs are used and the studies properly executed, epidemiologic studies of cancers in dogs are likely to be most useful to human epidemiology when the tumors in the two species are clinically and histologically similar. Studies are also most likely to be useful to understanding cancer etiology in humans and dogs when the exposure of interest can be and is measured accurately and reliably. Biomarkers of exposure could be more widely used in studies of dogs to improve measurement. The recent study of osteosarcoma by Ru et al. (56), which included 3,062 cases and 3,959 controls and was based on data already collected in the VMDP, provides an example of how much can be learned when numbers of cases and controls are sufficiently large. Unfortunately, funding for studies with a large number of dogs is often not available. The Veterinary Cancer Society, which has been instrumental in organizing multi-institutional collaborative trials of treatment efficacy in dogs, could provide large numbers of dogs for participation in case-control studies. The establishment of a few population-based cancer registries for dogs would greatly facilitate the identification of a less select group of cases for case-control studies and also would allow examination epidemiologic studies of trends over time and of geographic differences in incidence. Finally, further collaboration between epidemiologists focusing on veterinary diseases and epidemiologists specializing in humans diseases would be highly desirable, since each has a great deal to offer to the other.

In conclusion, it is hoped that more well designed studies of cancer etiology in dogs will be undertaken, and that particular attention will be paid to adequacy of sample size and quality of measurement. Such studies have the potential to lead to better cancer prevention in humans as well as dogs.

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