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Association between Waste Management and Cancer in Companion Animals

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Background: Increased cancer rates have been documented in people residing in areas around Naples characterized by illegal dumping and incineration of waste.

Hypothesis: Risk of cancer in dogs and cats is associated with waste management.

Animals: Four hundred and fifty-three dogs and cats with cancer and 1,554 cancer-free animals.

Methods: Hospital-based case-control study in Naples (low danger) and nearby cities having a history of illegal waste dumping (high danger). Odds ratio (OR) between high- and low-danger areas was calculated for all tumors and various malignancies in dogs and cats.

Results: An increased risk for cancer development was identified in dogs but not in cats residing in high-danger areas (OR: 1.55; 95% confidence interval: 1.18–2.03; $P < .01$). A 2.39-fold increased risk of lymphoma ($P < .01$) accounted for the greater tumor frequency in dogs residing in high-danger areas. The risk of mast cell tumor and mammary cancer did not differ in dogs residing in high- or low-danger areas.

Conclusions and Clinical Importance: Waste emission from illegal dumping sites increases cancer risk in dogs residing in high-danger areas. An increased prevalence of lymphoma has been previously recognized in humans living close to illegal waste dumps. Thus, epidemiological studies of spontaneous tumors in dogs might suggest a role for environmental factors in canine and human carcinogenesis and can predict health hazards for humans.

Key words: Carcinogenicity; Cat; Dioxin; Dog; Epidemiology; Lymphoma.

The waste piling up in the streets of Naples and nearby cities has well-documented implications for the health of local residents and for the environment.[1,2] Unlike most Italian cities, where recycling and differential waste collection is routinely and successfully performed, in the Campania region, safe waste disposal is often not adequate. Rather, organic and toxic garbage, including industrial waste, is dumped on the streets, leading to progressive accumulation and pollution of water, air, and land.[1,2] Furthermore, household waste is illegally burned, thereby leading to toxic emissions and further health fear.[1,2]

Considerable interest has focused on environmental contaminants having the potential to affect cancer risk in people.[3] Emissions from the processing of urban and industrial waste contain various substances being classified as certain or probable carcinogens that enter the food chain through the way of air-plants-animals and water-sediments-fish.[3] In particular, dioxins, which are formed during combustion processes (including waste incineration) as well as during some industrial processes, have been classified by the US Environmental Protection Agency and the International Agency for Research on Cancer as human carcinogens and the mechanism underlying their carcinogenic effect is tumor promotion.[4,5]

Data obtained in 2002 from the Cancer Registry of the Sanitary Local Unit Naples 4 indicated a high mortality rate in humans because of leukemia, lymphoma, colorectal, liver, kidney, bladder, and lung cancer in a region known as the "triangle of death" (close to Naples), where illegal waste dumping is a major concern, suggesting a link between the level of pollution caused by illegal hazardous dumping and the high cancer mortality.[6] Dogs and cats share the same environment with human beings, being chronically and sequentially exposed to outdoor pollutants, yet they do not indulge in occupational activities or lifestyles, including active tobacco smoking and alcohol consumption, which can confound interpretation of epidemiological studies. Furthermore, pets have a physiologically shorter life span when compared with people, leading to a shorter latency period between exposure to a potential hazardous substance and development of disease. Pets, therefore, play a useful tool as sentinel hosts for disease, including cancer, possibly leading to early identification of carcinogenic hazards in the environment, predicting human risk, and assessing health effects.[7–12] Several epidemiological studies have identified an association between cancer development in pets and environmental pollutants.[13–21]

To date, no epidemiological studies have examined the relationship between environmental carcinogen exposure because of waste emission and cancer in pets. Thus, the purpose of this investigation was to examine, through a hospital-based case-control study, whether pets residing

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in proximity to hazardous waste disposal sites had an increased cancer danger. We hypothesized an increased cancer risk associated with residence close to toxic waste dump sites.

Materials and Methods

Study Area

The area involved in the study included Naples and the nearby cities of Acerra, Nola, and Marigliano (the ''triangle of death''), Afragola, Arzano, Aversa, Capodrise, Casoria, Castel Volturno, Frattamaggiore, Giugliano in Campania, Marano, Marcianise, Melito, Mugnano, Pianura, Pomegliano D'Arco, Pozzuoli, Qualiano, Sant'Antimo, Villaricca, and Volla (Fig 1), having a history of illegal waste dumping, including landfilling and unauthorized incineration, for which the Campania Region's Environmental Protection Agency conducted a census since 2003.[22] Safe waste disposal according to legal guidelines has not been followed in these locations.[22] With such conditions, it could be expected that hazardous substances were released into the environment in the past years.

Whereas the above-mentioned municipalities constantly deal with hazardous waste emissions, the city of Naples only faces the problem when dumps are filled to capacity and garbage is no longer being picked up. For the present study, animals living in Naples were defined as ''low danger,'' whereas animals living in the adjacent above-mentioned geographic locations were defined as ''high danger.''

Selection of Cases and Controls

A case-control study was undertaken at the Clinica Veterinaria L'Arca, Naples, Italy. Histologically confirmed cases of malignant solid tumors and cytologically confirmed cases of lymphoma and leukemia in both dogs and cats permanently living (at least 2 years before the diagnosis) in the study area and detected in the period between October 2003 and February 2008 were extracted from the database of the Veterinary Oncology Service of the Clinica Veterinaria L'Arca. The residential history of the animals before admission was reconstructed and cases were excluded if not residing at the same address for at least 2 years before presenting to the clinic. Further data extracted included age, sex, breed, and case type (1st opinion or referral). All dogs and cats with nonneoplastic diseases admitted during the same period of time and coming from the above areas served as controls.

In addition, as a routine at our institution, owners of tumor-bearing pets were asked to complete a questionnaire on the day of 1st presentation, specifically developed to elicit information on the habits of the animals. Information pertained to type of diet (home-made or commercial), source of drinking water (running water or bottle), exposure or not to passive tobacco smoke, administration or not of antiparasites, and environmental history (use or not of herbicides, presence or not of nearby electromagnetic fields).

Data Analysis

The analyses were conducted in dogs and cats separately for total tumors and for specific tumors, with at least 50 cases available per

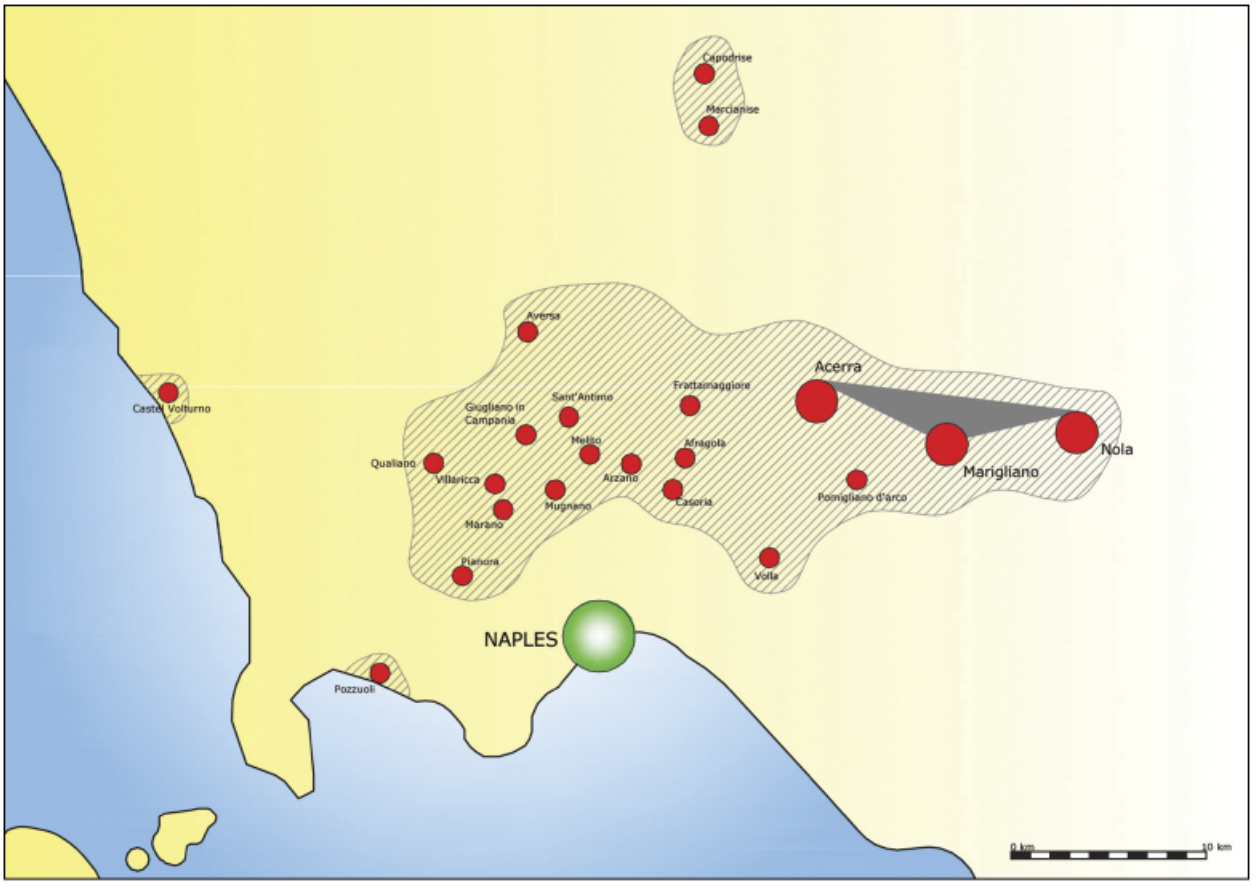

Fig 1. Map of the area under study showing the low-danger area (Naples) and the high-danger area (marked by shading). The ''triangle of death'' is highlighted.

cancer type. Other than area, factors that were investigated to assess whether they had an influence on tumor development included age, sex, and breed. Age was considered as a continuous covariate whereas area, sex, and breed were considered as categorical covariates. Area included the categories high danger and low danger and sex comprised the categories male and female. Because of the high number of breeds represented, dogs were assigned to pure- or cross-bred and cats to shorthair- or longhair-bred. The influence of the above factors was studied with univariate analysis. Factors, which on univariate analysis had $P < .15$, were further used to evaluate their confounding effect employing multivariate logistic regression.

To verify whether a relative excess of tumor versus control cases was referred from high-danger areas thus leading to a selection bias, the frequency of case types was compared between dogs or cats with and without neoplasia in the 2 areas, with the χ^2 test.

The variables listed in the questionnaire to owners of tumor-bearing pets were used to study whether they had an influence on lymphoma development in dogs. We specifically studied lymphoma in dogs because it is one of the most common malignancies for which single responsible factors have yet not been identified. The effect of diet, source of drinking water, exposure to passive tobacco smoke, administration of antiparasites, and environmental history was investigated with univariate analysis followed by multivariate analysis, as previously described. Area, age, sex, and breed were also included in the analysis. All variables except age were considered as categorical covariates. Calculation was performed using all non-lymphoma tumor-bearing dogs as controls. In addition, considering the group of tumors in dogs, the proportion of World Health Organization (WHO)/Tumor Node Metastases (TNM) clinical stages in the 2 areas was compared for selected malignancies with the χ^2 test. Significance was defined as $P < .05$.

Results

Between October 2003 and February 2008, 4,920 cases coming from Naples and nearby areas were seen at the Clinica Veterinaria L'Arca. Among these, 2,913 were excluded from the analysis because they were clinically healthy or not permanently residing in the areas under study, as defined in the inclusion criteria. Four hundred and fifty-three cancer cases (353 dogs, 77.9%; 100 cats, 22.1%) were diagnosed in Naples (low danger) and nearby cities (high danger). Of them, 256 tumors (56.5%) were diagnosed in animals coming from the high-danger zone (212 dogs, 82.8%; 44 cats, 17.2%) and 197 tumors (43.5%) in animals residing in the low-danger zone (141 dogs, 71.6%; 56 cats, 28.4%). During the study period, from the same areas, 1,554 (1,217 dogs, 78.3%; 337 cats, 21.7%) pets with nonneoplastic diseases were diagnosed. Among them, 805 animals (51.8%) lived in the high-danger zone (655 dogs, 81.4%; 150 cats, 18.6%) and 749 animals (48.2%) in the low-danger zone (562 dogs, 75.0%; 187 cats, 25.0%).

Information pertaining to residence history allowed to ascertain that for both cases and controls, in- and out-migration had not occurred in the last 2 years preceding admission.

Results of univariate analysis for tumor occurrence in dogs and cats are shown in Table 1. Multivariate analysis was performed for all tumors, lymphoma, and mast cell tumor in dogs (Table 2). An increased odds ratio (OR) for cancer development was identified in dogs but not in cats residing in high-danger areas (OR in dogs: 1.55; 95% confidence interval [95% CI]: 1.18–2.03; $P < .01$). In dogs living in high-danger areas, the OR of developing lymphoma increased by 2.39-fold ($P < .01$). Excluding lymphoma cases from analysis, cancer risk in dogs was not different between areas ($P = .19$). The odds of mast cell tumor and mammary cancer did not differ between high- and low-danger areas in dogs. Mast cell tumors were more often observed in dogs bearing another tumor. Altogether, 16 of 63 (25%) mast cell tumors were associated with a concurrent primary malignancy, making up 8 of 22 (36%) mast cell tumor cases in the low-danger area and 8 of 41 (20%) in the high-danger areas.

To verify whether bias occurred during case selection, the frequency of case types was calculated for tumor and controls in dogs and cats residing in high- and low-danger areas. The frequency of referred dogs with tumor and nonneoplastic diseases was equally higher in the

Table 1. Univariate analysis of tumor occurrence and area, age, sex, or breed in dogs and cats.

Tumor Type	Area (High versus Low Danger)	Age (per year)	Sex (Male versus Female)	Breed (Pure- versus Cross-Bred)
All tumors (dogs)	OR: 1.29 (95% CI: 1.01–1.64) $P = .04$	OR: 1.15 (95% CI: 1.11–1.19) $P < .01$	OR: 0.90 (95% CI: 0.70–1.16) $P = .43$	OR: 1.13 (95% CI: 0.93–1.39) $P = .18$
All tumors (cats)	OR: 0.98 (95% CI: 0.61–1.59) $P = .94$	OR: 1.12 (95% CI: 1.06–1.18) $P < .01$	OR: 1.12 (95% CI: 0.69–1.83) $P = .65$	OR: 0.93 (95% CI: 0.51–1.68) $P = .80$
Lymphoma (dogs)	OR: 2.01 (95% CI: 1.17–3.47) $P = .01$	OR: 1.15 (95% CI: 1.09–1.15) $P < .01$	OR: 0.87 (95% CI: 0.53–1.44) $P = .59$	OR: 1.20 (95% CI: 0.95–1.65) $P = .23$
Mast cell tumor (dogs)	OR: 1.60 (95% CI: 0.93–2.72) $P = .09$	OR: 1.08 (95% CI: 1.02–1.14) $P = .01$	OR: 0.73 (95% CI: 0.43–1.21) $P = .21$	OR: 1.83 (95% CI: 1.12–2.90) $P = .02$
Mammary tumors (dogs)	OR: 0.95 (95% CI: 0.60–1.50) $P = .83$	OR: 1.18 (95% CI: 1.11–1.25) $P < .01$	NA	OR: 1.30 (95% CI: 0.90–1.77) $P = .23$

OR, 95% CI and *P*-values were calculated.

OR, odds ratio; 95% CI, 95% confidence interval; NA, not available.

Table 2. Tumor frequency in dogs living in high- versus low-danger areas.

Tumor Type	Frequency (High Danger)	Frequency (Low Danger)	OR	CI 95%	Significance
All tumors (353)	24.5% (212)	20.1% (141)	1.55	1.18–2.03	$P < .01$
Lymphoma (67)	6.70% (47)	3.43% (20)	2.39	1.43–4.18	$P < .01$
Mast cell tumor (63)	5.89% (41)	3.77% (22)	1.05	0.85–1.80	$P = .25$

Odds ratio (OR), confidence interval (CI) 95%, and *P*-value were calculated with multivariate logistic regression. Age, sex, and breed were included in the analysis if the univariate analysis had a $P < .15$.

high- versus low-danger area (approximately 2-fold; $P < .01$). In cats, the proportion of case types for tumor and controls was equal in the 2 areas.

In relation to lymphoma in dogs, in univariate analysis, area, age, sex, and passive tobacco smoke were associated with the tumor (Table 3). In multivariate analysis, exposure to passive tobacco smoke remained significantly associated with tumor development (OR: 3.37; 95% CI: 1.84–6.19; $P < .01$). The WHO/TNM clinical stage of lymphoma[23] slightly varied across high- and low-danger dogs, with the darkest spots being represented by the high-danger zones, showing a trend toward increased proportion of stage V disease ($P = .056$; Table 4). The proportion of tumor stages was equal in the 2 areas for mast cell and mammary tumors in dogs (Table 4).

Discussion

This epidemiological study found an increase in overall cancer risk because of increased susceptibility to lymphoma in dogs permanently residing in areas exposed to hazardous waste emission substances. Here, a 1.55-fold significant increased odd for cancer development ($P < .01$) was identified in dogs residing in high-danger areas, which was because of a lymphoma excess (OR: 2.39; $P < .01$). The odd of mast cell tumors and mammary cancer in dogs was not different between areas.

Table 3. Univariate analysis of canine lymphoma and area, age, sex, breed, diet, source of water, passive tobacco smoke, administration of antiparasites, exposure to herbicides, or exposure to electromagnetic fields.

Variable	OR	CI 95%	Significance
Area (high versus low danger)	1.72	0.97–3.06	$P = .06$
Age	0.92	0.84–1.01	$P = .06$
Sex (male versus female)	1.97	1.15–3.37	$P = .01$
Breed (pure versus cross-bred)	0.99	0.57–1.74	$P = .98$
Diet (home versus commercial)	1.74	0.82–3.69	$P = .16$
Source of water (running versus bottle)	1.06	0.35–3.23	$P = .92$
Passive tobacco smoke (yes versus no)	3.37	1.84–6.19	$P < .01$
Administration of antiparasites (yes versus no)	NA	NA	NA
Exposure to herbicides (yes versus no)	NA	NA	NA
Exposure to electromagnetic field (yes versus no)	NA	NA	NA

Odds ratios (OR), confidence interval (CI) 95%, and *P*-values were calculated. Dogs affected by tumors other than lymphoma served as controls.

The effect of these variables could not be assessed because antiparasites were used in almost all dogs and exposure to herbicides and electromagnetic fields was very low.

NA, not available.

A plausible hypothesis is that the reported cancer pattern is, at least in part, an expression of risk resulting from sustained environmental exposures to waste emission substances. In addition, exposure to tobacco smoke contributes to lymphoma development in dogs. Because pets act as environmental sentinels, the results obtained in this study may indicate a progressive increase in the risk of selected cancers in the population living in exposed areas.

Domestic pets have acted as sentinels of environmental hazardous substances since a long time.[7,8,10–12] Dogs and cats sharing the same environment as humans are exposed to the same chemical carcinogens. It is interesting to note that pets may be even more exposed than humans to carcinogens and this is attributable to access to ground and surface water or soils contaminated with pesticides or hazardous substances and to cars' exhausts. Remarkably, pet studies are less subject to error with regard to assessment of hazardous exposure as companion animals have a shorter life span, thereby leading to an easier reconstruction of the individual's complete exposure history. Thus, epidemiological analysis in dogs and cats represent a valuable approach to define the carcinogenic potential of hazardous environmental substances or to anticipate the risk of tumor development in populations residing in areas with a high degree of pollution.

The etiology of lymphoma in dogs is likely multifactorial and multistep, combining the genetic predisposition of the individual and its immune status with various exogenous factors. Indeed, viral, environmental, and immunologic variables have been speculated to play a role in the development of canine lymphoma[23]; yet, there are no proven causes.

In this investigation, in addition to living in high-danger areas, passive tobacco smoke significantly increased lymphoma danger in dogs, suggesting that the exposure to owners' smoking may be an important risk factor in cancer development. Tobacco smoke contains at least 60 known human or animal carcinogens[24] and, in people, it is known to increase the risk of various tumors,[25] including non-Hodgkin lymphoma.[26] It has been suggested that the leukemogenic substances contained in tobacco smoke may increase the risk of lymphoid neoplasia.[25] Passive cigarette smoke has been previously linked

Table 4. The proportion of WHO/TNM clinical stages in high- versus low-danger areas was compared for lymphoma, mast cell tumors, and mammary cancer in dogs.

Tumor Type	Frequency (High-Danger Area)	Frequency (Low-Danger Area)	χ^2 Test
Lymphoma			Stage V versus I–IV
Stage I	0% (n = 0)	5.0% (n = 1)	OR: 3.22
Stage III	6.4% (n = 3)	20.0% (n = 4)	CI 95%: 0.93–11.23
Stage IV	48.9% (n = 23)	55.0% (n = 11)	$P = .06$
Stage V	44.7% (n = 21)	20.0% (n = 4)	
Mast cell tumor			Stage II and IV versus I and III
Stage I	39.0% (n = 16)	45.5% (n = 10)	OR: 0.92
Stage II	14.6% (n = 6)	22.7% (n = 5)	CI 95%: 0.32–2.66
Stage III	22.0% (n = 9)	13.6% (n = 3)	$P = .88$
Stage IV	24.4% (n = 10)	18.2% (n = 4)	
Mammary cancer			Stage IV and V versus I–III
Stage I	22.2% (n = 8)	13.5% (n = 5)	OR: 0.76
Stage II	25.0% (n = 9)	27.0% (n = 10)	CI 95%: 0.30–1.90
Stage III	8.3% (n = 3)	8.1% (n = 3)	$P = .56$
Stage IV	19.4% (n = 7)	8.1% (n = 3)	
Stage V	25.0% (n = 9)	43.2% (n = 16)	

Odds ratios (OR), 95% confidence interval (CI), and *P*-values were calculated.

(*) For lymphoma, comparison was made between stage V and stages I–IV. Stages I–IV were grouped together because they were biologically less aggressive than stage V (meaning bone marrow involvement).[24] For mast cell tumors, comparison was made between stages II and IV grouped together (metastatic to regional lymph nodes and distant sites, respectively) and stages I and III (nonmetastatic). For mammary tumors, comparison was made between stages IV and V grouped together (metastatic to regional lymph node and distant sites, respectively) and stages I–III (nonmetastatic).

to lymphoma in cats, with proposed routes of exposure being inhalation and oral ingestion during grooming of particulate matter deposited on the fur.[18] The same could hold true for dogs.

In several human epidemiological studies, an increased occurrence of lymphoma was found in people exposed to toxic waste emission[27–29] with a relative risk of 1.27–1.50, which roughly corresponds to the risk observed in the present study. Dioxin has obvious hazardous effects and, specifically for human non-Hodgkin lymphoma, there is compelling evidence of increased risk resulting from its occupational or accidental exposure.[27,30,31] Bearing in mind that an investigation conducted in the area under study demonstrated the localized influence of waste incineration on the dioxin concentration of the milk of livestock farms raised nearby,[32] it can be speculated that illegal waste burning was a major source of environmental dioxin in high-danger areas. Besides impairing the immune system, an additional hypothesis concerning the mechanism of action of dioxin in tumorigenesis has been p53 (a tumor suppressor gene) repression,[33] and it is interesting to note that p53 is mutated in canine lymphoma.[34,35] These observations are of potential interest in relation to our finding of higher risk for lymphoma in the high-danger areas. However, a major obstacle in establishing causality is that dioxin was not measured in specimens collected from dogs.

According to the sparse literature, the simultaneous presence of multiple primary cancers is an uncommon event in veterinary medicine.[36] Despite concurrent tumors not being frequent in both areas, data analysis indicated that mast cell tumors were very often associated with other malignancies (25% of all mast cell tumors). The explanation for this finding remains elusive. The possibility of a chance effect seems probable.

In this study, cats in the high-danger areas did not have an increased cancer risk. Provided that the greatest majority of the included feline population lived strictly indoor, it is reasonable to suspect that exposure to adequate doses of environmental hazardous substances did not occur. The other alternative is that because of the relatively low number of animals (44 tumor-bearing cats in the high-danger areas), a significant difference was not detected.

Considering that all dogs spent some time outdoor for their daily walks, it would be assumed that exposure to environmental hazardous substances occurred. Although none of the dogs was permanently kept outdoor, the information on how long they were kept outdoor per day was not recorded thus precluding an assessment of exposure dose.

When interpreting the results of tumor risk in this study, major confounding phenomena such as age, sex, and breed (pure- or cross-bred in dogs, shorthair- or longhair-bred in cats) were not observed. In addition, case selection bias because of different distribution of referral and 1st opinions between areas was not identified. Because of the retrospective nature of the investigation, it is possible that other not-considered factors had influenced the results. In addition, estimates of sample size were not attempted. The absence of increased risk for some of the tumor types in the high-danger area might have been because of low-power analysis.

Another limitation of this study may be because of grouping cases into geographic areas in spite of using geographic information system network analysis, which allows more precise investigation of spatial data and

downstream movement of a pollution incident than using just the township borders. Furthermore, the area under study is troubled by overpopulation and is involved in intensive agriculture and widespread industrial activity, all well-known environmental stressors. Waste exposure may have only contributed to increased cancer, not being the primary leading cause of this adverse health effect.

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