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Factors influencing malignant tumor development in cats from a multicenter retrospective study

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Abstract

Animal cancer registries (ACRs) are vital tools in veterinary oncology, offering insights into tumor epidemiology and supporting comparative research. Despite cancer being a major cause of feline mortality, data on feline tumor epidemiology remain limited. This study aimed to investigate temporal trends in histologically diagnosed feline tumors and assess how breed, sex, neuter status, age, and geographic origin affect malignancy and tumor distribution. A modified Vet-ICD-O-canine-1 coding system was applied to 5,289 tumors from two pathology-based ACRs in central Italy (2008–2023). Data were analyzed for time trends by the Cochran-Armitage test, and logistic regression was used to assess the impact of the variables on tumor behavior ("malignant" vs. "benign") and the development of major cancer types. Of all tumors, 4,264 (80.6%) were malignant. Fibrosarcomas (n = 926; 17.5%), adenocarcinomas (n = 814; 15.4%), squamous cell carcinomas (SCCs; n = 738; 14.0%), and lymphomas (n = 507; 9.6%) were the most common types of cancer. Malignancy risk increased by 8% per year of age (OR = 1.08; 95%CI 1.06–1.10). Females

(OR = 1.39; 95%CI 1.19–1.62) and non-purebred cats (OR = 1.89; 95%CI 1.47–2.38) had higher odds of malignancy. Neutered status was associated with reduced adenocarcinoma risk (OR = 0.79; 95% CI 0.66–0.94). Temporal trends included rising SCCs ($p = 0.001$) and declining fibrosarcomas ($p < 0.001$). These findings support previous findings and identify previously unknown risk factors, underscoring the value of multicenter ACR-based surveillance.

Keywords

animal cancer registry; malignancy; cat; veterinary oncology; fibrosarcoma; squamous cell carcinoma

1. Introduction

Cancer represents a major health concern in both humans and animals, with millions of new cases diagnosed annually worldwide^{1,2}. Among companion animals, cats are one of the most popular species worldwide, with an estimated 600 million individuals—including pets, strays, and feral cats—distributed across all continents except Antarctica^{3,4}. These figures also rank the cat among the most common terrestrial mammals⁵. Their popularity as pets has steadily increased in recent decades⁶. In Europe, cat ownership is estimated at nearly 130 million, with more than 10 million in Italy alone, underscoring their growing societal and clinical importance as companion animals⁷.

Cats also bear a particularly high cancer burden: the proportion of malignant tumors is reported to be higher in felines than in other species, including dogs and humans^{8–12}. Clinically, the species presents additional challenges, as cats often conceal illness and tend to exhibit non-specific clinical signs. As a result, neoplasms are frequently detected at an advanced stage, when therapeutic options are limited and prognosis is poor^{13,14}. This combination of biological predisposition and clinical presentation highlights the need for a deeper epidemiological understanding of feline cancer.

Animal cancer registries (ACRs) are essential to fill this gap, providing structured data that support the identification of risk factors and patterns in tumor occurrence. They also represent a cornerstone for comparative oncology, given the significant histopathological, genetic, and molecular similarities between tumors in cats, dogs, and humans^{1,14,15}.

The close cohabitation of cats and humans further strengthens the relevance of feline cancer studies. Sharing the same domestic environments, pets are exposed to similar allergens, dietary components, and environmental pollutants as their owners¹⁶. This parallel exposure makes them potential epidemiological sentinels for human cancer development^{17,18}, particularly in a *One Health* context.

Additional advantages of companion animals in cancer research include shorter latency periods following carcinogen exposure and shorter life expectancy, which result in faster disease progression and make them ideal subjects for prospective studies^{17,19}. Moreover, pets are exposed to fewer lifestyle-related confounding factors—such as smoking, alcohol consumption, or occupational hazards—and their relatively stable environments enhance the reliability of epidemiological findings^{20,21}. Feline cancers offer valuable translational models: oral squamous cell carcinoma resembles human head and neck cancer, mammary tumors are often aggressive and triple-negative, and injection-site sarcomas

reflect inflammation-driven tumorigenesis. These tumor types could allow investigation of disease mechanisms, individual susceptibility, and potential therapeutic strategies¹⁴.

Despite these benefits, veterinary oncology still lacks the systematic data collection available in human medicine, where established registries guide the decision-making process²². Most registries in companion animals have been historically constrained, covering small populations or short timeframes^{8,9,23–31}. Consequently, robust data on pet cancer distribution, biological behavior, and risk factors remain scarce.

While canine oncology has received more attention, the epidemiology of feline tumors has been investigated less extensively. Available information is still fragmentary and often limited to studies with restricted sample sizes, geographical coverage, or temporal duration^{10,31}. Recent international initiatives such as the Global Initiative for Veterinary Cancer Surveillance (GIVCS) have promoted harmonized classification systems and standardized coding to enhance comparability across studies and species^{32–34}. These efforts are essential to integrate pet data into a broader epidemiological framework and to exploit their potential in a One Health perspective. Nonetheless, major gaps persist, and further efforts are needed to enhance the quantity and quality of ACR-based studies focused on cats, at both national and international levels.

This study aimed to retrospectively describe a collection of histologically diagnosed feline tumors recorded by the UNIPI pathology-based ACR of the Department of Veterinary Sciences at the University of Pisa and the Animal Tumour Registry of the Lazio region, Rome. The study analyzed temporal trends and assessed the influence of breed, sex, neutering status, age, and geographical origin on the odds of having a malignant tumor and on the odds of having the most common feline malignant tumor types: fibrosarcomas, adenocarcinomas, squamous cell carcinomas (SCCs), and lymphomas.

2. Results

2.1. Descriptive statistics

2.1.1. Sample size

Over the course of the research period (2008–2023), a total of 5,538 tumor records (including metastases, recurrences, and tumors with uncertain biological behavior) were collected. After coding and cleaning, 3,518 records from the ACR of Pisa and 1,771 cases from the ACR of Lazio were included, totaling 5,289 primary tumor diagnoses in 5,154 cats. The number of primary tumors ranged from one to six per cat. The data set consisted mostly of tumor cases from the Tuscany ($n = 2,513$; 47.5%), Lazio ($n = 1,785$; 33.8%), and Liguria ($n = 741$; 14.0%) districts of origin (Supplementary Figure 1).

2.1.2. Tumor topographies and morphologies

Figure 1 depicts the distribution of the most frequent tumor morphologies and the malignancy proportions by topography. The three most common tumor localizations were the *skin* [C44] ($n = 1,543/5,289$; 29.2%), the *soft tissues* [C49] ($n = 1,387/5,289$; 26.2%), and the *mammary gland* [C50] ($n = 765/5,289$; 14.5%) (Figure 1).

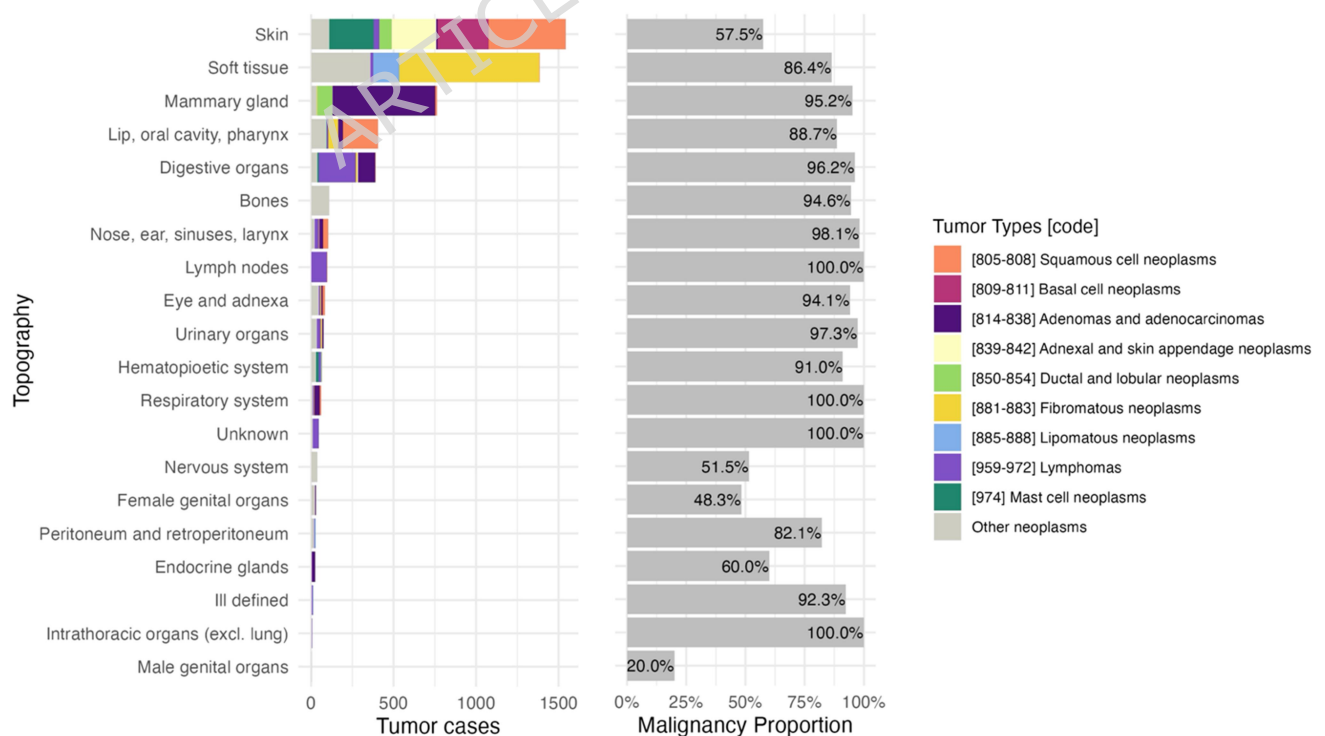


Figure 1. Absolute number of the top ten most common tumor types and malignancy proportions (%) per topographical site in the 5,289 tumor cases included in the study.

Fibromatous neoplasms [881–883] were the most diagnosed morphologies (n = 942/5,289; 17.8%), followed by *adenomas and adenocarcinomas* [814–838] (n = 856/5,289; 16.2%), *squamous cell neoplasms* [805–808] (n = 756/5,289; 14.3%), and *lymphomas* [959–972] (n = 507/5,289; 9.6%).

The *fibromatous neoplasms* were mainly located in the *soft tissues* (n = 848/942; 90.0%), and only few were diagnosed in the *lip, oral cavity, pharynx* [C00–14] (n = 58/942; 6.2%), and *digestive organs* [C15–26] (n = 9/942; 1.0%). The 72.7% (n = 622/856) of the *adenomas and adenocarcinomas* were in the *mammary gland*, comprising 81.3% (n = 622/765) of all mammary gland tumors, while the 12.0% (n = 103/856) were diagnosed in the *digestive organs*. The *squamous cell neoplasms* were mainly located in the *skin* (n = 465/756; 61.5%), in which they comprise the most common tumor type (n = 465/1,543; 30.1%), followed by *basal cell neoplasms* [809–811] (n = 312/1,543; 20.2%), *adnexal and skin appendage neoplasms* [839–842] (n = 270/1,543; 17.5%), and mast cell neoplasms (n = 269/1,543; 17.4%). The 28.2% of remaining *squamous cell neoplasms* were in the *lip, oral cavity, pharynx* site, comprising 52.3% of all tumors affecting this area (213/407 cases). Other oral neoplasms were the previously mentioned *fibromatous neoplasms* (58/407 cases; 14.3%), and *odontogenic tumors* [927–934] (32/407; 7.9%). For *lymphomas*, the most common localizations were the *digestive organs* (224/507; 44.2%), the *lymph nodes* (94/507; 18.5%), and the *unknown* [C80]—including the *multiple sites* [C80.91] code—localization (36/507; 7.1%) (Figure 1).

The anatomical localizations with the highest (100.0%) malignancy proportion were the *lymph nodes, the respiratory system, unknown topography, and intrathoracic organs (excl. lung)*. The lowest malignancy proportions were observed in the *male genital organs* (20.0%), *female genital organs* (48.3%), *nervous system* (51.5%), and the *skin* (57.5%) (Figure 2). The absolute number of cases and the relative frequency of all tumor topographies and morphologies are reported in Supplementary Table 2.

2.1.3. Demographic features and age at tumor diagnosis

Female cats were slightly more represented (n = 2,911; 55.0%) than males (n = 2,065; 39.0%). The majority of collected cases involved neutered animals (n = 3,371; 63.7%) in both registries and sexes (Table 1). The median age at tumor diagnosis was 11 years (range: <1–24), with a lower median age at diagnosis in males than females (median: 10.1 years for males and 11.0 years for females). Median ages of intact and neutered felines

were close in both sexes. Moreover, cats with malignant tumors tended to be older (median: 11.0 years) than those with benign tumors (10.0 years). These descriptive comparisons are provided to contextualize the study population, while detailed inferential analyses of age are beyond the scope of this study.

Table 1. Absolute numbers, percentages, and median age at tumor diagnosis for 5,289 tumors from the Animal Cancer Registries (ACRs) of Pisa and Lazio and subdivided by sex and neuter status. The overall number and percentage of malignant tumors (malignancy proportion) are also provided.

Sex	Neuter status	Pisa ACR		Lazio ACR		Total				
		All tumors		All tumors		All tumors			Malignant tumors	
		n°	%	n°	%	n°	%	Age ¹	n°	MP
Male	Intact	455	12.9%	153	8.6%	608	11.5%	9.7 (7-12.3)	468	77.0%
	Neutered	937	26.6%	520	29.4%	1457	27.5%	10.3 (8-13)	1120	76.9%
	Total	1392	39.6%	673	38.0%	2065	39.0%	10.1 (8-13)	1588	76.9%
Female	Intact	740	21.0%	257	14.5%	997	18.9%	10.7 (8-13.3)	829	83.1%
	Neutered	1114	31.7%	800	45.2%	1914	36.2%	11.0 (9-13.6)	1584	82.8%
	Total	1854	52.7%	1057	59.7%	2911	55.0%	10.9 (8.7-13.6)	2413	82.9%
N.d.		272	7.7%	41	2.3%	313	5.9%	11.2 (8-13)	263	84.0%
Total		3518		1771		5289		10.6 (8-	4264	80.6%

								13.3)		
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¹ The median age and the Q1-Q3 (in brackets) are reported in years; n° = absolute number of cases; MP = malignancy proportion; N.d.: not determined. Percentages are reported out of the total.

2.1.4. Breeds

Most cases were from House Cat Shorthair/Longhair (HCS/HCL) (n = 4,562/5,289; 86.3%). Purebred cats comprised 7.2% of the total (n = 378/5,289), and the breed was unknown in 6.6% of the cases (n = 349/5,289). Overall, 21 different feline breeds were included (Supplementary Table 3). Among purebreds, the predominant breeds were the Persian (n = 164/5,289; 3.1%), the Siamese (n = 54/5,289; 1.0%), the Maine Coon (n = 35/5,289; 0.7%), and the Chartreux (n = 31/5,289; 0.6%). Figure 2 presents a summary of the tumor type distribution across these breeds. In HCS/HCL and Chartreux cats, *fibromatous neoplasms* were the prevalent diagnoses, while in Persian and Siamese cats, *adenomas and adenocarcinomas* were the most frequently observed tumor types. Conversely, *basal cell neoplasms* were the most common diagnosis in the Maine Coon.

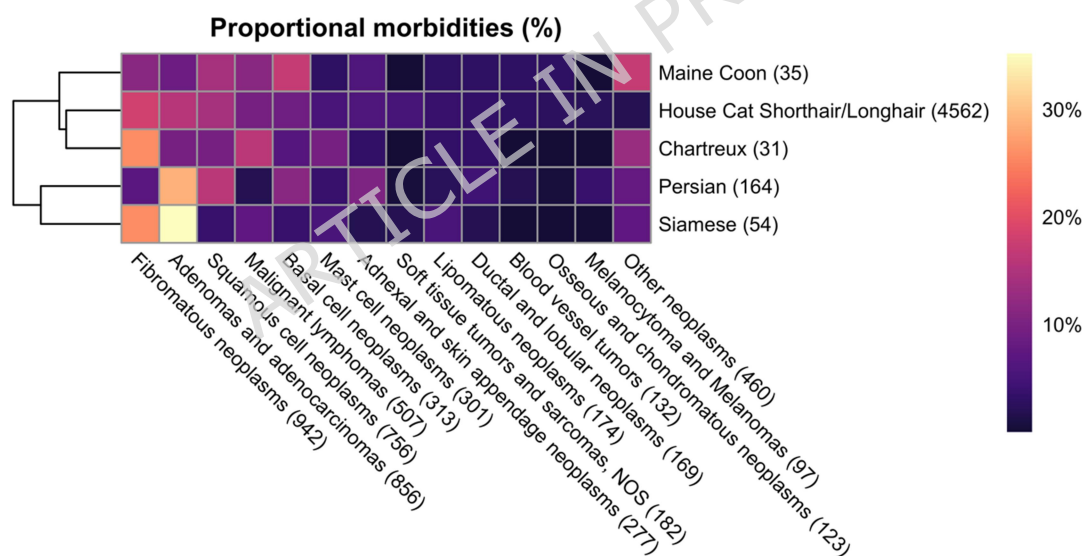


Figure 2. Heat map showing the proportional morbidity (% out of the total tumors for each breed) for the 4,846 tumor cases detected in the 5 most common feline breeds. Each row sums up to 100%. The breeds are clustered according to their similarities in the tumor distribution patterns by hclust() function in R, regardless of their phylogenetic relationships. The total number of cases is reported in round brackets

2.2. Malignancy Analysis

Malignant tumors constituted 4,264 (80.6%) of the total. Predictor variables for the regression analysis were selected based on the results of the univariate analysis (Supplementary Table 4). Based on logistic regression analysis, Figure 3b illustrates the impact of age, sex, neuter status, breed, and district on the proportion of malignancies. The risk of malignancy increased by 8% per year (OR = 1.08; 95% CI 1.06–1.10). Females exhibited an increased risk in comparison to males (OR = 1.39; 95% CI 1.19–1.62), and neuter status was not associated with malignancy ($p = 0.537$). In terms of districts, a marginally significant rise in malignancy was noted in the Liguria region (OR = 1.40; 95%CI 1.09–1.82), whereas the "breed" variable emerged as the predominant factor influencing malignancy risk, with a protective effect of being purebred compared to HCS/HCL (OR = 0.53; 95%CI 0.42–0.68). Unfortunately, an individual breed-based analysis had to be omitted due to the low number of purebred cats.

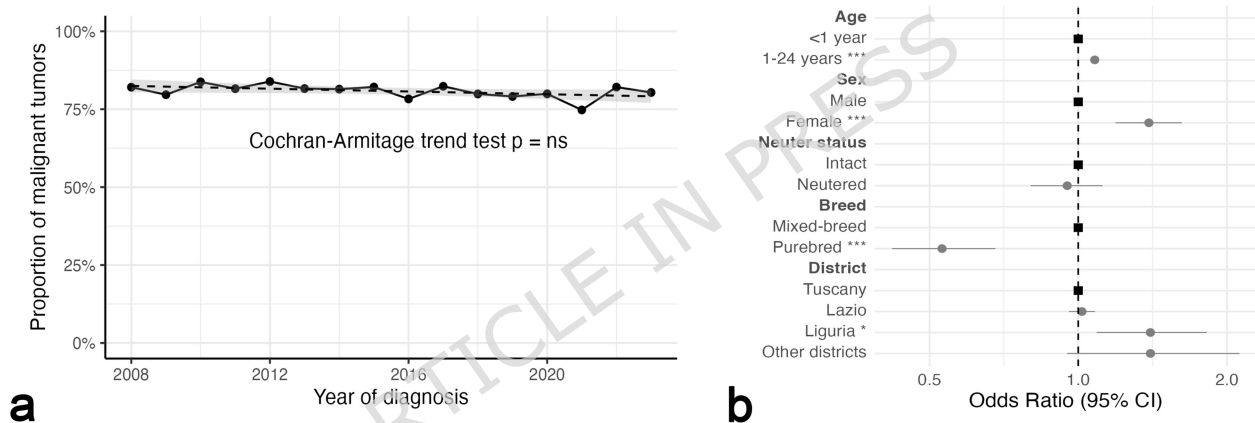


Figure 3. Temporal trend and logistic regression results (forest plot) for malignant tumor risk. (a) Relative frequency (%) of malignant tumors on the total number of tumors diagnosed by year over the study period. $p = 0.083$. (b) Odds ratios (ORs) and 95% confidence intervals (95% CI) for receiving a malignant tumor diagnosis. CI = Confidence Interval; <1 year, male, intact, Tuscany district, and mixed-breed (i.e. House Cat Shorthair/Longhair) were taken as reference (black square); * ($p < .05$), ** ($p < .01$), *** ($p < .001$).

Over the course of the years, there was no discernible upward or downward trend in the malignancy proportion (Figure 3a).

The next part will delve more deeply into the most commonly diagnosed malignant tumor types within the datasets, evaluating the effects of the aforementioned factors as well as their frequency over time.

2.3. Risk by tumor types

2.3.1. Fibrosarcoma

Out of 942 diagnosed *fibromatous neoplasms*, 98.3% (n = 926) were malignant, while benign tumors (mainly *fibroma, NOS [8810/0]*, and *dermatofibroma [8832/0]*) accounted for just 1.6% (n = 15). The following investigations focused only on fibrosarcoma, including both *fibrosarcoma, NOS [88100/3]* and feline injection-site sarcomas (FISSs) *[8800.2/3]*. The logit model showed a 5% risk increase for each year of age (OR = 1.05; 95% CI 1.03–1.07). The risk of a female cat receiving a fibrosarcoma diagnosis was significantly lower than that of a male cat (OR = 0.59; 95% CI 0.50–0.69) (Figure 4b).

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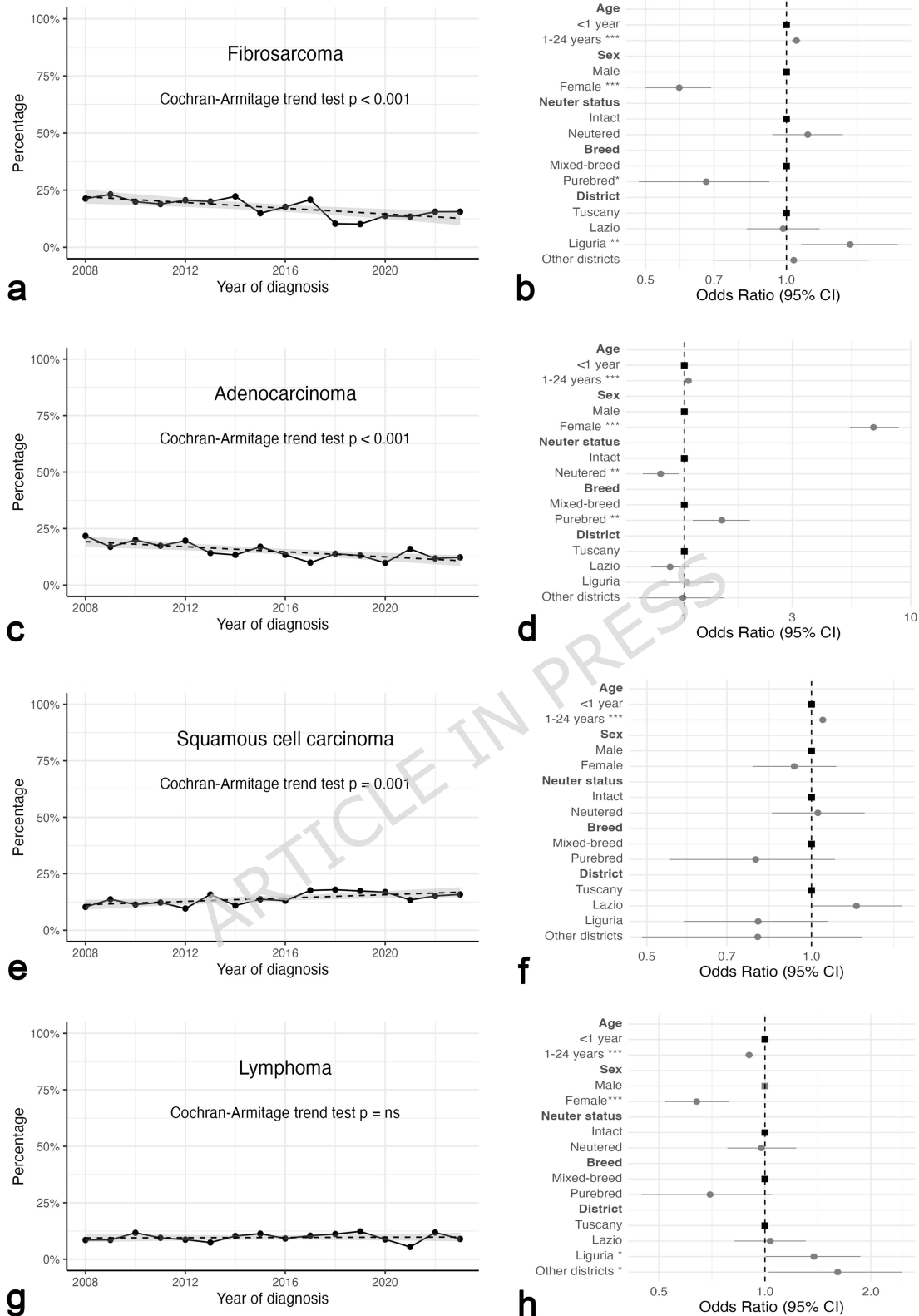


Figure 4. Temporal trend and logistic regression results (forest plot) for the four most common feline cancer types. (a-b) fibrosarcoma, (c-d) adenocarcinoma, (e-f) squamous cell carcinoma, (g-h) lymphoma. (a,c,e,g) *Relative frequency (%) of the cancer type diagnoses on the total number of tumors diagnosed by year over the study period.* ns = not

significant. (b,d,f,h) Odds ratios (ORs) and 95% confidence intervals (95% CI) for each cancer type. CI = Confidence Interval; <1 year, male, intact, Tuscany district, and mixed-breed (i.e. House Cat Shorthair/Longhair) were taken as reference (black square); * ($p < 0.05$), ** ($p < 0.01$), *** ($p < 0.001$).

Neutered and intact cats had no differential risk of fibrosarcoma diagnosis. Purebred cats had a markedly reduced risk of fibrosarcoma in comparison to HCS/HCL (OR = 0.67; 95% CI 0.48–0.92). Cases from the Liguria district showed a higher risk compared to Tuscany (OR = 1.37; 95% CI 1.08–1.73). The relative frequency of fibrosarcoma diagnoses has significantly decreased ($p < 0.001$) since the beginning of the study period (Figure 4a).

2.3.2. Adenocarcinoma

Out of 856 diagnosed *adenoma and adenocarcinomas*, 95.1% ($n = 814$) were malignant (i.e. adenocarcinomas). Benign tumors accounted for 4.9% ($n = 42$). This lower proportion of adenomas was strongly marked in mammary tumors (2.4%; $n = 15/622$), in tumors from the *respiratory system* (0%; $n = 0/35$) and *nose, ear, sinuses, larynx* (0%; $n = 0/21$). Conversely, in the *endocrine glands* (42.9%; $n = 9/21$) and *eye and adnexa* (57.1%; $n = 4/7$), the proportions of adenomas were much higher. The following assessments focused only on adenocarcinomas (Figure 4d). Older cats were more commonly affected, with a 4% risk increase for each year of age (OR = 1.04; 95% CI 1.02–1.07). Female cats had a markedly increased risk of adenocarcinoma compared to males (OR = 6.85; 95% CI 5.39–8.83). Neutered cats showed a reduced risk (OR = 0.79; 95% CI 0.66–0.94). Purebred cats had a significantly increased risk of developing adenocarcinoma in comparison to HCS/HCL (OR = 0.67; 95% CI 0.48–0.92). The relative frequency of adenocarcinoma diagnoses has significantly decreased ($p < .001$) since the beginning of the study period (Figure 4c).

2.3.3. Squamous cell carcinoma

Out of 756 diagnosed *squamous cell neoplasms*, 97.6% ($n = 738$) were malignant (i.e. squamous cell carcinoma (SCC)), while *papilloma, NOS [8050/0]* accounted for 2.4% only ($n = 18$). SCCs were the most diagnosed tumor type in both the skin and oral cavity (Figure 1). Considering the skin, 82.0% ($n = 370/451$) of SCCs affected the head, with the majority of them at the *external ear [C44.2]* (37.0%; $n = 167/451$), *skin of other and*

unspecified parts of head [C44.3] (24.8%; n = 112/451), *eyelid, NOS [C44.1]* (10.4%; n = 47/451), and *skin of occiput, nape and neck [C44.4]* (8.7%; n = 39/451).

The risk of developing SCC increased with age (OR = 1.05; 95% CI 1.02–1.07), while all the other variables didn't seem to significantly affect the SCC-risk (Figure 4f). The relative frequency of SCC diagnoses has constantly increased during the study period ($p = 0.001$), starting from 10.3% in 2008 and reaching up to 15.9% in 2023 (Figure 4e).

2.3.4. Lymphoma

Compared to other tumor diagnoses, older cats showed a reduced risk for lymphoma (OR = 0.90; 95% CI 0.88–0.93) (Figure 4h). The risk of a female cat being diagnosed with lymphoma compared with that of a male was significantly lower (OR = 0.64; 95% CI 0.52–0.79), while neuter status didn't show any significant contribution. In addition, there were no significant differences between the risk for purebred cats and HCS/HCL. Cases from Liguria (OR = 1.37; 95% CI 1.00–1.87) and other districts (OR = 1.61; 95% CI 1.02–2.45) showed a higher risk compared to Tuscany (Figure 4h). During the research period, the relative frequency of lymphoma diagnoses remained stable ($p = 0.671$), without significant increasing or decreasing trends (Figure 4g).

The output of all the logistic regressions, including confidence intervals and statistical significance for each tumor type and overall malignancy risk, is detailed in Supplementary Table 5.

3. Discussion

This study provides one of the most comprehensive assessments of risk factors for feline tumor malignancy, based on 5,289 samples collected over 15 years^{10,35,36}.

With an overall malignancy proportion of 80.6%, the findings align with previous reports^{8–11,35,37–42}, though notable exceptions—such as a recent 54.1% rate reported in South Korea—highlight potential geographic variability³⁶. The high incidence of malignancy in cats may be linked to evolutionary and dietary traits common to obligate carnivores⁴³. Age emerged as a significant risk factor, with the risk of malignancy increasing by approximately 8% per year, supporting the cumulative nature of oncogenic mutations over time^{35,36}.

Females showed higher odds of malignant tumors, likely reflecting the high prevalence of mammary neoplasms in cats^{9,11,35,36,41}. Neutering didn't affect overall malignancy risk but was associated with variations in specific tumor types. However, limitations concerning the exact timing of neutering prevent definitive conclusions, and further prospective studies focused on the influence of neutering on feline cancer development are warranted.

We included the district covariate to balance the model given the uneven number of cases across districts. Geographic origin had a modest yet statistically significant influence on malignancy risk, echoing findings in canine studies^{44,45}. While this may reflect differences in diagnostic practices rather than environmental exposures, it underscores the need for more granular, region-focused research capable of assessing potential geographic variation in risk through hypothesis-driven study designs—an approach that was beyond the scope of this exploratory analysis⁴⁶.

Unfortunately, the limited number of purebred cats prevented statistical analysis at the individual breed level, although differences in tumor distribution were noted among the five most common breeds. Nevertheless, purebred status showed a strong contribution to malignancy risk, with an almost 50% reduction compared to HCS/HCL cats. This protective role was previously highlighted by Graf et al.¹⁰. No differences in the proportion of malignancy by breed were found in other studies, albeit with smaller sample sizes^{35,36}. Unlike dogs, several feline breeds still maintain moderate genetic diversity and show lower levels of inbreeding, potentially explaining this paradoxical finding^{47,48}. As a result, exogenous factors such as viral agents and environmental exposures may play a more prominent role in shaping malignancy risk in cats.

The four most common feline malignant tumor types were specifically addressed for risk factor identification and temporal trends. Fibrosarcomas, adenocarcinomas, SCCs, and lymphomas are frequently reported as the most common malignancies in cats, albeit in varying proportions^{11,41,42,46,49,50}.

Our study identified fibrosarcoma as the most commonly diagnosed neoplasm from 2008 to 2023, accounting for 17.5% of the total cases. These data overlap with those of Graf et al.⁴⁹. An increased risk in older, male, and HCS/HCL cats was found. Prior studies have shown no breed or sex predisposition; however, a higher risk in females⁴⁹ and neutered cats⁴⁶ has been recently reported, and certain breeds were significantly less likely to develop fibrosarcoma than non-purebred cats^{49,51,52}, a result consistent with our findings. The relative frequency of fibrosarcoma has decreased by nearly 50% since 2008. A significant proportion of fibrosarcomas in our study were FISSs, and the etiopathogenesis of these tumors remains a subject of controversy. Numerous studies demonstrate the impact of the vaccine adjuvant alum, which is incorporated to stimulate the immune response when utilizing an inactivated aetiological agent, mainly rabies or FeLV vaccination^{53–55}. There are limited registers that monitor the temporal trends of tumors for comparative analysis. However, our data confirm the observations made by the Swiss Feline Cancer Registries, which have noted a similar decreasing trend since 2009, correlating it with the introduction of a non-adjuvanted FeLV vaccine⁵¹. The current situation in Italy mirrors that of Switzerland, where rabies vaccination is not mandatory. Recent introductions of non-adjuvanted and recombinant vaccines support an increased risk of fibrosarcoma development in cats following the administration of adjuvanted vaccines, particularly those containing alum⁵¹.

Feline adenocarcinomas predominantly originated from the mammary gland, which exhibited a high proportion of malignant tumors (95.2%). This finding elucidates the marked predisposition of female and intact animals to this tumor type, and corroborates the more aggressive biological behavior of these tumors in cats compared to dogs^{35,36,40,41,49,56–59}. Purebred cats showed a significantly increased risk of developing adenocarcinoma in comparison to HCS/HCL. The logit result is consistent with the tumor distribution findings, as adenocarcinoma was the most common tumor type in Persians and Siamese^{14,49,58,60,61}.

In our study, no sex or breed predispositions were observed for SCC^{49,62}. Notably, the temporal trend analysis revealed a consistent and significant increase in SCC diagnoses. While the role of papillomavirus remains debated, chronic sunlight exposure is regarded as

the primary factor implicated in the development of cutaneous SCC^{37,63,64}. Research indicates that countries offering a complete or semi-outdoor lifestyle for cats exhibit a higher incidence of SCC^{11,37,50,65,66} compared to those with restricted UV light exposure and predominantly indoor cat populations^{36,49,52}. Southern latitudes may lead to increased exposure to ultraviolet (UV) light, which could account for the discrepancies observed in various studies^{11,36,50} and the higher occurrence reported here. In a One Health approach, the observed increase in feline SCC occurrence supports concerns regarding climate change and the global increase in UV irradiation, specifically in the Mediterranean area^{11,67}. While an improvement in the diagnosis of feline UV-induced lesions in recent years should not be ruled out, this temporal trend is noteworthy and closely aligns with the ones observed in human skin cancers^{68–70}.

Our findings on lymphoma are consistent with previously reported data, confirming that this neoplasm primarily occurs in the digestive tract^{11,41,49,71}, with an enhanced risk in males^{8,49,72,73} and relatively young individuals compared to other tumor types^{49,73,74}.

This study benefits from a multi-center design, a representative sample of feline tumors, and alignment with previous pathology- and population-based registries^{9–11,39,41,46,49}. Nevertheless, some limitations must be acknowledged. The retrospective nature of the analysis and reliance on histopathologic diagnoses, while ensuring diagnostic accuracy, may introduce selection bias, as cytologically diagnosed neoplasms were not included. Submission for histology in clinical practice is influenced by multiple factors and may affect tumor representation^{44,75}.

Conversely, the adoption of Vet-ICD-O represents a valuable asset for standardizing data collection, inclusion criteria, and data sharing³⁴. In the absence of feline-specific codes, the use of Vet-ICD-O-canine-1 codes for tumors with similar biological and prognostic features, the creation of *de novo* codes for feline-specific entities, and the provided criteria for defining biological behavior (detailed in Supplementary Table 1) may support broader application of this system to feline oncology and promote more consistent epidemiological research.

While logistic regression offers adjusted estimates and facilitates between-group comparisons, odds ratios should not be interpreted as direct measures of incidence⁷⁶. The lack of reliable population denominators further limits external validation. In Italy, the expansion of national pet registries offers a promising avenue for improving denominator estimates. A centralized system—the Sistema Informativo Nazionale degli Animali da Compagnia (SINAC)—is currently being implemented within the Ministry of Health's

national digital database (BDN), in accordance with D. Lgs. 134/2022 and EU Regulation 2016/429. In this scenario, multicentric initiatives such as the Italian Network of Laboratories for Veterinary Oncology (NILOV), to which both research centers involved in this study are affiliated, represent an important step toward more structured and harmonized pet cancer surveillance systems in Italy and may support future population-based studies in the feline species^{45,46}.

4. Conclusion

We analyzed malignancy patterns and risk factors, confirming an age-related increase in malignancy and a higher risk in females. Unlike in dogs, purebred cats showed a lower malignancy risk than mixed breeds. While the overall proportion of malignant tumors remained stable over time, fibrosarcoma and adenocarcinoma decreased, whereas squamous cell carcinoma diagnoses increased. These findings highlight the importance of standardized, collaborative data collection and support future investigations into endogenous and environmental cancer risk factors, with implications for translational research in a One Health framework.

5. Material and methods

5.1. Data collection and processing

Data were obtained from routine diagnostic histological examinations performed between January 2008 and December 2023. The owners' informed consent and the use of anonymized data in research activities was collected by clinicians and provided along with clinical information including the species, breed, age, sex, neutering status, date of diagnosis, postal code area, individual ID, symptoms, anamnestic information, tumor staging.

The data collected by the two ACRs were extracted from their respective laboratory information management systems and processed using Microsoft Excel version 16.84 (Microsoft 2024, www.microsoft.com) and R Language and Environment for Statistical Computing studio R version 4.4.0⁷⁷, with the *dplyr* package⁷⁸. Only confirmed primary tumor diagnoses were retained, whilst metastases or recurrences were omitted. Multiple

tumors (i.e., distinct tumors with different histotypes in the same feline subject) were maintained separately and managed in accordance with the WHO ICD-O-3.1 criteria^{79,80}.

Since a tumor classification and coding system specifically developed for the feline species has not yet been published, the tumor's histological type (morphology) and anatomical localization (topography) were coded using Vet-ICD-O-canine-1³⁴. Topographic sites were grouped according to Dhein et al.⁸⁰.

For tumor morphologies, minor adaptations were applied to harmonize the canine coding system to the feline species, implemented as suggestions to handle specific tumor types. Peripheral odontogenic fibroma was considered a tumor⁸¹ and was therefore included in the group of *odontogenic tumors* [927–934], using the term and ICD-O-3.2 code *peripheral odontogenic fibroma* [9322/0]⁸⁰.

For the practical purpose to facilitate identification and data extraction in this study, two not yet officially defined codes were used. Code [8070/2.1] was used to identify cases of actinic keratosis that, according to the WHO classification⁸², show a partial overlap of pre-neoplastic changes with early in situ neoplastic features. Code [8800.2/3] was used to identify *Feline injection-site sarcomas* (FISSs), in analogy to the *sarcoma associated with Spirocerca lupi* [8800.1/3] from the Vet-ICD-O-Canine1³⁴, but were added to the group of *fibromatous neoplasms* [881-883] according to the Swiss Feline Cancer Registry^{49,51}. Mammary carcinomas with '*in situ*' tumor behavior were excluded as previously stated^{83,84}. The binary variable "malignancy" (benign "B" vs. malignant "M") was assigned to each case based on the Vet-ICD-O behaviour code^{35,44,84}. Tumors bearing the labels [/0] and [/3] were grouped as benign and malignant, respectively. Neoplasms *uncertain whether benign or malignant* [/1] and *in situ* [/2] were classified according to the scheme provided in Supplementary Table 1.

Feline breeds were classified according to the Fédération Internationale Féline⁸⁵. To avoid any confusion with the FIFe-recognized "European" (EUR) breed, the cats defined as "tabby" or "Common European" or "Domestic Shorthair/Domestic Longhair" have been classified as "House Cat Shorthair/Longhair" (HCS/HCL) (i.e., "mixed-breed", as having undocumented or unknown parentage).

5.2. Statistical analysis

Categorical data were summarized as absolute counts and percentages. Continuous data (i.e. age) were described by median and range. For the descriptive analysis, proportional

morbidity (expressed as the percentage of total tumors within each breed) was determined for the most frequently represented feline breeds. Clustering of breeds was performed with the `hclust()` function in R, based on similarities in tumor distribution patterns, without considering phylogenetic relationships, to provide an at-a-glance overview of tumor distribution across breeds. Pearson's Chi-square test and a subsequent multiple logistic regression model were used to assess the influence of the independent variables "age", "sex" (male/female), "neuter status" (intact/neutered), "district of origin" (Tuscany, Lazio, Liguria, and other districts) and "breed" (mixed-breed/purebred) on the dichotomous "malignancy" outcome, as detailed in Fonti et al. for the canine species⁴⁴. In the logistic regression model, age was included as a numeric variable (`as.numeric()`), representing the effect of each one-year increment, while all remaining covariates were modeled as categorical⁴⁴.

The logit model was applied to the four most diagnosed malignant tumors (fibrosarcomas, adenocarcinomas, SCCs, and lymphomas), too. In these models, two distinct groups were compared: those cases with the specific category of tumor, and those that were not diagnosed with the tumor of interest, with a case-case study design⁴⁴. Adjusted Odds Ratios (ORs) were therefore obtained. To ensure clarity, the words "risk" and "OR" were used interchangeably throughout the paper.

To determine if the overall malignancy proportions and the relative frequencies for the 4 most common malignant tumor types increased or decreased during the 16-year research period,

the Cochran-Armitage trend test was applied. The minimum conditions for significant differences were a 95% confidence interval (95% CI) that did not overlap 1 and a p value < 0.05. All statistical analyses were performed using R Language and Environment for Statistical Computing studio R version 4.4.0⁷⁷. Data were plotted using the *heatmap* and *ggplot2* packages^{86,87}.

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8. Declaration of competing interest

The authors of this research paper have no financial or personal interests that could have influenced this paper.

9. Data availability statement

Data and code implemented for this study are available on request.

10. Credit authorship contribution statement

N. Fonti: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. A. Carnio: Data curation, Investigation, Writing – review & editing. C. Cocumelli: Investigation, Writing – review & editing. E.S. Dhein: Data curation, Formal analysis, Methodology, Writing – review & editing. C. Eleni: Investigation, Resources, Writing – review & editing. V. Galietta: Investigation, Writing – review & editing. F. Guscelli: Conceptualization, Supervision, Writing – review & editing. A. Lachi: Formal analysis, Methodology, Validation. F. Parisi: Investigation, Writing – review & editing. A. Poli: Funding acquisition, Investigation, Supervision. P. Scaramozzino: Resources, Validation, Writing – review & editing. F. Millanta: Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – review & editing.

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12. Figure legends

Figure 1. Absolute number of the top ten most common tumor types and malignancy proportions (%) per topographical site in the 5,289 tumor cases included in the study.

Figure 2. Heat map showing the proportional morbidity (% out of the total tumors for each breed) for the 4,846 tumor cases detected in the 5 most common feline breeds. Each row sums up to 100%. The breeds are clustered according to their similarities in the tumor distribution patterns by `hclust()` function in R, regardless of their phylogenetic relationships. The total number of cases is reported in round brackets.

Figure 3. Temporal trend and logistic regression results (forest plot) for malignant tumor risk. (a) Relative frequency (%) of malignant tumors on the total number of tumors diagnosed by year over the study period. $p = 0.083$. (b) Odds ratios (ORs) and 95% confidence intervals (95% CI) for receiving a malignant tumor diagnosis. CI = Confidence Interval; <1 year, male, intact, Tuscany district, and mixed-breed (i.e. House Cat Shorthair/Longhair) were taken as reference (black square); * ($p < .05$), ** ($p < .01$), *** ($p < .001$).

Figure 4. Temporal trend and logistic regression results (forest plot) for the four most common feline cancer types. (a-b) fibrosarcoma, (c-d) adenocarcinoma, (e-f) squamous cell carcinoma, (g-h) lymphoma. (a,c,e,g) Relative frequency (%) of the cancer type diagnoses on the total number of tumors diagnosed by year over the study period. ns = not significant. (b,d,f,h) Odds ratios (ORs) and 95% confidence intervals (95% CI) for each cancer type. CI = Confidence Interval; <1 year, male, intact, Tuscany district, and mixed-breed (i.e. House Cat Shorthair/Longhair) were taken as reference (black square); * ($p < 0.05$), ** ($p < 0.01$), *** ($p < 0.001$).