



Breed predispositions and malignancy analysis for canine tumors: A multicenter histopathological retrospective study from Central Italy

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ABSTRACT

Animal Cancer Registries (ACRs) enhance our understanding of oncology by providing insights into epidemiologic and clinical trends and fostering comparative research. This study analyzed a large dataset of canine tumors, evaluating their distribution and malignancy profiles by breed, sex, neuter status, age, and district of origin. Histologically diagnosed tumors from two pathology-based ACRs in central Italy (2008–2023) were coded using Vet-ICD-O-canine-1. Logistic regression assessed the influence of variables on tumor behavior, modeled as a binary outcome (“malignant” vs “benign”). Of 26,218 tumors, 41.6 % were benign and 58.4 % malignant. Malignancy risk increased by 8 % per year of age. Females had higher risk of malignancy (OR = 2.16; 95 %CI 2.04–2.29). Neuter status didn't affect malignancy risk (OR = 1.02; 95 %CI 0.96–1.09) but influenced risk for specific tumor groups. Highest malignancy risk was in Dogo Argentinos (OR = 2.18; 95 %CI 1.49–3.25), Rottweilers (OR = 2.00; 95 %CI 1.56–2.57), Pugs (OR = 1.99; 95 %CI 1.38–2.92), and Doberman Pinschers (OR = 1.79; 95 %CI 1.35–2.40); lowest in West Highland White Terriers (OR = 0.54; 95 %CI 0.38–0.76), Siberian Huskies (OR = 0.66; 95 %CI 0.49–0.90), Cocker Spaniels (OR = 0.69; 95 %CI 0.58–0.83), and Poodles (OR = 0.72; 95 %CI 0.60–0.87). Potential new predispositions emerged in Cane Corsos (lymphomas, basal cell tumors, histiocytic tumors) and Maremma Sheepdogs (odontogenic, adnexal, and skin appendage neoplasms). This study confirms known patterns, reveals novel risk factors, and highlights the importance of multicenter collaboration in identifying high-risk oncology patients.

1. Introduction

Cancer poses a significant threat to global public health, with millions of new cases diagnosed annually in both humans and animals (Schiffman and Breen, 2015; Bray et al., 2024). The life expectancy of companion pet dogs in developed countries has increased significantly since the late 20th century, leading to a rise in age-related diseases (Cozzi et al., 2017; Sarver et al., 2022). Cancer is the leading cause of death in adult dogs, accounting for up to 34 % of all deaths (Adams et al., 2010; Fleming et al., 2011; Roccaro et al., 2024). Neoplastic diseases in dogs have a wide phenotypic and genetic variability among individuals of different breeds (Dobson, 2013). In fact, canine breeds can be

considered as genetic clusters, providing genetic population information for studies on incompletely understood genetic disease predisposition (Dobson, 2013; Marsden et al., 2016; Comazzi et al., 2018). In addition, canine cancer data can provide an innovative animal model for studying cancer in the comparative oncology field, as several canine malignancies closely resemble human counterparts from various perspectives (Khanna et al., 2006; Schiffman and Breen, 2015; Gardner et al., 2016; Oh and Cho, 2023).

The Global Initiative for Veterinary Cancer Surveillance (GIVCS) aims to standardize and guide veterinary cancer registries worldwide (Pinello et al., 2020). The use of shared and up-to-date tumor classifications and coding systems is pivotal for comparing studies from

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different geographic areas as well as canine and human data in the *One Health* perspective (Pinello et al., 2020; Meuten et al., 2021; Pinello et al., 2022a). However, unlike human cancer registries, animal cancer registries (ACRs) have historically been fragmented and based on non-mandatory participation (Brønden et al., 2007; Nødtvedt et al., 2012; O'Neill et al., 2014). For instance, ACRs with limited spatial and temporal scopes have been realized since the 1980s in Italy (Merlo et al., 2008; Vascellari et al., 2009; Baioni et al., 2017; Manuali et al., 2019; De Biase et al., 2023; Di Teodoro et al., 2024), and only in recent years the Network of Italian Laboratories for Veterinary Oncology (NILOV) has started to collect epidemiological data at the national level (Crescio et al., 2022), but still with some constraints on their potential use for epidemiological studies (e.g., the lack of data on the population at risk).

While population-based ACRs are primarily concerned with tumor incidence rates (IRs) (Dorn et al., 1968a, 1968b; MacVean et al., 1978; Dobson et al., 2002; Merlo et al., 2008; Vascellari et al., 2009; Komazawa et al., 2016; Baioni et al., 2017; Graf et al., 2018; Dhein et al., 2024), other pathology-based ACRs, which do not account for the population at risk, usually employ other effect size measures of cancer risk, including odds ratios (ORs), proportional morbidity ratios (PMRs), or standardized morbidity ratios (SMRs) (Richards et al., 2001; Brønden et al., 2010; Rodríguez et al., 2021; Pinello et al., 2022b, 2022c; Aupperle-Lellbach et al., 2022; Crescio et al., 2022; Di Teodoro et al., 2024). Among these studies, few have conducted aggregated data analyses of the distribution of tumor biological behavior (i.e., malignancy) across breeds and other risk factors (Komazawa et al., 2016; Tompkins et al., 2020; Pinello et al., 2022c; Śmiech et al., 2023). This type of investigation (i.e., malignancy analysis) represents a useful tool for identifying high-risk patients and providing evidence-based cancer screening, in the absence of population-at-risk data (Pinello et al., 2022c). Moreover, no inferential statistics have been published to date on the canine Italian population at the level of the individual breed.

The aim of this study was to characterize a large set of histologically diagnosed canine tumors from central Italy and to analyze their malignancy profile and tumor type distribution by individual breed, sex, neuter status, age, and district of origin.

2. Material and methods

2.1. Data collection

This retrospective multicenter cross-sectional study includes confirmed canine tumor diagnoses collected from January 2008 to December 2023 by two pathology-based Animal Cancer Registries (ACRs) located in central Italy. The ACRs were the University of Pisa (UNIPI) ACR of the Department of Veterinary Sciences and the Animal Tumor Registry of the Lazio region, located in Rome, Italy. All data were derived from routine histological examinations of formalin-fixed tissue samples.

Submitting clinicians collected owners' informed consent for privacy and the use of anonymized data in research activities. Each diagnostic record ideally included: species, breed, age, sex, neuter status, date of diagnosis, owner postal code area, individual ID, signs (including anamnestic information and tumor staging), tumor diagnosis, and anatomical tumor localization. Tumor cases missing one or more items in the information submitted by clinicians were not excluded. Only records with definitive primary tumor diagnoses were included. *Peripheral odontogenic fibroma* was classified as a tumor (Munday et al., 2016) and coded as [9322/0] (Dhein et al., 2024). Recurrences and metastases were eliminated, but the first primary tumor diagnosis was retained. Multiple tumors (e.g., several tumor diagnoses from the same dog) were handled as described by Dhein et al. (2024), according to World Health Organization (WHO) ICD-O-3.1 guidelines (World Health Organization, 2013).

2.2. Data processing

The Vet-ICD-O-canine-1 coding system (Pinello et al., 2022a) was used to code the tumor's histological type (morphology) and anatomical localization (topography). Tumor topographies were further clustered into 20 topographic groups (Table S1) (Dhein et al., 2024).

A dichotomous variable termed "malignancy" (benign "B" vs. malignant "M") was added to each diagnosis based on the Vet-ICD-O behavior code (Pinello et al., 2022b). Tumors labeled with [0] and [3] were categorized as benign and malignant, respectively. Neoplasms *uncertain whether benign or malignant* [1] and *in situ* [2], were classified according to Fonti et al. (2024) (Table S2). Such malignancy classification was based on the Dhein et al. (2024) scheme, except for *cutaneous mast cell tumor* [9740], which was considered malignant regardless of grade (Kiupel, 2016; Bellamy and Berlato, 2022; Pinello et al., 2022b), and *in situ* carcinomas arising in the *mammary gland* [C50], which were excluded due to the lack of standardized criteria for differentiating them from epitheliosis (Burrai et al., 2022).

Breeds were classified according to the Fédération Cynologique Internationale (Fédération Cynologique Internationale, 2021) and national kennel clubs. Unspecified phylogenetically close breeds were grouped as "not otherwise specified" (NOS), as previously described (Edmunds et al., 2023; Dhein et al., 2024; McMillan et al., 2024).

2.3. Statistical analysis

Data cleaning and statistical analysis were performed using Microsoft Excel version 16.84 (Microsoft 2024, www.microsoft.com) and R Language and Environment for Statistical Computing studio R version 4.4.0 (R Core Team, 2024). Continuous data (i.e., age) were described using median and range, while categorical data were summarized using counts and percentages.

The influence of the independent variables age, sex (male/female), neuter status (intact/neutered), district, and breed on the binary outcome tumor behavior (malignant/benign) was assessed using the Chi-Square test and subsequently by a multiple logistic regression model (Venables and Ripley, 2013). After removing rows with missing values, we controlled the probability of malignancy in the logistic regression by using the predictors age, sex, neuter status, district, and breed. We chose the better model using the Akaike information criterion, following a step-wise procedure. Odds ratios (ORs) and 95 % confidence intervals (95 % CI) were provided (*confint(glm)* function of R). The same logit model was applied to the 15 most common tumor groups identified in our study from the Vet-ICD-O morphology coding system (including both benign and malignant tumors), to further explore the results of the malignancy analysis (e.g., *mast cell neoplasms* [974] vs. all the other tumor diagnoses as a binary outcome) (Aupperle-Lellbach et al., 2022). The age was modeled as numeric, and all the other covariates as categorical variables. From a geographic perspective, the districts of origin of the cases from the two ACRs were classified using second-level administrative levels (Nomenclature of Territorial Units for Statistics level 2; NUTS 2, i.e., Regions) (Eurostat, 2024) by owner postal code area. The three most frequently occurring districts (i.e., Tuscany, Lazio, and Liguria) were considered. Only the 30 breeds with at least 100 cases were considered; all the remaining breeds were grouped as "other breeds". Dogs <1 year of age, male, intact, and mixed-breed dogs were set as references. The terms "risk" and OR were used interchangeably throughout the paper for the sake of clarity. When the term "risk" is used in reference to breeds, it always refers to the OR compared to mixed-breeds (Grüntzig et al., 2016; Aupperle-Lellbach et al., 2022).

We decided not to include the tumor "topography" as a covariate in the model. Tumor coding is inherently binary: the code for topography followed by a code for morphology, both forming part of the outcome, rather than being predictors (De Biase et al., 2023).

The Cochran–Armitage trend test was employed to evaluate the presence of an increasing or decreasing trend in the malignancy

proportions over the years of the study. For the *p*-value, we considered an alpha equal to 0.05 as the level of significance. Data plotting was performed using *heatmap* and *ggplot2* packages (Wickham, 2016; Kolde, 2019).

3. Results

3.1. Descriptive statistics

3.1.1. Sample size

A total of 28,799 oncological diagnoses (including metastases, recurrences, and tumors with unknown biological behavior) were collected over the course of the study period (2008–2023), comprising 17,124 cases from the ACR of Pisa and 11,675 from the ACR of Lazio. After the coding and data cleaning, 16,851 cases from the ACR of Pisa and 9373 cases from the ACR of Lazio were included, for a total of 26,224 tumor cases. For the 24,062 dogs that were included in the analysis, the number of primary tumors varied from one to ten per dog (mean = 1.09).

3.1.2. Districts of origin

As illustrated in Fig. 1, the data set mainly comprised tumor cases from the Tuscany ($n = 12,262$; 46.8 %), Lazio ($n = 9500$; 36.2 %), and Liguria ($n = 3054$; 11.6 %) districts, while the remaining samples were from “other districts” ($n = 1408$; 5.4 %).

3.1.3. Main tumor topography and morphology

The distribution of the most common tumor groups and the malignancy proportion by the topographical site are depicted in Fig. 2. The three most common tumor localizations were the skin [C44] ($n = 9497$; 36.2 %), the mammary gland [C50] ($n = 6249$; 23.8 %), and the soft tissue [C49] ($n = 3329$; 12.7 %). Adenomas and adenocarcinomas [814–838] were the most common morphologies ($n = 3143$; 12 %), followed by

complex mixed and stromal neoplasms [893–899] ($n = 2947$; 11.2 %), adnexal and skin appendage neoplasms [839–842] ($n = 2849$; 10.9 %), and mast cell neoplasms [974] ($n = 2770$; 10.6 %). Of the 3143 adenomas and adenocarcinomas, 81.9 % were in the mammary gland [C50], representing 41.2 % of all mammary tumors. The same applies to the complex and mixed stromal neoplasms, which represented the majority (46.8 %) of all mammary tumors. In this study, mast cell tumors represented 28.2 % of all skin tumors. The proportion of malignant tumors varied widely across different topographical sites. The lowest proportions were observed in the male genital organs [C60–63] (5.2 %), soft tissue (37.9 %), and female genital organs [C51–56] (39.9 %), while the highest were found in the intrathoracic organs (excluding lung) [C37–38] (98.0 %), unknown sites [C80] (98.6 %), and lymph nodes [C77] (99.0 %). The absolute number and relative frequency of all tumor topographies and morphologies included in the current study are described in Table S1.

3.1.4. Sex and neuter status

Female dogs were more represented ($n = 14,675$; 56.0 %) compared to males ($n = 10,786$; 41.1 %), and most of the tumors were observed in intact animals ($n = 18,253$; 69.6 %). This feature was consistent across both registries and was more pronounced in the male group, in which neutered dogs represented 5.6 % of the total (Table 1).

3.1.5. Age

The median age at first tumor diagnosis was 9 years (range: <1–25) in both sexes. Neutered dogs were slightly older at the time of diagnosis compared to intact ones (Table 1). In addition, malignant tumors were diagnosed in older dogs than benign tumors (median: 9.6 and 9.0 years, respectively). A detailed analysis of the influence of sex, neuter status, breed, phenotypic features, and biological tumor behavior on the age at tumor diagnosis in dogs is beyond the scope of this paper and is provided in Fonti et al. (2024).

3.1.6. Breed

In addition to 10,002 cases from mixed-breed dogs (38.1 %), 16,222 cases from 178 different breeds were included in the study population (Table S3). The most frequent breeds were the German Shepherd ($n = 1567$; 6.0 %), Boxer ($n = 1324$; 5.0 %), Labrador Retriever ($n = 1313$; 5.0 %), Setter ($n = 836$; 3.2 %), and Golden Retriever ($n = 731$; 2.8 %). Fig. 3 provides an overview of the distribution of the most common tumor morphological groups by breed, expressed as the proportion out of the total number of tumors for each breed.

3.2. Malignancy analysis

Malignant tumors accounted for 15,316 (58.4 %) of the total. Fig. 4 depicts the influence of the different variables (age, sex, neuter status, district, and breed) on the odds of having a malignant tumor, assessed by logistic regression analysis. The variables to be included as predictors in the multivariate analysis were chosen based on a univariate analysis (Table S4). The risk of malignancy showed an increase by 8 % for each year of age ($p < .001$). Females had a higher risk compared to males (OR = 2.16; 95 %CI 2.04–2.29), and the neuter status didn't affect the overall risk of developing a malignant tumor ($p = .526$). The “breed” variable represented the most significant contributor to the malignancy risk. Dogo Argentinos (OR = 2.18; 95 %CI 1.49–3.25), Rottweilers (OR = 2.00; 95 %CI 1.56–2.57), Pugs (OR = 1.99; 95 %CI 1.38–2.92), Doberman Pinschers (OR = 1.79; 95 %CI 1.35–2.40), Boxers (OR = 1.60; 95 %CI 1.41–1.83), American Staffordshire Terriers (ASTs) (OR = 1.59; 95 %CI 1.10–2.31), American Pit Bull Terriers (APBTs) (OR = 1.56; 95 %CI 1.24–1.97), Setters (OR = 1.47; 95 %CI 1.25–1.73), Brittany Spaniels (OR = 1.36; 95 %CI 1.07–1.75), Miniature Pinschers (OR = 1.24; 95 %CI 1.02–1.52), and German Shepherds (OR = 1.16; 95 %CI 1.03–1.30) had a significant increased malignancy risk. By contrast, West Highland White Terriers (WHWTs) (OR = 0.54; 95 %CI 0.38–0.76), Siberian Huskies (OR = 0.66; 95 %CI 0.49–0.90), Cocker Spaniels (OR = 0.69; 95



Fig. 1. Choropleth map depicting the Italian districts of provenance for the 26,224 tumor cases included in the study. The color gradient is proportional to case numerosity. The geographic location of both registries is also shown: A = ACR of Pisa; B = ACR of Lazio.

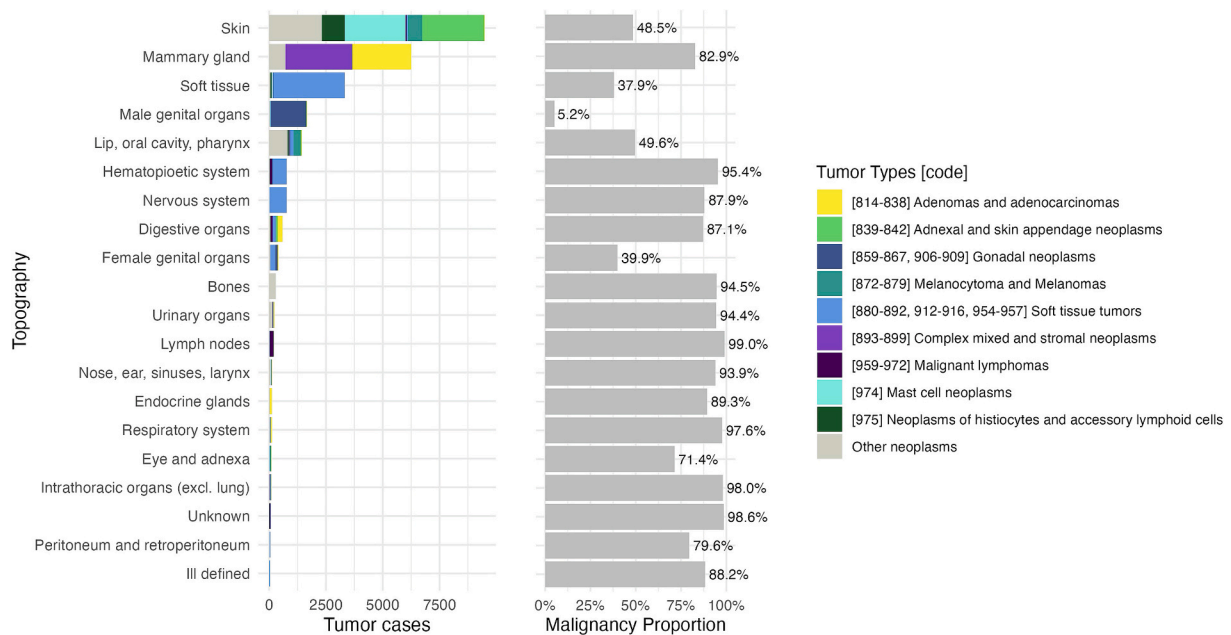


Fig. 2. The distribution (absolute number of cases) of the most common tumor groups and the malignancy proportion (% of malignant tumors out of the total) in the 20 topographies. [880] Soft tissue tumors and sarcomas, [881–884] Fibromatous and myxomatous neoplasms NOS, [885–888] Lipomatous neoplasms, [889–892] Myomatous neoplasms, [912–916] Blood vessel tumors, [954–957] Nerve sheath tumors were combined in the “[880-892, 912-916, 954-957] Soft tissue tumors” group for readability reasons.

Table 1

Absolute numbers, percentages, and median age at tumor diagnosis for 26,224 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 (range) ¹	n°	%
Male	Intact	6221	36,9 %	3084	32,9 %	9305	35,5 %	9.0 (<1–25)	4301	46,2 %
	Neutered	749	4,4 %	732	7,8 %	1481	5,6 %	9.4 (<1–19)	850	57,4 %
	Total	6970	41,4 %	3816	40,7 %	10,786	41,1 %	9.0 (<1–25)	5151	47,8 %
Female	Intact	6136	36,4 %	2812	30,0 %	8948	34,1 %	8.7 ((1–22)	5989	66,9 %
	Neutered	3065	18,2 %	2662	28,4 %	5727	21,8 %	9.4 ((1–21)	3721	65,0 %
	Total	9201	54,6 %	5474	58,4 %	14,675	56,0 %	9.0 (<1–22)	9710	66,2 %
NA		680	4,0 %	83	0,9 %	763	2,9 %	8.8 (<1–16)	455	59,6 %
Total		16,851		9373		26,224		9.0 (<1–25)	15,316	58,4 %

¹ The median age and the range (in brackets) are reported in years; n° = absolute number of cases; NA: not available. Percentages are reported out of the total.

%CI 0.58–0.83), and Poodles (OR = 0.72; 95 %CI 0.60–0.87) showed a reduced risk compared to mixed-breed dogs (Fig. 4).

No significant increasing or decreasing trend in the proportion of malignancy was observed over the 16-year study period (p = .129), with values remaining relatively stable, ranging from 52.6 % to 62.7 % (Fig. 5).

3.3. Risk by tumor types

Table 2 summarizes the breed-specific adjusted ORs and their statistical significance for increased or decreased risk across the 15 most common tumor groups (including both benign and malignant tumors), as derived from tumor-specific logistic regression models. The highest risks were observed for mast cell neoplasms in Pugs (OR = 8.73; 95 %CI 6.09–12.5) and Boxers (OR = 4.75; 95 %CI 4.09–5.51), melanocytoma and melanomas [872–879] in Rottweilers (OR = 6.19; 95 %CI 4.47–8.45), and for squamous cell neoplasms [805–808] in Dogo Argentinos (OR = 5.31; 95 %CI 3.45–7.96). Conversely, nerve sheath tumors [954–957] were particularly rare in Yorkshire Terriers (OR = 0.04; 95 %CI 0.002–0.18) and in Shih Tzus (OR = 0.10; 95 %CI 0.005–0.46), as well as lipomatous neoplasms [885–888] in Schnauzers (OR = 0.10; 95 %

CI 0.006–0.44), basal cell neoplasms [809–811] in Doberman Pinschers (OR = 0.10; 95 %CI 0.006–0.45), and blood vessel tumors [912–916] in Chihuahuas (OR = 0.10; 95 %CI 0.006–0.45).

The sex and neuter status also showed a strong contribution to specific-tumor risks. A markedly elevated risk of complex and mixed stromal neoplasms (OR = 106.99; 95 %CI 73.73–163.29) and adenomas and adenocarcinomas (OR = 8.65; 95 %CI 7.59–9.89) was observed in females, while gonadal neoplasms [859–867, 906–909] (OR = 14.29; 95 %CI 12.06–18.10) and adnexal and skin appendage neoplasms (OR = 3.90; 95 %CI 3.54–4.30) were more common in males. Intact dogs showed a higher risk of complex and mixed stromal neoplasms (OR = 2.09; 95 %CI 1.28–3.47) and adenomas and adenocarcinomas (OR = 1.43; 95 %CI 1.30–1.57), while the tumors with the highest risk in neutered dogs were mast cell neoplasms (OR = 1.74; 95 %CI 1.57–1.93) and lipomatous neoplasms (OR = 1.59; 95 %CI 1.38–1.82). The output of all the logistic regressions, including confidence intervals and statistical significance for each tumor type and overall malignancy risk, are detailed in Table S6.

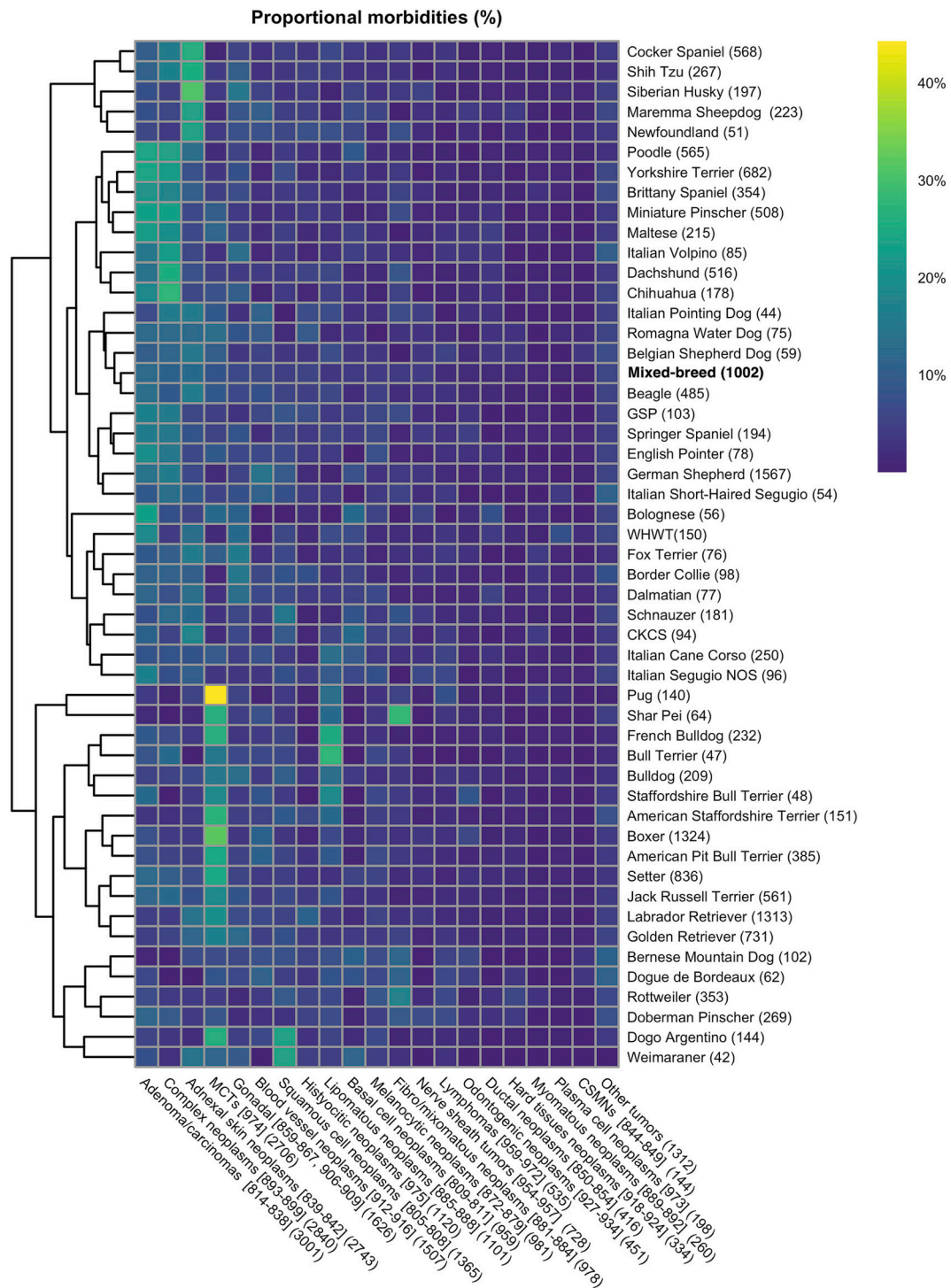


Fig. 3. Heat map showing the proportional morbidity (in %, out of the total number of tumors for each breed, indicated in parentheses after the breed name) for the most common breeds. Each row sums up to 100 %. The different breeds are clustered according to their similarities in the tumor distribution patterns by *hclust()* function in R, regardless of their phylogenetic relationships. Numbers in square brackets and in parentheses following tumor group names depict Vet-ICD-O codes and total number of cases, respectively. GSP = German Shorthaired Pointing Dog; WHWT = West Highland White Terrier; CKCS = Cavalier King Charles Spaniel; CSMNs = Cystic, mucinous and serous neoplasms; MCTs = Mast cell neoplasms.

4. Discussion

The present collaborative study represents an analysis of malignancy based on all canine tumor samples collected by two research centers located in central Italy during 2008–2023. It provides valuable information on the biological behavior of 26,224 tumors and represents the first survey of its kind in Italy and the second in Europe (Pinello et al.,

2022c). The assessment of the influence of sex, neuter status, age, breed, and district on the development of malignant versus benign tumors showed an 8 % increase per year in malignancy risk during aging. Females exhibited a higher risk, while neuter status did not significantly contribute to the overall malignancy risk. Additionally, breed emerged as a key predictor of cancer risk. To provide more detailed insights, we included breed-specific odds ratios (ORs) for malignancy as well as for

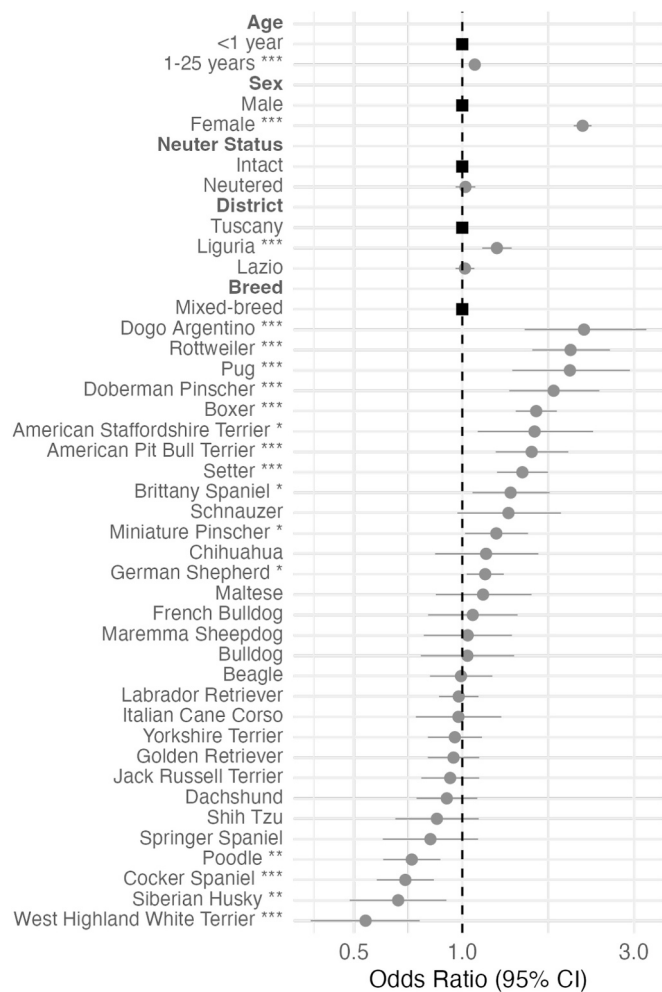


Fig. 4. Forest plot of Odds Ratios (ORs) for malignancy risk by age, sex, neuter status, district, and the top 30 most frequent breeds from the logistic regression model. CI = Confidence Interval; <1 year, male, intact, Tuscany district, and mixed-breed were taken as reference (black square); * ($p < .05$), ** ($p < .01$), *** ($p < .001$).

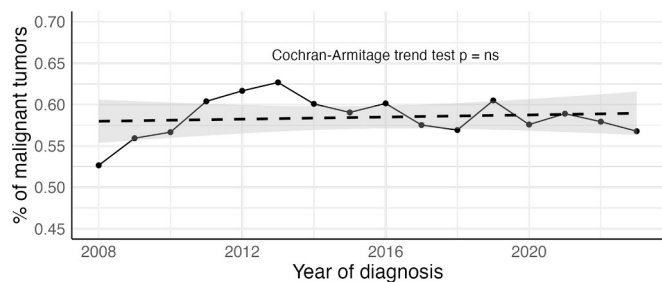


Fig. 5. Percentage of malignant tumors out of the total number of tumors by year during the study period. $p = .129$, Cochran-Armitage trend test.

the 15 most common tumor groups in our dataset.

4.1. Malignancy analysis

The proportion of malignant tumors was 58.4 %, exceeding the range reported in previous studies (28.0–48.9 %) (Brønden et al., 2010; Pinello et al., 2022c; Merlo et al., 2008; Baioni et al., 2017; Dobson et al., 2002; Grüntzig et al., 2015; Dhein et al., 2024), but similar to a Japanese and the majority of Italian studies (Vascellari et al., 2009; Komazawa et al.,

2016; Manuali et al., 2019; Crescio et al., 2022; De Biase et al., 2023; Di Teodoro et al., 2024), which reported proportions in the range from 51.0 to 64.7 %. The finding that malignancy risk increases by 8 % for each year of age is consistent with previous studies (Pinello et al., 2022c; Crescio et al., 2022; De Biase et al., 2023; Dhein et al., 2024; Aleksić-Kovačević et al., 2024) and support the notion that malignant phenotypes result from a complex process of cumulative random genetic and epigenetic mutations (Bozic and Wu, 2020). Females had higher odds compared to males, confirming data from the Vet-OncoNet (Pinello et al., 2022c) and the Swiss Canine Cancer Registry (SCCR) (Dhein et al., 2024). These findings may derive from the relatively high proportion of mammary tumors in the present and many previous European studies (Dobson et al., 2002; Merlo et al., 2008; Vascellari et al., 2009; Grüntzig et al., 2015; Manuali et al., 2019; Pinello et al., 2022c; Crescio et al., 2022; Dhein et al., 2024). Neuter status did not affect overall malignancy risk; however it seems to contribute to many histotype-specific risks. Since this variable was modeled as time-independent and the exact timing of neutering was not known, these findings should be interpreted with caution (Aupperle-Lellbach et al., 2022).

We included the district covariate for model balancing due to the unbalanced district sizes. A small but significant contribution to the risk of malignant tumors or a number of specific tumor types was found among the geographic areas. Differences in tumor distribution among Italian macro-regions have been previously reported by Crescio et al. (2022). These findings may derive from varying levels of case detection across clinical settings rather than exposure to risk factors. Nevertheless, they might warrant further epidemiological studies with a lower level of aggregation and a more precise focus on environmental factors.

Individual breeds significantly affected malignancy risk. We showed that the malignancy risk in the 30 most common breeds exhibits a huge variability, with several breeds having significantly reduced or increased risk compared to mixed-breeds. We confirmed, with a larger sample size, previously reported differences in the malignancy proportion among canine breeds (Komazawa et al., 2016; Pinello et al., 2022c). In general, our investigations confirm that smaller dogs tend to have a lower proportion of malignant tumors (Komazawa et al., 2016), except for Pugs and Miniature Pinschers. This type of study not only provides important information for clinical practice, but also suggest the need for a more breed-specific perspective in canine cancer epidemiology. Grouping and labeling different individual breeds together as “pure-bred” may elute significant tumor predispositions.

The different tumor distribution patterns among different breeds reported in Fig. 3 are useful for explaining the results of the malignancy analysis. Our data support the presence of putative differential cancer genetic drivers in different breeds as suggested by Dobson (2013). Breeds with similar tumor distribution patterns were clustered together, independently of their phylogenetic proximity. This could derive from processes of genetic homoplasy, i.e. the parallel acquisition, independent from lineage, of similar genetic features favoring the development of cancer (Parker et al., 2017), and could be a useful information for future studies aimed at identifying meaningful oncogenes and tumor suppressor genes in specific breed-related cancer types.

The following section provides an up-to-date discussion of the distribution and breed-specific risk of tumor types in Italian dogs.

4.2. Risk by tumor types

The majority of simple adenomas and adenocarcinomas [814–838] and complex mixed and stromal tumors [893–899] were associated with the mammary gland, largely in intact females, confirming previous findings (Moe, 2001; Beauvais et al., 2012; Dhein et al., 2024). Several breeds have been linked to a higher risk of mammary cancer (Edmunds et al., 2023; Engdahl et al., 2025). In the present study Brittany Spaniels and Miniature Pinschers showed an enhanced risk for developing both simple and complex mammary tumors, with an overall higher risk of malignancy compared to mixed-breed dogs. By contrast, other breeds

Table 2
Multiple adjusted Odds Ratios (ORs) by breed for the 15 most common tumor groups (morphologies) compared to mixed-breed.

Breeds	Adjusted Odds ratios for the indicated tumor groups (morphologies)														
	Adeno	Complex	Skin/adnex	MCTs	Gonadal	Blood vessel	SCT	Hystiocytic	Adipocytic	BCTs	Melanocytic	Fibro/Myxo	NSTs	Lymphoma	Odontogenic
APBT	0.63*	0.49**	0.42***	3.32***		1.76**				0.12**		1.67*			
AST	0.38*	0.15**	0.26**	3.86***											
Beagle			1.43**					1.74*		0.47*	0.41*			1.83*	
Boxer	0.68**	0.37***	0.39***	4.75***	0.51***	2.07***	0.53***		0.20***	0.32***					4.12***
Brittany Spaniel	1.70***	1.57**				0.39*									
Bulldog				1.57*	2.71***		1.96**	1.90**	0.27*						
Chihuahua	1.64*	2.28***			2.42**	0.10*			0.11*						
Cocker Spaniel		1.76***	2.78***	0.11***	0.64*	0.38***		2.23***	0.58*				0.38**	1.99**	
Dachshund		2.29***		0.57*				1.65*		0.50*	2.87***	0.43*	0.33**		
Doberman Pinscher			0.44*			0.38*				0.10*	3.60***		2.18**	3.54***	
Dogo Argentino	0.37*	0.28*	0.14**	3.40***			5.31***								
French Bulldog			0.38*	2.96***				3.28***		0.26*					
German Shepherd		1.50***	0.57***	0.15***		2.77***	2.05***	0.19***	0.26***	2.17***		0.71*			
Golden Retriever	0.42***	0.59**		2.05***	1.59***		1.38*	0.60*			1.58*		0.30**	1.67*	
Italian Cane Corso								2.59***	0.22**	2.17***				2.75**	
Jack Russell Terrier			0.61**	2.36***				1.89***			0.20**		0.26**		
Labrador Retriever	0.40***	0.43***	1.22*	2.69***					1.97***	0.47***		1.39*			
Maltese	1.87***			1.59*		0.34*			0.28*						2.32*
Maremma Sheepdog			2.18***	0.21**											2.46*
Miniature Pinscher	1.84***	1.82***		1.42*		0.36**			0.60*	0.16**	2.38***	0.27**	0.30**		
Poodle	1.89***	2.19***	1.40*	0.25***		0.23***			0.40**	2.59***	0.51*	0.48*	0.19***	0.23*	
Pug		0.08*	0.34*	8.73***		0.11*		2.73**						4.03***	
Rottweiler	0.58*	0.31***	0.41**	0.47**	0.29**	0.51*	1.72**			0.21**	6.19***	2.37***		3.53***	
Schnauzer				0.34*			3.12***		0.10*	2.49**	2.51**				
Setter			0.59***	3.83***		0.67*			0.33***	1.58**		1.49*	0.50*		
Shih Tzu		2.01***	2.55***	0.52*		0.25**							0.10*		
Siberian Husky	0.45*		2.28***												
Springer Spaniel															3.28**
WHWT	2.02**	0.43*		0.18*				3.12**							
Yorkshire Terrier	1.95***	1.93***	0.70*	0.43***	1.53*	0.18***	1.64**		0.32***			0.43**	0.04**		

Adeno = [814–838] Adenomas and adenocarcinomas; Complex = [893–899] Complex mixed and stromal neoplasms; Skin/adnex = [839–842] Adnexal and skin appendage neoplasms; MCTs = [974] Mast cell neoplasms; Gonadal = [859–867, 906–909] Gonadal neoplasms; Blood vessel = [912–916] Blood vessel tumors; SCT = [805–808] Squamous cell neoplasms; Histiocytic = [975] Neoplasms of histiocytes and accessory lymphoid cells; Adipocytic = [885–888] Lipomatous neoplasms; BCTs = [809–811] Basal cell neoplasms; Melanocytic = [872–879] Melanocytoma and Melanomas; Fibro/Myxo = [881–884] Fibromatous and myxomatous neoplasms; NSTs = [954–957] Nerve sheath tumors; Lymphoma = [959–972] Malignant lymphomas; Odontogenic = [927–934] Odontogenic tumors; APT = American Pit Bull Terrier; AST = American Staffordshire Terrier; WHWT = West Highland White Terrier; blank = not significant. * $p < .05$; ** $p < .01$; *** $p < .001$.

that showed a high risk for both tumor types exhibited a similar (Chihuahua and Yorkshire Terrier) or even reduced (Poodle) overall risk of developing a malignant tumor, in accordance with the previously described predisposition for benign mammary tumors in these breeds (Edmunds et al., 2023). In this study, a differential predisposition to mammary tumor types has been observed in Cocker Spaniels, Dachshunds, German Shepherds, and Shih Tzus (higher risk for complex tumors), and in Maltese and WHWTs (higher risk for simple tumors). A detailed distinction between the various proportions of tumor histotypes (malignant vs. benign or simple vs. complex) within mammary tumors may have clinical implications for treatment decisions in individual cases. In a previous Italian study, no differences were observed in the distribution of histological malignant categories proposed by Peña et al. (2013) and overall malignancy in mammary gland tumors by neuter status and breed (Burrai et al., 2020). However, recent findings have highlighted some differences among breeds in the Portuguese, German, English, Spanish and Polish (Aupperle-Lellbach et al., 2022; Rodríguez et al., 2022; Edmunds et al., 2023; Carvalho et al., 2023; Dolka et al., 2024) canine populations. A more detailed and in-depth analysis of the mammary gland tumor distribution in the Italian population is beyond the scope of this paper but is warranted to confirm this study's findings.

Regarding the adnexal and skin appendage neoplasms, the observed elevated risk in males can be readily attributed to the high percentage (44.4 %) of hepatoid gland tumors [8410.2], for which a pronounced sex predisposition is well documented (Pisani et al., 2006; Goldschmidt and Goldschmidt, 2016). Predisposed breeds, such as Cocker Spaniels and Siberian Huskies are consistent with the findings of previous studies (Goldschmidt and Goldschmidt, 2016; Graf et al., 2018; Kok et al., 2019), but we also identified an increased risk in Maremma Sheepdogs.

Our findings support mast cell tumors (MCTs) as the most often diagnosed malignant skin neoplasm in dogs, accounting for up to 28 % of skin tumors in our study (Kiupel, 2016; Bellamy and Berlato, 2022). The increased risk in neutered males suggest a putative, although uncertain, role for sex hormones in MCT formation (Śmiech et al., 2019). Previous research showed no clear sex predispositions (Shoop et al., 2015; Kok et al., 2019; Pierini et al., 2019; Reynolds et al., 2019; Martins et al., 2021; Rodríguez et al., 2023), although an increased risk for females was reported (Śmiech et al., 2018; Dhein et al., 2024). Neutered animals have previously been shown to have a higher risk of MCT development (White et al., 2011; Pierini et al., 2019; Reynolds et al., 2019; Oberbauer et al., 2019; Hart et al., 2020; Dhein et al., 2024). Mast cells express androgen and estrogen receptors in humans, but their role is unclear (Zierau et al., 2012). More research is needed on the influence of sex and neuter status on canine MCT development (Reynolds et al., 2019). Almost all the breed predispositions reported here are closely aligned with the literature (Villamil et al., 2011; Dobson, 2013; Mochizuki et al., 2017; Pierini et al., 2019; Śmiech et al., 2019; Kok et al., 2019; Aupperle-Lellbach et al., 2022; Rodríguez et al., 2023). A predisposition to MCT in Jack Russell Terriers has not been documented in the literature and is in disagreement with the findings presented by Shoop et al. (2015). It is therefore essential to consider any potential genetic variations within the same breed in different geographic regions, corroborating the tumor risk assessment at a local scale. Furthermore, predisposition in Dogo Argentinos has only recently been identified (Dhein et al., 2024) and is confirmed in this study.

The high occurrence of testicular tumors, among gonadal tumors, can be attributed to several factors. These may include the higher incidence of testicular than ovarian tumors (Agnew and MacLachlan, 2016; Manuali et al., 2020), the fact that testes are easier to examine clinically than ovaries, and the relatively high proportion of intact male subjects in the Italian population. Our data, comprising 1573 testicular tumors, confirm the reported elevated risk for Golden Retrievers (Nødtvedt et al., 2011; Manuali et al., 2020; Aupperle-Lellbach et al., 2022) and Yorkshire Terriers (Liao et al., 2009). Additionally, we identified Bulldogs and Chihuahuas to be at a higher risk. Small or toy-sized breeds have been recognized as being at high risk of cryptorchidism, a condition

associated with testicular tumors (Hayes Jr et al., 1985; Liao et al., 2009), which may explain our findings, at least for Yorkshire Terriers and Chihuahuas.

German Shepherds, Boxers, and APBTs showed the highest risk for blood vessel tumors, as stated by other authors (Carnio et al., 2020; Aupperle-Lellbach et al., 2022; Estabrooks et al., 2023; De Nardi et al., 2023). Of interest is the enhanced susceptibility of neutered males. Sex predisposition remains yet to be fully established (De Nardi et al., 2023), but this finding confirms the higher prevalence in male and neutered dogs observed in Italy (Carnio et al., 2020) and in other regions of the world (Clifford et al., 2001; Schultheiss, 2004; Yamamoto et al., 2013; Grüntzig et al., 2016).

Breed predispositions to squamous cell tumors corroborate literature findings, particularly regarding the predisposition for infundibular keratinizing acanthoma in German Shepherds and for squamous cell carcinoma in Schnauzers, which displayed a three times higher risk compared to mixed-breed dogs (Goldschmidt and Goldschmidt, 2016; Graf et al., 2018; Hauck and Oblak, 2020). For these tumors, no clear sex predisposition has been confirmed in the literature. Therefore, the slightly elevated risk in neutered males should be taken with caution and confirmed by further research.

Male sex and breed predisposition to histiocytic tumors, which in our study mainly consisted of *canine cutaneous histiocytomas* [9751.1/0], were similar to previous findings in North American, Swiss, Portuguese, and Spanish dog populations (Taylor et al., 1969; Graf et al., 2018; Martins et al., 2022; Rodríguez et al., 2023). In this study, Jack Russell Terriers and Italian Cane Corsos were newly identified as predisposed breeds. German Shepherds were the only breed with a reduced OR compared to mixed breeds (Aupperle-Lellbach et al., 2022).

Our findings on lipomas confirm the reported predisposition for female spayed dogs and for Labrador Retrievers (O'Neill et al., 2018). In this study, lipomas were the most common diagnosis among soft tissue tumors although they were not very frequent (4.4 % of all tumor diagnoses). In previous reports, they have been reported as the most common diagnosis at up to 14.5 % of all diagnosed tumors (Dobson et al., 2002; Brønden et al., 2010; Graf et al., 2018; Dhein et al., 2024). An underestimation of their actual occurrence may be attributed in our study to the exclusion of cytological and clinical diagnoses. Indeed, our findings are consistent with previous studies based only on histopathological diagnoses (Aupperle-Lellbach et al., 2022).

Concerning basal cell tumors, a high risk of trichoepitheliomas and trichoblastomas have previously been reported in neutered and male dogs, respectively (Goldschmidt and Goldschmidt, 2016). A number of breeds, including Poodles, Schnauzers, Setters, and German Shepherds, have been identified as being at an increased risk of developing basal cell tumors. The Italian Cane Corso appears to be a new addition to this list (Goldschmidt and Goldschmidt, 2016; Graf et al., 2018; Kok et al., 2019; Aupperle-Lellbach et al., 2022; Dhein et al., 2024).

The breed predispositions to melanocytic tumors are similar to the ones that have been previously reported (Nishiya et al., 2016; Grüntzig et al., 2016; Aupperle-Lellbach et al., 2022; Dhein et al., 2024). Likewise, earlier studies have shown that male dogs have a higher incidence of melanoma than female dogs (Smedley et al., 2011). However, the predisposing or prognostic role of sex in melanocytic tumors is still debated (Smedley et al., 2011; Nishiya et al., 2016; Smedley et al., 2022; Polton et al., 2024; Lo Giudice et al., 2024).

There is no established sex or breed predisposition to soft tissue sarcomas (STS), while middle-aged to older, medium-sized to large dogs seem to be more commonly affected (Bray, 2016; Liptak and Christensen, 2019; Aupperle-Lellbach et al., 2022). Our findings showed no influence of sex or neuter status in fibromatous and myxomatous neoplasms. Breeds at high risk were medium to large-sized (Labrador, Setter, APBT, and Rottweiler), while small-sized breeds, with the exception of German Shepherds, were at low risk (Bray, 2016; Graf et al., 2018; Pegram et al., 2021). Conversely, a slightly higher risk for peripheral nerve tumors in females, as well as a higher risk in Doberman

Pinschers were observed for the first time in our study.

In accordance with the European Canine Lymphoma Network (Comazzi et al., 2018) and other large studies (Villamil et al., 2009; Grüntzig et al., 2016; Bennett et al., 2018; Aupperle-Lellbach et al., 2022), we found a high risk for lymphoma in Rottweilers, Beagles, Doberman Pinschers, and in males. We confirmed a higher risk in Golden Retrievers, as reported in a recent German study (Aupperle-Lellbach et al., 2022) and previously only outside of Europe (Dobson et al., 2002; Dobson, 2013; Comazzi et al., 2018). We also reported for the first time higher ORs in Italian Cane Corsos and Pugs, the latter of which had previously been reported to be at reduced risk (Bennett et al., 2018). Moreover, the high risk in Cocker Spaniels may reflect the breed's predisposition to cutaneous lymphoma (Bennett et al., 2018), for which histologic diagnosis is crucial. It is important to note that the exclusion of cytological diagnoses may result in an underrepresentation of nodal lymphomas in the current study (Aupperle-Lellbach et al., 2022).

Historically, there has been a lack of consistency in odontogenic tumor classification. We included peripheral odontogenic fibroma/fibromatous epulis of periodontal ligament origin (POF/FEPLO) to align with recent investigations (Dhein et al., 2024) and with the human WHO classification (Munday et al., 2016; World Health Organization, 2024). A limited number of large-sized epidemiological investigations on breed predispositions to this type of tumor have been published (Aupperle-Lellbach et al., 2022; Dhein et al., 2024). Our findings, which confirm an increased risk for Boxers, corroborate the dysplastic proliferative pathogenetic hypothesis due to jaw malformation in brachycephalic dogs (Fiani et al., 2011; Aupperle-Lellbach et al., 2022). Moreover, we also revealed an elevated risk for some mesocephalic breeds, including Springer Spaniels, Maremma Sheepdogs, and Maltese dogs.

4.3. Strengths and limitations of the study

The study confirmed known and unveiled novel breed predispositions. The multi-center experimental design, canine demographic features, and tumor distributions of the research sample, which align with prior pathology- and population-based ACRs, ensure good representativeness (Slater et al., 2008; Merlo et al., 2008; Vascellari et al., 2009; Baioni et al., 2017; Manuali et al., 2019; Carvelli et al., 2020; Crescio et al., 2022; De Biase et al., 2023; Di Teodoro et al., 2024). Our data support a high intact/neutered ratio in Italy, especially in male dogs. This phenomenon represents a notable exception within the European context, exhibiting pronounced divergences from the data observed in North America and numerous other European countries (Slater et al., 2008; Nødtvedt et al., 2012; Dobson, 2013; Goldschmidt and Goldschmidt, 2016; Carvelli et al., 2020; Anderson et al., 2023). In addition, dog owners' changing fads and strong social media influence can shape different trends of breed distributions both temporally and geographically (Ghirlanda et al., 2014). It is important to consider that epidemiological investigations may overlook many breed predispositions due to lack of National Kennel Club recognition standardizations and country-specific ban of specific dog breeds, such as APBTs and Dogo Argentinos (Kogan et al., 2019). Similarly, this limitation may affect autochthonous breeds with limited international distribution, such as Italian Cane Corsos or Maremma Sheepdogs. Systematic cancer surveys across different regions are therefore essential to address existing gaps and accurately capture geographic and temporal trends.

We acknowledge that the retrospective nature of the study and the experimental design based on histopathologic diagnoses may be a limitation of this study. Cytological diagnosis of neoplasia has been omitted to ensure higher diagnostic reliability, although this may lead to selection bias as described above (Aupperle-Lellbach et al., 2022; Edmunds et al., 2023). Clinical decisions regarding histological submission in dogs are influenced by various factors. Severe disease and advanced age may result in euthanasia or palliative care, while some tumor types may be more likely to be sent for histology (e.g. mammary tumors in intact

female dogs) based on previously known risk or due to ease of detection (e.g. skin tumors). Socioeconomic status of the owners could also shape any ACR dataset, due to the cost of surgery procedures (Munafò et al., 2018; Edmunds et al., 2023). Thus, all these factors should be considered when comparing cancer distribution between different geographic areas (Nødtvedt et al., 2012; O'Neill et al., 2014). In this perspective, the adoption of Vet-ICD-O-canine-1 is an asset in terms of standardization of data collection, inclusion criteria, and data sharing (Pinello et al., 2022a).

In the absence of suitable denominators, relative measures of occurrence are widely used in exploratory investigations. Logistic regression allows the ORs to be adjusted for several covariates, which serves as a proxy of relative risk and facilitates comparison with other studies. However, ORs compare the relative presence of a specific type of tumor between groups and preclude full external validation of the findings (dos Santos Silva, 1999).

In Italy, population-based surveys for animal cancers often exhibited low granularity and oversimplification of breed-specific data. Pathology-based registries rely on routinely collected data, often with many years of activity and large sample numbers (Rodríguez et al., 2021). Currently, the Italian Network of Laboratories for Veterinary Oncology (NILOV), to which both research centers in the present study are affiliated, represents a valuable initiative to coordinate the efforts of the various Italian diagnostic laboratories (Crescio et al., 2022). In recent years, private institutions and universities have been included in this network. According to the authors, this type of initiative may be the closest proxy for a future national population-based ACR, such as the Danish Veterinary Cancer Registry (Brønden et al., 2010) and SCCR (Grüntzig et al., 2015; Dhein et al., 2024). Such ACRs are not yet well represented worldwide and could hopefully confirm and deepen the epidemiological hypotheses provided in the present study.

5. Conclusions

This is the first study providing a comprehensive malignancy analysis of the Italian dog population. Potential novel breed-specific predispositions were identified in Italian Cane Corsos (lymphomas, basal cell neoplasms, histiocytic neoplasms), Maremma Sheepdogs (adnexal and skin appendage neoplasms, odontogenic tumors), Jack Russell Terriers (mast cell neoplasms, histiocytic neoplasms), Doberman Pinschers (nerve sheath tumors), Pugs (lymphomas), as well as Springer Spaniels and Maltese (odontogenic tumors). In conclusion, we confirmed previous findings, revealed new potential risk factors and breed predispositions, and highlighted the value of standardization and multicenter collaboration in identifying high-risk cancer patients.

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CRediT authorship contribution statement

Niccolò Fonti: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Azzurra Carnio:** Writing – review & editing, Investigation, Data curation. **Cristiano Cocumelli:** Writing – review & editing, Investigation. **Elena Sophie Dhein:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Claudia Eleni:** Writing – review & editing, Resources, Investigation. **Valentina Galiotta:** Writing – review & editing, Investigation. **Franco Guscetti:** Writing – review & editing, Supervision, Conceptualization. **Alessio Lachi:** Validation, Methodology, Formal analysis. **Francesca Parisi:** Writing – review & editing, Investigation. **Alessandro Poli:** Supervision, Investigation, Funding acquisition. **Paola Scaramozzino:** Writing – review & editing, Validation, Resources. **Francesca Millanta:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization.

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Declaration of Competing Interest

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

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Data availability

Data will be made available on request.

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