

## Epidemiological study of canine mammary tumors: age, breed, size and malignancy

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**ABSTRACT.** A retrospective study was carried out on 858 female canine patients who were attended at the Surgery Service of the Clinical Veterinary Hospital of the University of Extremadura (Spain), during a period of 5 years (2008-2012). This study aims to determine the incidence of mammary tumors in the canine species of this region together with the analysis of several epidemiological variables (breed, age, and size) and the histopathological variable tumor malignancy. Three groups of patients were considered: (I) general group including all patients (n=858), (II) oncological patients (n=376), and (III) patients with mammary tumors (n=227). Oncology represented the most common pathology for female dogs (n=376, 43.82%), with mammary tumors being the most frequent neoplasms (n=227, 60.37%). Mixed breed dogs were more likely than purebred dogs to suffer from mammary tumors, with these tumors being more frequently malignant. It was also found that large-sized patients show a greater predisposition to malignant mammary tumors. In patients with tumors, age at diagnosis was significantly associated with a higher malignancy rate. The results of the study confirm the importance of oncology in the veterinary clinic in the region. Mammary tumors represent the most frequently diagnosed neoplasia in female dogs. Old age, mixed breed and large size predispose to its development and represent risk factors for malignancy.

*Key words:* epidemiology, malignancy, dog, mammary tumor.

### INTRODUCTION

The incidence of cancer continues to increase worldwide both in humans and companion animals (Pinho *et al* 2012). Despite the seriousness of this process and the large number of studies performed, current medical research in this area continues to be hampered by the complex biology of cancer (Pinho *et al* 2012).

The studies of spontaneous neoplasia in companion animals, particularly in canine species, provides useful information in the research on comparative epidemiology, pathogenesis, and therapeutics, since dogs have a shorter lifespan and develop tumors similar to those diagnosed in humans regarding both morphological and biological behaviour (Marconato *et al* 2009). Although rodents have been used for the development of highly standardised cancer models, they are often limited to very specific aspects of spontaneous human cancer such as latency period, recurrence, and metastasis (Thamm and Dow 2009, Ranieri *et al* 2013). Canine species share a greater proportion of its genome with humans than rodents representing a powerful model to study human mammary tumors (Pinho *et al* 2012).

Mammary tumors are one of the most common neoplasms in female dogs (Rivera and von Euler 2011). These processes are very similar to those that occur in humans, although the incidence in the dog is three times higher (Moe 2001, Rivera and von Euler 2011). Daily, veterinarians assess patients with mammary tumors establishing their clinical stage, prognosis and treatment (Perez Alenza *et al* 2000). Recently, an increase in the diagnoses of malignant mammary tumors in female dogs has been observed (Salas *et al* 2015), probably linked to the increased exposure to oncogenic substances such as pyrethroids, that represent an important environmental pollution agent (Andrade *et al* 2010).

The aim of this study was to describe the incidence of mammary tumors in female dogs in the region of Extremadura, Spain, and to determine the epidemiological characteristics (age, breed and size) and their relationship with tumor incidence and malignancy.

### MATERIAL AND METHODS

#### SAMPLE DESCRIPTION

In this study 858 female dogs attended in the Surgery Service of the Clinical Veterinary Hospital of the University of Extremadura (UEx) in Spain from 2008 to 2012 were evaluated. In order to homogenise the study population and considering that, in our practice, the age at diagnosis of mammary pathology is over 5 years old; we have only included in this retrospective study female canine patients above this age. This hospital is the only referral Veterinary Hospital in Extremadura, covering a region of 41,633 km<sup>2</sup>, with a population of 1,072,884 inhabitants and a demographic density of 25.77 h/km<sup>2</sup>; attending an annual average of 3,788 patients.

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The patients included in this study were distributed into three groups according to their pathology:

Group I: includes all study patients (n=858); Group II: includes group I patients diagnosed with any type of tumor (n=376); Group III: includes group II patients diagnosed with mammary tumors (n=227).

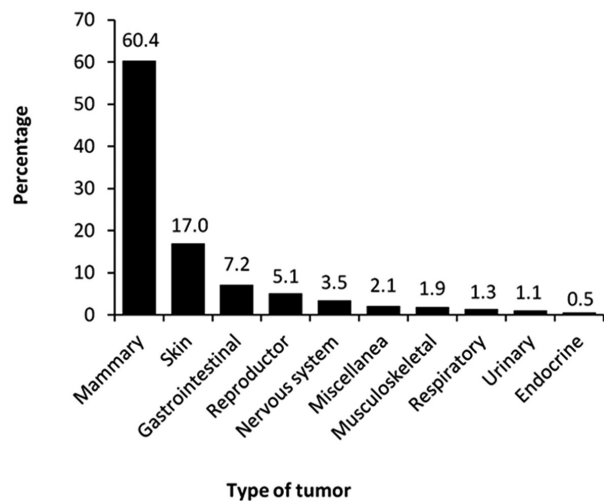
The epidemiological and clinical data were collected from their medical records. Histopathological evaluation was performed after surgery in those animals with oncologic processes. The epidemiological variables studied were breed (including the different groups of pure breeds according to the Fédération Cynologique Internationale (FCI 2013) and mixed breed), age and size (in accordance to their withers height: large size (> 50 cm) or medium-small (< 50 cm), as reported by the FCI Breeds Nomenclature (FCI 2013)). In groups II and III, the variable malignancy (benign or malignant tumors) was considered.

#### STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for Social Sciences, version 22.0 (SPSS, Chicago, USA), using descriptive analysis of variables, Shapiro Wilk and Kolmogorov-Smirnov tests were used for assessing normality. Wilcoxon-Mann-Whitney (non-parametric contrasts for two independent samples), the Pearson Chi-Square test (to compare two discrete variables) and logistic regression were applied. A *P*-value of less than 0.05 was considered significant.

#### RESULTS AND DISCUSSION

In this study, we analysed the relevance of mammary tumors in female dogs and the influence of 4 variables (breed, age, size, and tumor malignancy). Neutering status and spay age were not analysed in this study because only 11.69% of the patients were spayed at the time of diagnosis and none of them before the fourth estrous. There are not many records about the incidence of mammary tumors in dogs (Evengall *et al* 2005). Our results support the importance of oncological pathology in female dogs with a prevalence of 43.8% (95 percent of confidence interval, CI<sub>95%</sub>: 40.48-47.12%). In addition, the prevalence of mammary tumors within tumor-bearing patients (figure 1) was 60.37% (CI<sub>95%</sub>: 55.42-65.31%). These results agree with other studies in which the most common tumor type in the female dog corresponded to neoplasms of the mammary gland (Lana *et al* 2007, Merlo *et al* 2008, Choi *et al* 2016). As several authors point out, the fact that mammary tumors together with skin tumors represent the most frequent veterinary consultations might be because both locations are easily observed and accessed by both the owner and the veterinarian (Vascellari *et al* 2009, Dobson 2013, Gruntzig *et al* 2015). Thus, in this study, skin tumors are the second most frequent type of tumors diagnosed in female dogs (17.02%) as shown in figure 1.



**Figure 1.** Distribution of oncological patients (group II) according to the type of tumor.

The incidence of mammary tumors according to their histological type and stage of the patient is shown in tables 1 and 2, respectively. We observed a high impact of malignant mammary tumors (88.13%) (CI<sub>95%</sub>: 83.92%, 92.34%). Our results do not agree with those observed by other authors, who detected much lower percentages of histological malignancy, with studies showing an incidence between 30% (Salas *et al* 2015) and 50% (Gilbertson *et al* 1983). The reason for this might be that our referral hospital is the only one in the entire region of Extremadura and patients with clinical signs of malignancy are habitually attended at the hospital, whereas those patients with small tumors, with slow growth ratio and with no visible signs of malignant disease are frequently treated by local veterinarians. As reported by Olivera *et al* (2003), we cannot exclude that neutering status is related to the high percentage of malignancy observed in our study with only 11.69% of spayed females; in addition, Vascellari *et al* (2016) observed a significantly proportion of complex carcinoma in intact females. However, we cannot exclude the role of other factors such as environmental pollution (e.g. pesticides and fertilizer) as the responsible for the high incidence of malignant tumors in the region. Thus, 64.74% of our patients were classified in stages II to V (table 2).

Regarding the risk factors that favour the appearance of the different types of tumors, it was possible to observe that the onset age of the disease does not have an effect on the type of oncological process developed (mammary tumor versus other tumors; *P*=0.073). In group II (oncological patients) age is directly correlated with tumor malignancy (*P*=0.012). In mammary tumors our results confirm previous reports suggesting a remarkable increase in mammary neoplasms in females between 6 and 10 years, with an average age of 10 years. The highest peak of presentation is reached at 10 years old which is followed by a marked decrease in the incidence of tumors of the

**Table 1.** Distribution of patients with mammary tumors according to histological type.

Histological type*	n	%
Benign	21	11.86
Malignant	156	88.13
Complex carcinoma	37	23.72
Simple carcinoma	49	31.41
Mixed malignant tumors	19	12.18
Special types of carcinoma	17	10.9
Other carcinomas	34	21.79

\* Patients (n=50) without typified histological diagnosis have not been included.

**Table 2.** Distribution of patients with malignant mammary tumors according to their staging.

Staging	n	%
Stage I (T <sub>1</sub> N <sub>0</sub> M <sub>0</sub> )	55	35.26
Stage II (T <sub>2</sub> N <sub>0</sub> M <sub>0</sub> )	48	30.77
Stage III (T <sub>3</sub> N <sub>0</sub> M <sub>0</sub> )	32	20.51
Stage IV (T <sub>x</sub> N <sub>1</sub> M <sub>0</sub> )	13	8.33
Stage V (T <sub>x</sub> N <sub>x</sub> M <sub>1</sub> )	8	5.13

Tumor staging was established using the TNM system. T: size of the primary tumor and its spread into nearby tissue; N: spread of cancer to nearby lymph nodes; M: presence of metastasis to distant organs.

mammary tissue (Misdorp 2002, Evengall *et al* 2005, Lana *et al* 2007, Salas *et al* 2015). There was a trend between a more advanced age at diagnosis and malignancy of mammary tumors ( $P=0.065$ ), in agreement with Sorenmo *et al* (2009) and Vascellari *et al* (2016), who indicate that patients with benign tumors have a mean age of 8.5 years while those with malignant tumors are older (9.5 years of age), with statistically significant differences. However, these observations differ from those reported by Salas *et al* (2015), who did not observe a relationship between these variables. These discrepancies may be due to the smaller size of our sample and the low percentage of benign mammary tumors observed in our study (table 3).

The relationship between the age of onset of canine mammary tumors and the animal size was analysed in this study, observing a trend between the size of the patient and the age at diagnosis of mammary tumors ( $P=0.058$ ). This is in line with the results of Sonnenschein *et al* (1991) who suggested that animals of larger breeds have, by their very nature, a shorter lifespan, aging faster than animals of smaller breeds and, therefore, present neoplasms at an earlier age.

In this study a high incidence of tumors in purebred dogs was observed, which is likely to reflect the large number of purebreds attended at this particular Hospital. The evidence for the increased frequency of purebred dogs that suffer from mammary tumors (64.32%) is consistent with the findings of several studies (Perez Alenza 2012, Perez Alenza *et al* 2000, Evengall *et al* 2005, Vascellari *et al* 2016). However, Karayannopoulou *et al* (1989) observed the contrary and these discrepancies were attributed to the differences in the populations analysed (Perez Alenza *et al* 2000). Moreover, it was found that breed affects the type of tumor developed ( $P=0.000$ ), with approximately 1.32 times (OR) being more likely to have a mammary tumor than any other oncological process if the patients are mixed-breeds. It was also observed that breed affects tumor malignancy in group II ( $P=0.000$ ) and III ( $P=0.000$ ), concluding that the likelihood to develop a malignant tumor in mixed-breeds compared to purebred patients is approximately 1.47 and 1.76 times, respectively. There is no explanation for this observation; further studies are required to identify those factors influencing tumor malignancy in mixed-breeds compared to purebred dogs. Otherwise, age at diagnosis of any type of tumor (group II) and mammary tumors (group III) in this study did not differ between mixed-breed or purebred dogs ( $P=0.092$  and  $P=0.436$ , respectively).

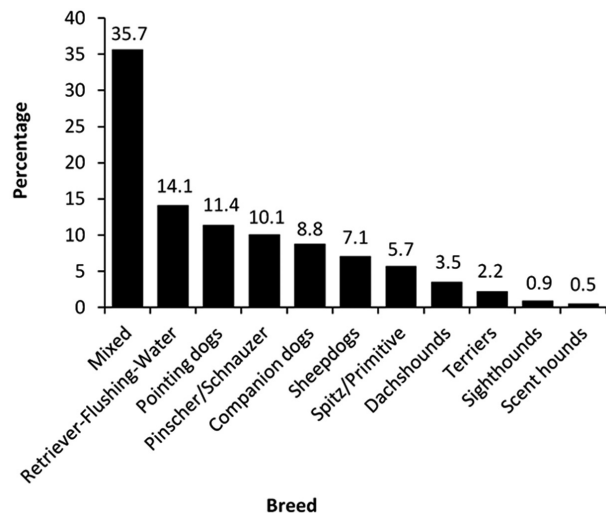
In this study, the group of breeds with the highest incidence of mammary tumors is Retrievers- Flushing Dogs-Water Dogs (breed distribution of female dogs with mammary tumors is shown in figure 2). These results are similar to those observed by Perez Alenza *et al* (2000). However, other studies describe an increased risk for Teckels

**Table 3.** Distribution of patients with benign and malignant mammary tumors according to their age, breed and size.

	Benign tumors n (%)	Malignant tumors n (%)	p value	OR
Age ≤8	14 (66.67%)	67 (42.95%)	0.065	
Age >8	7 (33.33%)	89 (57.05%)		
Pure breeds	17 (80.95%)	100 (64.10%)	0.000	1.76*
Mixed breeds	4 (19.05%)	56 (35.90%)		
Large size	3 (14.71%)	41 (26.28%)	0.000	2.34**
Medium-small	18 (85.71%)	115 (73.72%)		

\* times more likely to develop a malignant tumor in mixed-breeds.

\*\* times more likely to develop a malignant tumor in large size.



**Figure 2.** Distribution of female dogs with mammary tumors (group III) classified according to their breed.

and Molossoïdes (Moe 2001), Grazing breeds (Sorenmo *et al* 2009, Andrade *et al* 2010) and Companion Dog group (Lana *et al* 2007). Our results could be explained to a great extent by the outstanding presence of Retrievers-Flushing Dogs-Water Dogs in our region due to the fact that hunting plays an important role in the regional economy. Thus, 14.6% of all patients treated in the Surgery Service at the Veterinary Clinical Hospital of the UEx belong to this group, supporting our assertion.

On the other hand, the majority (66.1%) (CI<sub>95%</sub>: 59.94%, 72.26%) of female dogs with mammary tumors were medium-small sized; furthermore, the size of animals influenced the development of a particular type of neoplasia ( $P=0.000$ ), being 0.49 times (OR) more likely to have a mammary tumor if the female dog is large than if it is medium-small sized dog.

Finally, animal size affected the tumor malignancy in groups II and III ( $P=0.000$ ), with approximately 0.85 times (OR) more likely to have a malignant tumor (group II) and 2.34 times more likely to be a malignant mammary tumor (group III) when the patients are large sized dogs. These results agree with the findings of Itoh *et al* (2005) in mammary tumors and differ with Salas *et al* (2015) who found no association when the occurrence of malignant tumors was compared to the size category, suggesting that there might be an effect caused by the different classification system used to group patients according to their size.

It is concluded that oncological pathology is the most frequent clinical condition observed in female dogs attended at the Surgery Service of the Veterinary Clinical Hospital of the UEx and mammary tumors represent the most common neoplasia in female dogs. Mixed-breed and large size represent risk factors for malignancy. Likewise, older age should be considered as a risk factor for the development of malignant neoplasia.

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