



EPIDEMIOLOGICAL RETROSPECTIVE STUDIES OF FELINE MAMMARY GLAND TUMOURS IN BULGARIA

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Summary

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The research was performed on biopsy materials from spontaneous mammary gland tumours in cats referred for examination and treatment at the Department of Veterinary Surgery, Faculty of Veterinary Medicine, Trakia University, Stara Zagora, as well as from private veterinary clinics from all over Bulgaria for the period 2000–2010 year. One hundred and twenty tumours were examined (one hundred and two malignant and eighteen – benign). Of all investigated tumours, 75 (62.5%) affected mixed breeds and 45 (37.5%) – purebred cats. From the investigated 120 mammary gland tumours, 117 (97.5%) were found in female cats and 3 (2.5%) in males. All benign neoplasms were solitary formations. From malignant tumours, 60 (58.82%) were multiple and 42 (41.18%) – solitary formations. Based on the final histopathological diagnosis, 102 (85%) of all mammary gland tumours were determined as malignant and 18 (15%) as benign. Of all neoplasms, 115 (95.84%) were diagnosed as epithelial and 5 (4.16%) as mesenchymal. The average age of affected animals was 10 (5–15) years. The most common feline mammary gland tumours according to our study were: tubulopapillary carcinoma – 60 (50%), solid carcinoma – 15 (12.5%), fibroadenoma – 13 (10.83%), squamous cell carcinoma – 10 (8.33%) and cribriform carcinoma – 7 (5.83%).

Key words: Bulgaria, cats, mammary gland tumours, retrospective epidemiological studies

INTRODUCTION

Feline mammary gland tumours rank third after haematopoietic and skin tumours (Carpenter *et al.*, 2009; Misdorp *et al.*, 2009; Cassali *et al.*, 2019; Vail *et al.*, 2020; Mawada *et al.*, 2021; Ameer, 2023). The majority (85–90%) are malignant (Carpenter *et al.*, 2009; Gabor *et al.*, 2000; Sorenmo, 2020; Ameer, 2023). Mammary gland carcinomas affect most

commonly adult animals, have high metastatic potential and mortality (Carpenter *et al.*, 2009; Misdorp *et al.*, 2009; Vail *et al.*, 2020). It is considered that the prognosis is worse in adult cats, although data from the different studies are inconsistent (Manuali *et al.*, 2020; Ameer, 2023). In cats up to 10 years of age, there is no relationship between age, recurrence and sur-

vival (Ito *et al.*, 1996; Zappulli *et al.*, 2019). Most of the affected animals are intact females, but the disease also occurs in castrated individuals (Zappulli *et al.*, 2019; Sorenmo, 2020; Ameer, 2023). In one study, intact female cats were found to have a sevenfold higher risk of developing mammary gland tumours than ovariectomised animals. In addition, cats that are castrated before the first year have a lesser chance of developing mammary carcinomas (Vilhena *et al.*, 2019; Sorenmo, 2020; Ameer, 2023). Mammary gland tumours affect cats aged 9 months to 23 years (average age 10–12 years) (Ito *et al.*, 1996; Viste *et al.*, 2002; Carpenter *et al.*, 2009). Neoplasms are also observed in tomcats, with mean age of occurrence 12.8 years (Sorenmo, 2020; Ameer, 2023; Zhelavskiy & Dmytriv, 2023). The biological behaviour of neoplasms in both sexes is similar. Breed predispositions are found in Siamese and Oriental cats (Vilhena *et al.*, 2019; Zhelavskiy & Dmytriv, 2023; Price *et al.*, 2023). In the long-haired breeds (Persian) the prognosis is worse than in other breeds (Ameer, 2023). In cats there is no relationship between the breed and the biological behaviour of tumours (Overlay *et al.*, 2005; Viste *et al.*, 2002; Dagher *et al.*, 2019; Price *et al.*, 2023).

Macroscopically, feline mammary gland tumours are solid, nodular, single or multiple nodules, most commonly affecting the caudal mammary glands (Carpenter *et al.*, 2009; Sammarco *et al.*, 2020). Approximately 80% of animals have more than one tumour (Dagher *et al.*, 2019; Price *et al.*, 2023). According to one study, about 25% of neoplasms are ulcerated (Carpenter *et al.*, 2009). The rate of metastases ranges from 22.7% to 70.6% (Tawfik *et al.*, 2021; Price *et al.*, 2023). More than 80% of the mammary tumours

in the cat are histopathologically classified as adenocarcinomas (Sorenmo, 2020; Ameer, 2023). The most common benign lesion in this animal is fibroepithelial hyperplasia. It affects one or more glands and is often observed 1–2 weeks after oestrus or hormonal therapy as well as in pregnant animals (Torrighiani *et al.*, 2021). This condition is associated with progesterone stimulation (Thike *et al.*, 2019). In many animal species, ovarian hormones are necessary for normal mammary gland development and maturation, but few studies have examined hormonal effects of mammary carcinogenesis in cats (Nascimento & Ferreira, 2021). It is biologically plausible that the carcinogenic effects on mammary tissue are similar across species and that the same general mechanism is involved, specially sex hormones and growth hormones (Vail *et al.*, 2020). In recent years, there has been substantial progress in the molecular portraying of human breast cancer, leading to a more detailed classification beyond the histological diagnosis (Günther, 2015; Soler, 2019). Molecular studies using different approaches (e.g. genomic, transcriptomic, proteomic and metabolomic) suggest that human breast cancer represents a heterogeneous group of diseases with distinctive molecular traits influencing therapeutic response, disease-free survival, and overall survival (Hart *et al.*, 2016; Soler, 2019). Next-generation sequencing allows rapid high-resolution characterisation of potentially clinically relevant genomic and transcriptomic features of cancer (Soler, 2019). In small animal medicine, the heterogeneity of the feline and canine mammary cancers and cells composing the tumour microenvironment have been realised through the conventional histopathological examination and immunohistochemical profiling (Goldschmidt *et al.*,

2011; Soler, 2019). Nonetheless, the actual extent of diversity among mammary cancer in dogs and cats can be appreciated only through extensive molecular analyses.

The aim of the present study was to investigate the relative prevalence and distribution of feline mammary gland tumours in bioptic samples, collected and analysed between 2000–2010 in Bulgaria. Up to now, such information has not been previously published for the Bulgarian feline population.

MATERIALS AND METHODS

The research was performed on biopsy materials from spontaneous mammary tumours in cats referred for examination and treatment at the Department of Veterinary Surgery, Faculty of Veterinary Medicine, Trakia University, Stara Zagora, as well as from private veterinary clinics from all over Bulgaria for the period 2000–2010 year. One hundred and twenty tumours were examined (one hundred and two malignant and eighteen benign). Most neoplasms were observed in mixed breed patients – 75 (62.5%) followed by pure-bred cat races: 35 Siamese cats (29.16%), 5 Persian cats (4.16%), 2 Angora cats (1.66%), 2 British shorthair cats (1.66%) and one Blue russian cat (0.83%). After surgical removal, neoplastic formations were fixed in 10 % neutral formaldehyde and routinely processed. Where necessary, the final diagnosis was established using histochemistry and immunohistochemistry. Finally, all neoplasms were classified according to the WHO International Histological Classification of Tumors in Domestic Animals (Misdorp *et al.*, 1999) supplemented by Histologic Classification of Feline Mammary Gland Neoplasm

(Meuten, 2017). In the presence of metastases, they were verified morphologically.

RESULTS

For the period 2000–2010 120 cats with mammary gland tumours were registered at the Department of General and Clinical Pathology, Stara Zagora. In the follow-up, the distribution of neoplasms by year showed a tendency towards gradual increase, as most neoplasms were diagnosed during the last year of the research period (Fig. 1). From the investigated 120 mammary gland tumours, 117 (97.5%) were found in female cats and 3 (2.5%) in males.

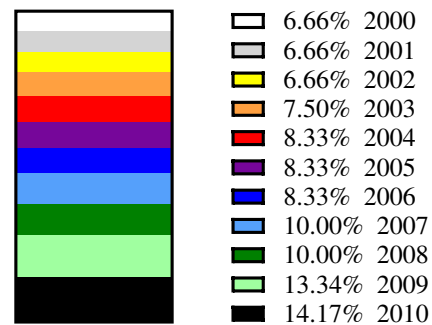


Fig. 1. Distribution and prevalence of feline mammary gland tumours.

The average age of affected animals was 10 (5–15) years. The mean age of patients with benign neoplasms was 9 (4–12) years, and with malignant tumours: 11 (5–15) years. Most neoplasms occurred in animals aged 8–12 years: 90 (75%), followed by both those aged 0–7 years: 15 (12.5%), and ≥ 12 years: 15 (12.5%). Most benign tumours were observed in animals aged 8–12 years: 10 (55.55%), followed by those 0–7 years of age: 5 (27.78%) and older than 12 years:

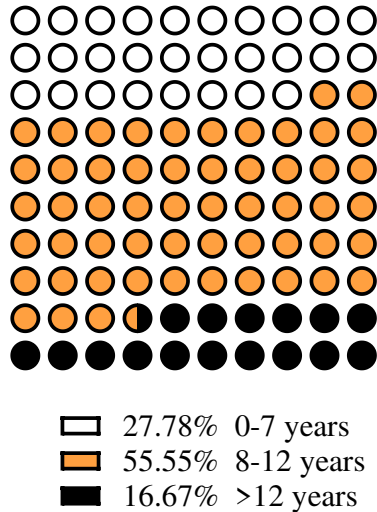


Fig. 2. Distribution of benign tumours according to the age.

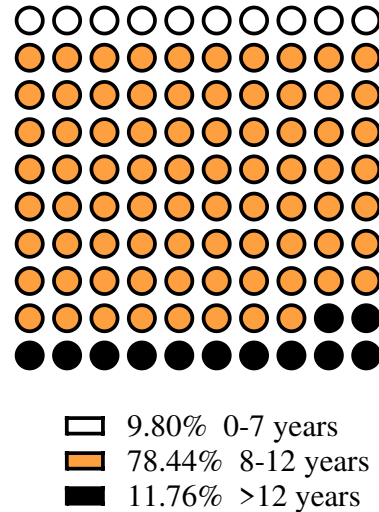


Fig. 3. Distribution of malignant tumours according to the age.

3 (16.67%) (Fig. 2). The majority of malignant tumours occurred in animals in the age range 8–12 years – 80 (78.44%), followed by those \geq 12 years – 12. (11.76%) and under 7 years – 10 (9.80%) (Fig. 3).

All benign neoplasms were solitary formations. From malignant tumours, 60 (58.82%) were multiple and 42 (41.18%) solitary. Twelve types of tumours were identified in the study, of which 2 benign and 10 malignant. Based on the final histopathological diagnosis, 102 (85%) of all mammary tumours were determined as malignant and 18 (15%) as benign. Of all neoplasms, 115 (95.84%) were diagnosed as epithelial and 5 (4.16%) as mesenchymal.

The distribution of feline mammary gland tumours in our study was as followed: tubulopapillary carcinoma: 60 (50%), solid carcinoma: 15 (12.5%), fibroadenoma: 13, (Fig. 4), squamous cell carcinoma: 10 (8.3%) (Fig. 5), cribriform carcinoma: 7 (5.83%), adenoma: 5 (4.16%), carcinoma *in situ*: 1 (0.83%),

anaplastic carcinoma: 1 (0.83%), mucinous carcinoma: 1 (0.83%), spindle cell carcinoma: 1 (0.83%) and inflammatory carcinoma: 1 (0.83%). From mesenchymal neoplasms, only 5 fibrosarcomas (4.16%) were diagnosed (Fig. 6).

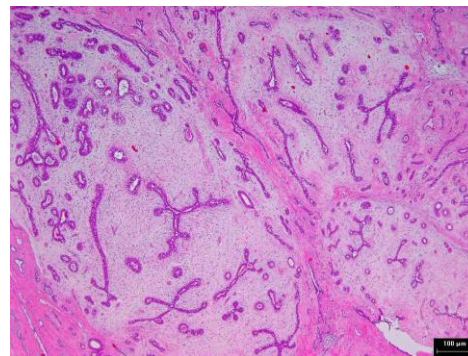


Fig. 4. Fibroadenoma. H/E staining. Bar=100 μ m.

The most common feline mammary gland tumours according to our study were: tubulopapillary carcinomas – 60 (50%), solid carcinomas – 15 (12.5%),

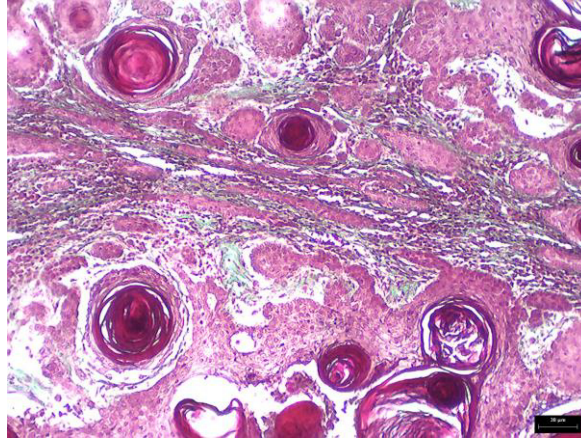


Fig. 5. Squamous cell carcinoma. Masson-trichrome-Goldner staining. Bar=30 μ m.

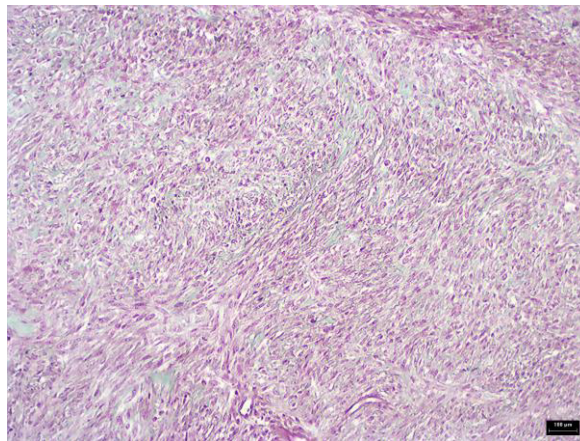


Fig. 6. Fibrosarcoma. Masson-trichrome-Goldner staining. Bar=100 μ m.

fibroadenomas – 13 (10.83%), squamous cell carcinomas – 10 (8.33%) and cribriform carcinomas – 7 (5.83%).

DISCUSSION

The results of our study (2000–2010) showed that mammary gland tumours were one of the commonest neoplasms in the cat. Of all tumours registered during the research period in this animal species, mammary gland neoplasms ranked third, followed by tumours of the haematopoiet-

ic system and the skin. These results are in line with the studies of other authors working on the problem (Carpenter *et al.*, 2009; Manuali *et al.*, 2020; Ameer, 2023).

Tracking the incidence of feline mammary gland tumours during the research period, a gradual increase over the years was established, with the highest number during the last year of the study. This trend has been observed in a number of research studies as well and could be explained by the increase in the number of cats in the country and environmental pol-

lution (Carpenter *et al.*, 2009; Manuali *et al.*, 2020; Ameer, 2023). Tsvetkov's dissertation (Tsvetkov, 1998) investigated the increase in carcinogenic factors in Bulgaria since 1960, which according to the author correlated positively with the registered oncological diseases in the dog. It is no secret that harmful environmental factors have a positive correlation with carcinogenesis in humans and animals (Kovacevic *et al.*, 2003; Kaldrymidou, 2012; Zappulli *et al.*, 2019). In addition, the global trend to increased prevalence of neoplasms in cats is observed not only for mammary tumours, but also for all neoplasms in general (Carpenter *et al.*, 2009; Vilhena *et al.*, 2019; Manuali *et al.*, 2020; Ameer, 2023).

Obesity and an unbalanced diet have been linked to increased risk of tumours of the mammary gland (Antunes, 2014.). Nunes *et al.* (2011) found that sixteen cats (66.7%) with neoplasia were fed a mixed diet (homemade food and commercial feed), while five cats (20.8%) received only animal commercial feed, and only three cats (12.5%) ate homemade diet. An unbalanced diet with high caloric levels could predispose to an occurrence of feline mammary gland tumours in cats but the correlation between diet and mammary gland tumours needs to be clarified.

In our study, most tumours were found in mixed breed cats compared to purebred ones. According to the breed distribution, our study differs from those of other researchers which indicate that the Siamese cats were most frequently affected with mammary neoplasms (Zappulli *et al.*, 2015; Vilhena *et al.*, 2019; Manuali *et al.*, 2020). According to Dobson (2013) the breed distribution of the animal species depends on personal preferences, fashion, and last but not least on the economic capabilities of the owners.

In our opinion, Siamese cats were popular in recent years in Bulgaria, but now preferences have shifted to mixed breeds that are not fastidious and are easy to breed. At the same time, mammary gland tumours were observed in non-traditional breeds for our country (British shorthair cat, Blue russian cat).

Feline mammary gland tumours are rare in males, but in a report of 22 cases, 8 (36%) had a history of progestin administration (Skorupski *et al.*, 2005). In another study, cats repeatedly injected with medroxyprogesterone acetate for inter-cat aggression and urinary house soiling, also demonstrated development of mammary adenocarcinoma (Jacobs *et al.*, 2010). In our study the sex distribution of cats with mammary neoplasms showed a domination of females (117 cats and 3 tomcats), which did not differ from that described in the literature (Zappulli *et al.*, 2015). No differences in the biological behaviour of tumours between the two sexes was identified.

Data from a number of studies show that mammary gland tumours are observed in cats at 10–12 years of age (Ito *et al.*, 1996; Viste *et al.*, 2002; Carpenter *et al.*, 2009; Manuali *et al.*, 2020). In our study, the average age of the animals affected by neoplastic growth was 10 (5–15) years, indicating no change from the global trend. It should be noted that in the last third of the research period we observed an increase in the number of both benign and malignant mammary tumours in younger animals. Similar results were established in the studies of Tsvetkov (1998) and Sharif (2006) on canine neoplasms. Interestingly, the number of tumours was the same (15) in cats aged 0–7 and over 12 years of age. In this way, this study does not confirm the results of a report indicating that the risk of neoplastic

growth increases between 12–14 years of age. At the same time, the study shows that malignant tumours in cats were observed in older animals – 11 (5–15) years compared to benign tumours – 9 (4–12) years, comparable to the results of other studies (Misdorp *et al.*, 1991; Carpenter *et al.*, 2009; Sorenmo *et al.*, 2020).

In our study, most of the mammary gland tumours (benign and malignant) affected the caudal mammary glands. In 70 cats (58.33%) the presence of several formations was macroscopically found and 40 malignant tumours (39.21% of the total number) were ulcerated. Similar results were found in the studies of Hayes & Mooney (1995) and Carpenter *et al.* (2009).

In this study, 102 (85%) out of 120 spontaneous feline mammary gland tumours were malignant and 18 (15%) benign. Among benign tumours, fibroadenomas prevailed. The commonest malignant tumours were tubulopapillary, followed by solid and squamous cell carcinomas. Of all neoplasms, 115 (95.83%) were epithelial and 5 (4.17%) mesenchymal. The most frequent tumours were tubulopapillary carcinomas – 60 (50% of the total). Therefore, our study is in line with the investigations of other researchers working in this field (Ito *et al.*, 1996; Viste *et al.*, 2002; Carpenter *et al.*, 2009; Manuali *et al.*, 2020; Ameer, 2023).

Based on this the retrospective study performed for a 10-year period (2000–2010), it can be concluded that mammary gland tumours are a serious problem in the feline pathology in Bulgaria. Follow-up of the neoplastic process in dynamics, would contribute to the timely diagnosis and therapy of these common diseases in the cat.

Accurate collection of information for most retrospective studies is difficult, the

methodology of study design, patients' inclusion criteria are different, the major part of such surveys are on a random basis and on a small number of subjects. With this regard, the creation of a feline mammary gland cancer registry in Bulgaria requires standardisation of epidemiological data from state and private diagnostic laboratories. We believe that these efforts are not a waste of time.

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