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Canine Mammary Tumors - Breed, Age and Malignant Characteristics as Risk Factors

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ABSTRACT

***Background*:** Canine mammary tumor (CMT) is a benign or malignant neoplasm originating from epithelium, myoepithelium and/or mesenchymal cells of the mammary gland. CMTs are the most often diagnosed neoplasia and age, breed, tumor characterizations as risk factors are important in CMTs. Canine mammary tumors are mostly in the malignant form, not in the benign features. There is a connection between the characters and localizations of the CMT and it frequently occurred in the 3rd, 4th and 5th lobes. These mammary lobes have more malignant characteristics than those in the other lobes, and there is no difference in terms of localization in the right and left lobes This study aimed to identify the variety and the differences occurring of breed, age and tumor characteristics in canine mammary tumors in recent years.
***Materials, Methods & Results*:** A total of 165 mammary tumors from 64 bitches were collected and investigated morphologically and histopathologically. The tumors were usually elastic or hard in consistency. The cut surfaces were homogeneous or lobular in appearance and gray-white in color. Most tumors were hard and difficult to cut, so had gray-white bone-like areas on the cut section the histopathological examination of tumors; benign mixed tumor (n = 7), carcinoma *in situ* (n = 9), simple carcinoma (n = 22), comedocarcinoma (n = 1), mucinous carcinoma (n = 1), carcinosarcoma (n = 114), squamous cell cancer (n = 4), basal cell cancer (n = 1), lipoma (n = 5), fibrosarcoma (n = 1) were diagnosed The formation of CMTs especially malignant tumors was mostly in the 9-12 age range (45.31%). According to the breed of other tumors were distributed as follows: Boxer (n = 15), mongrel (n = 9), German Shepherd (n = 7), Cocker Spaniel (n = 6), Poodle (n = 5), Kangal (n = 4), Rottweiler (n = 2) and Golden Retriever (n = 2), unknown breed (n = 11), Pekingese, Russian Poodle and Labrador retriever (n = 1 each). Half of the cases (50%) were Terrier, and it is followed by the mongrel dogs (12.5%). Malignant CMTs were detected in 95% of Terriers (95/101), while 100% were detected in Cocker Spaniel and Mongrel breeds. Although multiple simultaneous tumors in both the right and left mammary lobes (23/64 = 35.94%), CMTs occurred in the 5th mammary lobe with a rate of 15/64 (23.44%). Benign tumors were noticed less frequently (7.2%) in all mammary tumors, while malignant tumors were much more (92.8%). Of these malignant tumors, 13.3% were simple carcinomas and 69.1% were carcinosarcomas. Out of 64 animals, 23 cases (35.94%) had multiple growths and 41 cases (64.06%) had solitary growths. Lymph node metastases were also detected in 13.16% of them; therefore, benign mixed tumors and carcinosarcomas were excluded from grading for similar reasons, and only simple carcinomas were graded. Since the number of subtypes of simple carcinomas is different from each other and few [tubular type (n = 2), tubulopapillary type (n = 1), papillary type (8) and cystic papillary type (n = 4)], there is no statistically significant difference between the gradings.
***Discussion*:** In this study, older age, terrier and mongrel breeds, and medium-sized indicate risk factors for malignancy. Likewise, the occurrence of multiple CMTs should be considered a significant risk factor for the development of malignant mammary tumors. Tumor localization and grading in dogs of various ages and breeds in CMTs were updated and examined in detail in the study.

Keywords: bitch, neoplasm, tumor type, grading scores, malignancy, myoepithelial cells, metastases, mammary lobes.

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INTRODUCTION

Canine mammary tumor (CMT) is a benign or malignant neoplasm originating from epithelium, myoepithelium and/or mesenchymal cells of the mammary gland [1,8].

There is no specific breed predisposition in CMT, but the tumors are detected more frequently in breeds used for hunting and sports, such as Pointer, English Setter, Retriever, Cocker Spaniel, Terrier and Dachshund [19,23,24].

The age factor is important in the formation of the tumor. Although the tumor is rarely observed in those younger than 2 years old, the incidence of this tumor increases together with age, especially between the ages of 6 and 15 years [3,4,8].

The size, shape, and consistency of CMTs were variable. CMTs are mostly found in the 3rd, 4th and 5th mammary lobes [15]. In the bitches, sometimes a single tumor may occur only in the mammary gland, or more than 1 tumor may develop in different mammary glands. The bitches can have malignant and benign tumors simultaneously or have a history of benign tumors and then develop a malignant tumor [19,26].

Today, the modified Bloom-Richardson system, known as Nottingham Grading System (NGS), is commonly used to grade mammary carcinomas. Tubule formation, nuclear pleomorphism and the number of mitotic figures are evaluated in this system under a light microscope. However, if the tumor has formed in more than 1 mammary lobe in an animal and their grading scores are different, the treatment protocol is determined by accepting the highest grade among them [6,22].

This study aimed to identify the variety and the differences occurring of breed, age and tumor characteristics in canine mammary tumors in recent years.

MATERIALS AND METHODS

Animals and samples

In the study, 64 mammary tumor tissues [operation (n = 61) or necropsy (n = 3) materials] sent by the Department of Obstetrics and Gynecology, were used belonging to different ages (1 to 18 years old) and various breeds of bitches (Table 1). However, a total of 165 mammary tumors from 64 bitches were collected because of the formation of multiple (more than 1) mammary tumors in different lobes in one animal.

Table 1. Distribution of mammary tumors of bitches according to ages and breeds.

Breed	Age					Total	
	1-4	5-8	9-12	13-18	Unknown	N	%
Terrier	2	4	16	9	1	32	50.00
Cocker Spaniel		-	2	-	1	3	4.69
Pekingese	-	-	1	-	-	1	1.56
Boxer	-	-	2	1	-	3	4.69
Rottweiler	-	1	-	-	-	1	1.56
Russian Poodle	-	1	-	-	-	1	1.56
Labrador Retriever	-	-	-	1	-	1	1.56
Kangal	-	2	-	-	1	3	4.69
German Shepherd	-	1	2	-	-	3	4.69
Poodle	-	-	-	1	-	1	1.56
Golden Retriever	-	2	-	-	-	2	3.13
Mongrel	1	1	5	-	1	8	12.50
Unknown	-	2	1	2	-	5	7.81
Number	3	14	29	14	4	64	-
Percentage	4.69	21.87	45.31	21.87	6.25	-	100

Macroscopic examinations

After localizations of the tumors were detected, tumors were examined in terms of weight, size, consistency, color and cut sections. In addition, inguinal lymph nodes sent with mammary tissue were examined for size, consistency, shape, color and cut section. Then, tissue samples were placed in 10% buffered formalin solution (pH 7.2-7.4) for fixation.

Microscopic examinations

After routine tissue procedures, tissues were blocked in paraffin. Sections were prepared at 5 µm thickness and were stained Hematoxylin-Eosin[1] and Periodic Acid Schiff1 methods. The simple carcinomas were graded according to Elston's modified Bloom-Richardson system [6]. All findings were evaluated under light microscopy[2] and photographed[2].

Statistical analysis

Statistically, the chi-square test and SPSS 14.01 packet program[3] (Licence number: 9869264) were used for evaluation of the tumor types according to breeds, tumor incidence between breed and age, and their distribution of tumor types in the right and left mammary lobes.

RESULTS

Macroscopic findings

The materials belonged to 64 animals and composed of total mastectomy (unilateral or bilateral) or necropsy materials. A total of 165 tumors were detected in animals because of the presence of the tumors in 1 (n = 31) or multiple mammary lobes (n = 33). In 23 animals, the tumors were scattered in both the right and left mammary lobes (Table 2).

In the left mammary lobes (n = 89), more tumors were defined than in the right mammary lobes (n = 76). Most of the tumors were in the 5th mammary lobes (n = 23 on the left, n = 25 on the right). In some cases, the tumors (n = 21 on the left, n = 19 on the right) were located between the mammary lobes. While there is no significant difference in tumor numbers in the left (n = 42) and right (n = 44) 4th and 5th mammary lobes, the specific localization was not seen in benign tumors. However, malignant tumors were mostly formed in the 3rd, 4th and 5th mammary lobes (Table 2). When more than 1 tumor was found in the mammary lobes, these tumors were noticed mostly to be malignant.

The smallest of the tumors was in the size of the pin needle head, and the largest one was 27 x 9 x 17 cm. Ulcerative areas on the skin (n = 3) were found 2 x 1 x 2 cm in size, with raised and irregular marginal edges.

The tumors were usually elastic or hard in consistency. The cut surfaces were homogeneous or lobular in appearance and gray-white in color. Most tumors were hard and difficult to cut, so had gray-white bone-like areas on the cut section. The cut surfaces of some mammary tumors were cystic and papillomatous/cauliflower-like growths were observed from the cyst wall towards the lumen, and yellowish or greenish-brown exudate was noted in some. The inguinal lymph nodes were often quite enlarged; the cut surfaces were moist, gray-white or red in color.

In this study, CMTs were frequently found in Terrier (n = 101) and most of them showed malignant features (n = 95). These malignant tumors consisted of carcinosarcoma (n = 69) and simple carcinomas (n = 16). According to the breed of other tumors were distributed as follows: Boxer (n = 15), mongrel (n = 9), German Shepherd (n = 7), Cocker Spaniel (n = 6), Poodle (n = 5), Kangal (n = 4), Rottweiler (n = 2) and Golden Retriever (n = 2), unknown breed (n = 11), Pekingese, Russian Poodle and Labrador retriever (n = 1 each) [Table 3].

Microscopic findings

In the histopathological examination of tumors; benign mixed tumor (n = 7), carcinoma *in situ* (n = 9), simple carcinoma (n = 22), comedocarcinoma (n = 1), mucinous carcinoma (n = 1), carcinosarcoma (n = 114), squamous cell cancer (n = 4), basal cell cancer (n = 1), lipoma (n = 5), fibrosarcoma (n = 1) were diagnosed (Table 3).

Simple carcinomas were typed and graded according to Elston's modified Bloom-Richardson system. According to this, tubular type (n = 2), tubulopapillary type (n = 1), papillary type (n = 8) and cystic papillary type (n = 4) were detected (Table 4).

Hemorrhagic lymphadenitis (n = 18), lymphadenitis simplex (n = 11), metastases (n = 5) and hemorrhage and/or hemosiderosis (n = 4) were noted in all inguinal lymph nodes (n = 38). Ulcer (n = 6), recurrence (n = 1), inflammation (n = 16), lymph node metastasis (n = 5) and death (n = 3) were detected in some cases. More than 1 tumor in both chains was noted in dead dogs. Inflammation, ulcer and lymph node metastases were also more common in carcinosarcoma.

Statistical findings

There was no significant difference in terms of tumor types in breeds, incidence of tumors between breed and age, and the incidence of tumor types in the right and left mammary glands ($P > 0.001$).

Table 2. Frequency of benign and malignant tumors according to localizations in the mammary lobes of bitches.

Mammary Lobes	Benign (8)		Malignant (56)		Total Tumors (64)	
	N	%	N	%	N	%
Cranial + Caudal thoracic (1st and 2nd)	2	25.00	6	10.71	8	12.50
Cranial + Caudal abdominal (3rd and 4th)	5	62.50	13	23.21	18	28.12
Inguinal (5th)	1	12.50	14	25.00	15	23.44
Various*	0	-	23	41.07	23	35.94

*Multiple simultaneous tumors in both the right and left mammary lobes.

Table 3. Distribution of mammary tumor types according to breed of bitches.

Breed	Benign		Malignant								
			Carcinoma						Sarcoma		Total
	Lipoma	Benign Mixed Tumor	*In situ* carcinoma	Comedocarcinoma	Simple carcinoma	Squamous cell carcinoma	Basal Cell Carcinoma	Mucinous carcinoma	Fibrosarcoma	Carcinosarcoma	
Terrier	2	4	8		16		1	1		69	101
Cocker Spaniel										6	6
Pekingese										1	1
Boxer	2		1		2					10	15
Rottweiler					1					1	2
Russian Poodle						1					1
Labrador Retriever		1									1
Kangal					1					3	4
German Shepherd		1								6	7
Poodle										5	5
Golden Retriever		1								1	2
Mongrel	1			1	1				1	5	9
Unknown					1	3				7	11
Total (N)	5	7	9	1	22	4	1	1	1	114	165
Percentage	3.03%	4.24%	5.45%	0.61%	13.33%	2.42%	0.61%	0.61%	0.61%	69.09%	100%

Table 4. Types and grades of simple carcinomas according to Elston's modified Bloom-Richardson system*.

Number	Type	Grade
1	Tubular	2
2	Papillary	2
3	Cystic papillary	3
4	Papillary	3
5	Tubular	1
6	Papillary	3
7	Papillary	1
8	Tubulopapillary	1
9	Cystic papillary	2
10	Papiller	3
11	Cystic papillary	1
12	Papillary	1
13	Papillary	2
14	Papillary	2
15	Cystic papillary	1

*[6] Elston C.W. 1987. Grading of invasive carcinoma of the breast. In: Anderson T.J. (Ed). *Diagnostic Histopathology of the Breast*. London: Churchill Livingstone.

DISCUSSION

CMTs are the most often diagnosed neoplasia and age, breed, tumor characterizations as risk factors are important in CMTs. While CMTs are rarely seen especially under 5 years of age, it has been reported that it increases significantly at 7-12 years of age and 75-90% of cases are seen between 6-15 years of age [5,9,10]. In addition, the age group of 9-12 years has the highest incidence rates of both benign tumors (60.99% = 111/182) and malignant tumors (39.01% = 71/182) [26]. In this study, the formation of CMTs especially malignant tumors was mostly in the 9-12 age range (45.31%). These data seem to be confirmed by our study, in full agreement with what was reported by previous studies.

In some countries, CMTs have been reported in small-bodied animals such as Shih Tzu, Yorkshire Terrier, Maltese, and Poodle [9,18]. Some researchers [14,16] have detected CMTs more frequently in small-sized animals by looking at the size of the animals without specifying the breed. Maximum cases were recorded in the Spitz (41.66%) in Udaipur/India [10], in mongrel dogs (26.7%) and Poodles (25.5%) in Brazil [4], Mongrel dogs (35.7%) and Retrievers - Flushing Dogs - Water Dog (14.1%) in Spain [14] and in Poodle in China [26]. In a study in Turkey [2], the breeds that had the most occurred by mammary tumours were Poodle, Terrier, Wolfhound and Pinscher, respectively. In all these studies, breed predisposition varies by country. In some countries [such as South Korea and USA (Alaska)], country-specific breeds are preferred, while in others, preference is made according to the characteristics of small breeds with ease of care at home or large breeds bred for hunting, sports or protective purposes. For this reason, breed predisposition in CMT cannot be specified within definite limits. Since small breed dogs that are easily fed at home are in the majority in our country, half of the cases (50%) were Terrier dogs in the present study, and it is followed by the Mongrel dogs (12.5%). Malignant CMTs are frequently appeared in Cocker Spaniel and Mongrel breeds [9]. In the study, malignant CMTs were detected in 95% of Terriers (95/101), while 100% were detected in Cocker Spaniel and Mongrel breeds. However, although this rate is high in Cocker Spaniel and Mongrel breeds, the low number of these breeds (n = 6 and n = 8) should not be ignored.

There is a connection between the characters and localizations of the CMT and it frequently occurred in the 3rd, 4th and 5th lobes. These mammary lobes have more malignant characteristics than those in the other lobes, and there is no difference in terms of localization in the right and left lobes [9,20]. In this study, more tumors were found in the left mammary chain (n = 89) than in the right mammary chain (n = 76). However, there is no significant difference between the 2 chains regarding tumor localization. Devarathnam *et al*. [5], Kumar and Parasar [10] and Nunes *et al*. [13] also reported mammary tumors in 5th mammary glands, respectively 10/36 (27.77%), 424/1511 (32%) and 16/36 (44.44%). In this study, although multiple simultaneous tumors in both the right and left mammary lobes (23/64 = 35.94%), CMTs occurred in the 5th mammary lobe with a rate of 15/64 (23.44%).

CMTs are mostly in the malignant form, not in the benign features. While Pastor *et al*. [14], showed benign (11,86%) and malignant (88.13%) features in CMTs, Atalay Vural and Aydın [2] found that 28.8% benign and 71.2% malignant features in CMT. Approximately, mixed tumors (50-65%) and carcinomas (25-40%) form the majority of these malignant tumors [14,16,20]. In the study, benign tumors were noticed less frequently (7.2%) in all mammary tumors, while malignant tumors were much more (92.8%). Of these malignant tumors, 13.3% were simple carcinomas and 69.1% were carcinosarcomas.

Out of 64 animals, 23 cases (35.94%) had multiple growths and 41 cases (64.06%) had solitary growths. Many tumors differed in size and character and showed heterogeneity. Each mammary lobe has a separate lymphatic system. In addition, since each mammary lobe has its own lymphatic system anatomically independent of the others, tumor development may be histopathologically different in each mammary gland. Because of this, both benign and malignant mammary tumors can occur in an animal, and each detected tumor is diagnosed independently of the others. In previous studies [9,21] multiple tumors were seen to occur in more than 50% in rate. Unfortunately, in this study, this rate for multiple tumors remained at 35%, showing a lower rate.

In a previous study [9], most simple carcinomas were evaluated as grade 1 or 2 and were not graded benign mixed tumors and carcinosarcomas. Complex and mixed malignant mammary tumors frequently exist in dogs, and parts containing myoepithelial proliferation or mesenchymal areas are not among the current grading criteria [16]. On the other hand, the presence or absence of myoepithelial cells has been considered important in the diagnosis, especially in complex and mixed canine mammary tumors, unlike humans [7,11,16], and these cells have been used effectively in the grading of tumors [16]. In addition to myoepithelial cells, were evaluated tubule formation, nuclear pleomorphism, and mitosis. Mixed tumors were most of the tumors examined [16]. Tumor heterogeneity increases, especially in metaplastic areas. In this study, therefore, benign mixed tumors and carcinosarcomas were excluded from grading for similar reasons, and only simple carcinomas were graded. Since the number of subtypes of simple carcinomas is different from each other and few [tubular type (n = 2), tubulopapillary type (n = 1), papillary type (8) and cystic papillary type (n = 4)], there is no statistically significant difference between the gradings. Grading of mammary tumors is very important as it informs clinicians about the treatment and prognosis of the tumor in terms of deciding whether a new operation or chemotherapy will be needed after the removal of the tumors, and whether the animal will be followed up with blood charts and radiographs throughout its life. Because it gives important information in terms of the selection of chemotherapy agents and/or other treatment alternatives that are started to be applied to animals.

Statistical analysis have shown that the risk of recurrence of malignant mammary tumors in bitches is 13 times higher than in benign ones [12]. In particular, solid carcinoma, simple carcinoma, spindle carcinoma, and carcinomas have recurred and/or metastasized to the lymph node or lungs [16,17,25]. In this study, malignant tumors (92.8%), especially carcinosarcomas (69.1%), were more common than benign tumors (7.2%). Lymph node metastases were also detected in 13.16% of them. In most cases, performing unilateral/bilateral radical mastectomy is an important factor in the low rate of metastasis. However, it should not be overlooked that in mastectomies performed in the form of chain removal, the wide operation area may cause problems in the healing process and infection from time to time.

CONCLUSION

In Turkey and even in the world, most bitches are occurred by mammary tumors at different rates. Older age, terrier and mongrel breeds, and medium-size indicate risk factors for malignancy. Likewise, the occurrence of multiple CMTs should be considered a significant risk factor for the development of malignant mammary tumors. Tumor localization and grading in bitches of various ages and breeds in CMTs were updated and examined in detail in the study.

MANUFACTURERS

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***Ethical approval*.** This research was carried out with the approval of the Ankara University Animal Experiments Local Ethics Committee (approval number: 2014-16-100).

***Declaration of interest*.** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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