

## Comparative Study of Several Cases of Human Breast Cancer and Mammary Cancer in Domestic Dogs and Cats

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A useful model for studying tumor systems, which is close to the human analogue, is very necessary for development of modern approaches and methods in cancer researches. As breast cancer is the second leading cause of cancer deaths in women, spontaneous mammary tumors in domestic animals are feasible solution for valid tumor systems model. In this study we present histological diagnosis and grading of human, canine and feline mammary tumors and evaluate their histological and biological behavior. Histological diagnosis of animal tissue samples found five cases of ductal carcinoma (n=5, 62.5%), one lobular carcinoma, one squamous cell carcinoma and one case of metaplastic carcinoma with osteosarcomatous differentiation, graded from I to III: I (n=1, 12.5%), II (n=4, 50%) and III (n=3, 37.5%). Four of the human cases were diagnosed as invasive ductal (n=2, 40%) and lobular (n=2, 40%) carcinoma, one case - metaplastic carcinoma, all scored as grade III.

*Key words:* mammary cancer in dogs and cats, breast cancer, histological grading.

### Introduction

The most common breast malignant tumors in women are epithelial ductal and lobular cancer. They invade the nearby tissues or spread on distant organs of the body. Staging of the cancer is crucial for successful treatment and most often the TNM classification is used. It is based on the primary tumor size (T) and whether it has invaded nearby tissue, if the tumor has reached regional lymph nodes (N), and its distant metastases (M) [21].

The breast cancer is the second leading cause of cancer deaths in women in Europe and the United States [8], and a useful model for studying tumor systems which is close to the human analogue is very necessary.

Like in humans, spontaneous canine and feline malignant mammary tumors represent a heterogeneous group. The prevalence of mammary tumors in dogs is about three times more often than in human females [9]. They are the second most common tumors in dogs and the third most common malignant disease in cats [3, 22].

Histological diagnosis and grading of tumors are crucial for treatment and prognosis of neoplastic diseases and are accepted in the standard clinical practice. In women, the noninvasive proliferative breast lesions such as ductal and atypical ductal hyperpla-

sia, and ductal carcinoma *in situ*, found during regular medical checks, are recognized as risk preconditions preceding the invasive cancer development and they predetermine the subsequent management decisions [1, 18, 20]. In domestic dogs and cats, however, the tumor progress is seen only when growth of the formation is obvious. In middle-aged dogs and cats malignant mammary tumors with histological and biological behavior similar to human carcinomas occur spontaneously. Because the lifespan of animals is shorter, they can be used for a histological model of malignant mammary tumors for studies on the morphology, development and metastatic pattern, mainly at regional lymph nodes, lungs and liver, as it is done in humans.

In order to predict individual prognosis and respond to therapy in early stages of breast cancer and its hormonal dependence, immunohistochemical studies of markers of proliferation, hormone receptors and specific tumor markers are used, which revealed similarities in tumor development in humans, and in dogs and cats [2, 4, 5, 6, 7, 13, 14].

In this study, we evaluated a series of operable canine, feline and human mammary carcinomas, and compared their suitability for a routine assessment of histological diagnosis and grading with prognostic value of further development of this particular subset of carcinomas.

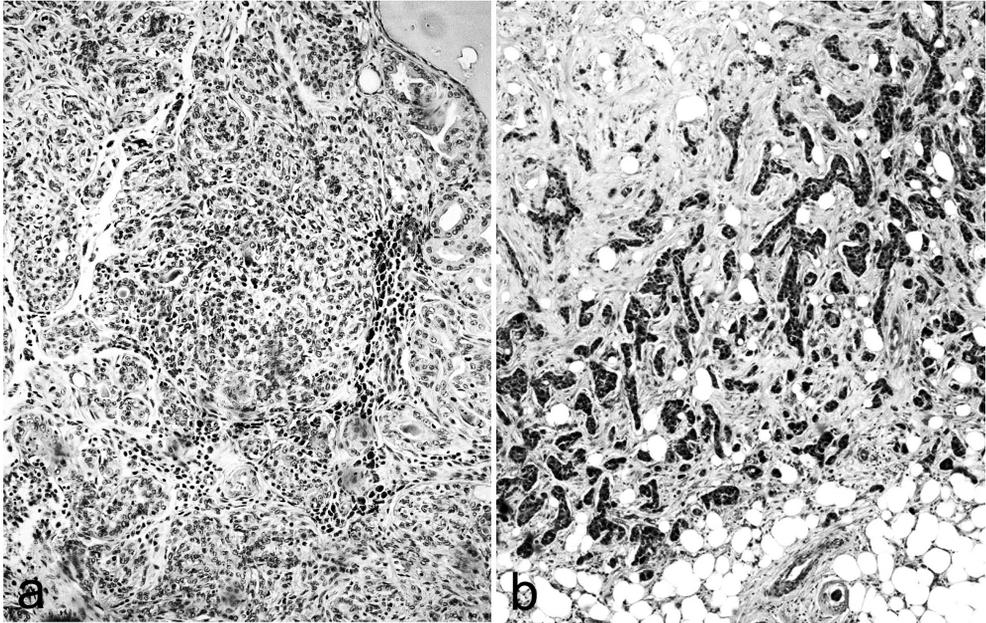
## Materials and Methods

**Patients.** Tissue samples from altered mammary glands of seven dogs and one cat, at the age between 7 and 16 years and incomplete data about their reproductive status, were compared with breast tissue excisions from five middle-aged women, diagnosed with breast cancer. The animals were not castrated before the surgical operation and some of them were sporadically treated with steroidal progestins. The animal tumor formations ranged between 0.5 and 15.6 cm in diameter and were collected mainly from the caudal mammary glands. The human tissue formations ranged between 6 and 9 cm in diameter and were accompanied by metastases in the adjacent lymph nodes.

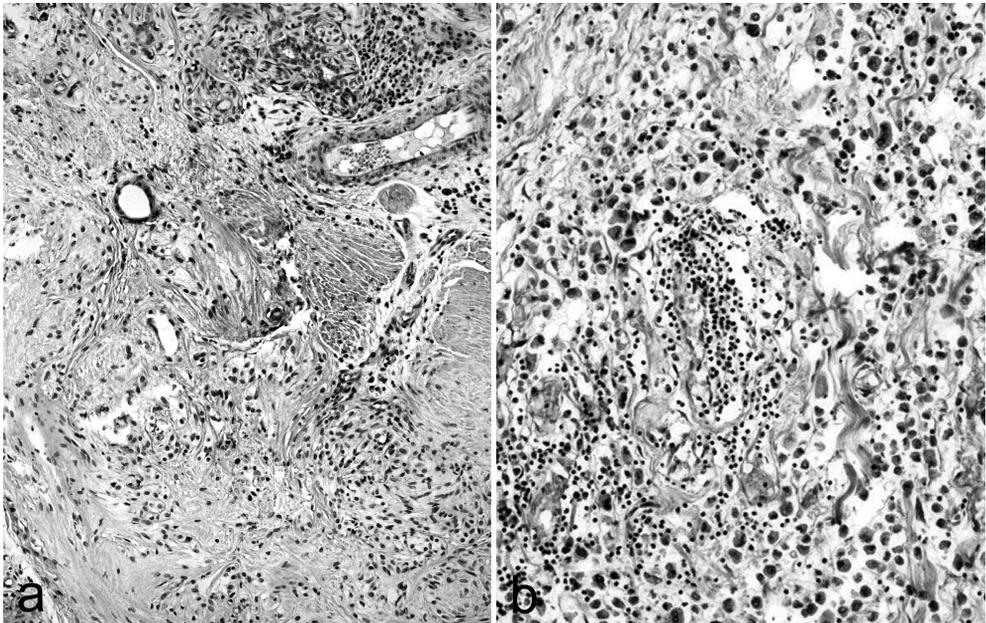
**Light microscopy.** Tissue samples from surgically removed tumors of mammary glands were routinely fixed in 10% buffered formalin, dehydrated in graded ethanol, and embedded in paraffin. Tissue sections, 3-5  $\mu\text{m}$  thick, were stained in H&E and examined by light microscope (Leica DM 5000B, Wetzlar, Germany). Nottingham Histologic Score system (the Elston-Ellis grading system) [7] was used to evaluate the results.

## Results

Histopathological diagnosis of animal tissue samples estimated seven cases of simple or complex carcinoma (n=7, 87.5%) and one carcinosarcoma subtype (n=1, 12.5%). Histological evaluation found five cases of ductal carcinoma (n=5, 62.5%) (**Fig. 1a**), one lobular carcinoma (**Fig. 2a**), one squamous cell carcinoma and one case of metaplastic carcinoma with osteosarcomatous differentiation. All duct carcinomas originated in the epithelial cells of ducts, while lobular carcinomas arose in alveoli and developed into progressively larger lobules. Invasion was observed in four cases (n=4, 50%), necrosis in one (n=1, 12.5%). According to the Nottingham Histologic Score system tumors were classified as stage of anaplasia: grade I (n=1, 12.5%), grade II (n=4, 50%) and grade III (n=3, 37.5%). One of the excisions was taken *post mortem*, with anamnesis of prolonged suffering of mammary tumors. Pathomorphological studies revealed ductal carcinoma grade III and changes that had taken place in the internal organs of an old animal, accompanied with disseminated metastases in the associated lymph nodes,



**Fig. 1.** Invasive ductal carcinoma, stage of anaplasia grade III - poorly differentiated pleomorphic epithelial cells, high mitotic counts and prominent nucleoli: in female dog (a) H&E, 10 $\times$ ; and in human female (b), H&E, 10 $\times$



**Fig. 2.** Invasive lobular carcinoma: in female dog, stage of anaplasia grade II - arranged in cords epithelial cells (a) H&E, 10 $\times$ ; in human female, stage of anaplasia grade III poorly differentiated epithelial cells with considerable nuclear and cellular pleomorphism and prominent nucleoli (b), H&E, 20 $\times$

lungs and liver, mainly causing the lethal end. During the one year follow-up period of observation of all cases, one more animal had died, diagnosed with invasive ductal carcinoma grade III, where disseminated metastases in nearby lymph nodes, lungs and liver resulted in a lethal end. Four of the human cases were pathomorphologically diagnosed as invasive ductal (n=2, 40%) (**Fig. 1b**), and lobular (n=2, 40%) (**Fig. 2b**), carcinoma. One case of metaplastic carcinoma was recognized. All five cases were scored as grade III. All women were undergoing chemotherapy.

## Discussion

Variety of etiological factors can result in severe abnormalities in the processes of cell proliferation and differentiation, consequently leading to non-cancerous (benign), pre-cancerous or cancerous (malignant) conditions. Domestic dogs and cats share almost the same living conditions as their owners, and usually use industrially made food and cosmetics containing the same carcinogenic chemicals as for the humans. In animals compared to humans, the role of stress factors in tumor development is less possible. In both humans and animals, among the most often causes for cancer development is the probable involvement of imbalances due to mutations in tumor suppressor genes such as: BRCA1, BRCA2, p53 and endocrine dysfunctions. The canine BRCA1 gene that has 84% homology with its human analog is very likely to play a role in malignancy as it is in humans, even though its role in mammary cancer in dogs has not been determined clearly yet [16]. The BRCA1-related protein TopBP1 is expressed at a higher percentage also in feline mammary malignant neoplasms [12]. Like in humans, in dogs and cats oophorectomy in early age significantly reduces tumor development frequency [15] showing connection with hormonal status in these species.

In this study we used the grading of canine mammary gland tumors which follows as much as possible on the classification of human breast tumors and dysplasias, approved by the World Health Organization [17]. As it was shown from our histological examinations, the neoplastic mammary parenchyma in mastectomy specimens from the operated pets was histologically similar to that of human breast tissue. Most often simple epithelial carcinomas and rarely complex carcinomas were identified. Carcinosarcomas were relatively rare and no sarcomas were found in our survey, as reported by other authors [10, 11]. The malignant neoplasia in the examined animals was expressed by abnormal growth of the mammary tissues and impairment of gland functions. Metastases were found on the lymph nodes, lungs and liver, which is common for the malignancy events also in the examined women. As our results showed, dogs, cats and humans develop tumors with similar frequency of histological subtype and their behavior can vary from indolent to very aggressive, according to the histological grade. The histological subtype of tumors is highly important for prognostic determination of the survival time and the treatment options [19].

We consider that the non-castrated domestic dogs and cats are suitable animal model for studies on mammary cancer in humans because of their short lifespan, comparable hormonal background and similarities in the shared with humans environmental risk factors. This model can be used for investigations in cancer biology, prognosis and therapies with possible potential in clinical researches of anticancer drugs.

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