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The Influence of Dog Body Conditions on the Risk of Mastopathy

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Abstract

The article is devoted to the study of mastopathy risk assessment in overweight dogs. According to histopathological verification, among malignant neoplasms, ductal carcinoma is the most common (25%, 95% CI: 22–28%), benign tumors are fibroadenoma (20.6, 95% CI: 19–23%), dysplasia / hyperplasia is ductal ectasia (22.8%, 95% CI: 19–27%). According to the results of the statistical analysis, 30.7% (95% CI: 25–36%) of overweight bitches suffered from mastopathy, 46.5% (95% CI: 40–54%) from benign neoplasia, and 52.7% (95% CI: 47–59%) from malignant mammary neoplasms. It was established that over the past 3 years (from 2020 to 2022), the incidence of fibrocystic disease in bitches with excess body weight increased from 18.8% (95% CI: 16–22%) to 41.0% (95% CI: 38–44%) against the background of a decrease among patients with optimal body weight from 72.3% (95% CI: 69–76%) to 49.7% (95% CI: 45–55%). The risk of mastopathy correlates with the degree of overweight: with the exceeding of the optimal condition within 20%, the incidence was 20.8% (95% CI: 17–24%), for 30–50% it was 30.8% (95% CI: 23–38%), and for more than 50% it was 48.4% (95% CI: 41–56%). Compared to bitches with malignant mammary tumors, average body mass indices in dogs with benign neoplasia and mastopathy are significantly higher ($p < .05$ and $p < .001$, respectively). The number of patients with mastopathy increases with age; the maximum indicators were set in 91-year-old (35.8%, 95% CI: 29–42%) and older 11-year-old (32.6%, 95% CI: 26–39%) animals. German shepherd, Labrador retriever, boxer, poodle, and dachshund females are the most susceptible to fibrocystic disease (12.5%, 10.0%, 9.2%, 8.3%, and 8.3%, respectively), as well as mixed breeds (13.4%). The dynamic increase in the number of overweight bitches suffering from mastopathy confirms the importance of obesity in its pathogenesis.

Keywords: Body condition, dogs, mammary gland, mastopathy, obesity

Introduction

Nowadays, obesity among people is a growing global problem, one of the biggest in the field of health care. Most researchers agree that, just as in humans, the incidence of disease among the companion animal population is also increasing.

It is a proven fact that the pathogenesis of dysplastic and neoplastic changes in humans and dogs are similar, so they are the best models for studying the role of excess body weight in the mechanisms of oncogenesis (Cleary et al., 1997).

The shared environment and lifestyles of humans and their pets provide a strong rationale for examining lifestyle and environmental exposures as risk factors for mammary neoplasms (Chandler et al., 2017).

On the other hand, a retrospective analysis of the incidence confirms the assumption of an increasing trend in the proportion of bitches with mammary gland neoplasms in the following years (Valenčáková-Agyagosová et al., 2011).

Studies in many countries have demonstrated a prevalence of obesity in dogs similar to that observed in humans. Chronic low-grade inflammation is an important framework used to explain how obesity leads to numerous negative health outcomes. This is well-known and understood, and recent studies have pointed to a link between obesity and susceptibility to certain types of cancer and their complications. Such explanations are important because, like obesity, the prevalence of canine cancer has increased in recent decades, establishing cancer as an important cause of death in these animals (Marchi et al., 2022).

The results of recent studies have changed views on certain risk factors for obesity in dogs. In particular, spaying dramatically increases the possibility of excessive body condition score (BCS) only in males, females are prone to obesity regardless of spaying status. Among old animals, females have an increased BCS compared to males. The risk of obesity significantly increases if owners have excessive body weight, a one-time feeding regime and feeding treats. The effect of duration and intensity of walks on BCS was related to the mode of movement of the animal (free walking of the dog or on a leash) and the owner (physical condition) (Bjørnvad et al., 2019).

The incidence rate of obesity in humans and dogs in the region is similar. Owners of overweight dogs are mainly women over 40 years old, who have low physical activity. A correlation was found between dog owners with a low level of education and the obesity of their pets, the majority of which were spayed bitches older than 6 years (Suarez et al., 2022).

In human medicine, considerable attention is paid to the study of the influence of obesity on chronic diseases and tumors of the mammary gland. In veterinary medicine, such studies have become relevant only recently, so the number of publications is insignificant. Currently, the pathogenetic relationship between obesity and

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mammary cancer remains poorly understood. One of the ways of initiation of neoplastic mechanisms in the mammary gland of bitches against the background of excess body weight and obesity is associated with increased aromatase expression due to an increase in the level of immune mediators: prostaglandin E2, nuclear factor kappa beta, and adipokines (leptin) (Shin et al., 2016).

Changes in prognostic markers prove the key role of excess body weight in oncogenesis. A significant increase in tumor-associated macrophages (TAM; $p < .005$) and density of intratumoral microvessels ($p < .001$), increased expression of Ki67 ($p < .005$), higher histological degree of malignancy ($p < .001$) are recorded for obesity (Lim et al., 2022). At the same time, TAMs are associated with vascular invasion and nodal metastases, and indicators of total (tTAM) and stromal (sTAM) numbers are correlated with overall survival (Monteiro et al., 2021).

A positive correlation between BCS and histological tumor grade ($p < .01$) is consistent with shorter survival in bitches with obesity, compared to normal weight animals after mastectomy. At the same time, it was not possible to prove the connection between the histological type of the tumor, the expression of adiponectin, and the diet with the risk of neoplastic changes in the functional mammary tissue (Tesi et al., 2020).

In the last decade, metabolic syndrome has attracted attention in human medicine, given its association with the development of type 2 diabetes and cardiovascular disease. In veterinary medicine, such studies are just beginning to be conducted in dogs. However, even during pilot studies, results were obtained that testify to the key role of metabolic syndrome in the development of many diseases, including mammary tumors. Metabolic dysfunction, which is accompanied by hypertension, hypertriglyceridemia, hypercholesterolemia, hyperglycemia (Montoya-Alonso et al., 2017), hypoadiponectinemia with hyperinsulinemia (Tvarijonaviciute et al., 2012), can initiate neoplastic mutation in the mammary gland of bitches.

Evidence is provided that in dogs with obesity and obesity-related metabolic dysfunction, there are changes in the expression of proteins involved in lipid metabolism, immune response, antioxidant and hemostasis status: albumin, apolipoprotein AI, C2, C3, C5, C4BPA, A2M, uncharacterized protein (fragment) (organism = *Canis familiaris*), fibrinogen, IGJ, ITIH2, and glutathione peroxidase. However, the clinical significance of these changes, in particular in the initiation of oncogenesis in the mammary gland, remains to be determined (Tvarijonaviciute et al., 2016, 2019). In addition, the relevance of studying the possible relationship between increased BCS and neoplastic changes of the mammary gland in bitches is substantiated by the use of dogs in oncology as biological models and the possibility of clinical approval of new drugs, the action of which is aimed at the treatment of diseases that may later lead to cancer (Gray et al., 2020).

Among the diseases of the mammary gland in dogs that can be initiated by BCS, mastopathy is the least studied. Currently, in contrast to human medicine, the study of mastopathy in veterinary is reduced to the description of pathohistological changes, without a detailed analysis of risk factors and pathogenetic mechanisms of disease progression.

Human medicine has collected enough evidence of the clinical significance of mastopathy as a harbinger of neoplasms. In veterinary medicine, the attention of practicing doctors is focused on tumors, which are the consequences of further structural disorders of the functional mammary tissue. At the same time, detection of mastopathy is not actually carried out.

According to the definition of the World Health Organization, mastopathy is a fibrocystic disease characterized by a violation of the ratio of epithelial and connective tissue components and a wide range of proliferative and regressive changes in mammary gland tissue (Tan et al., 2020).

"Fibrocystic changes" is a term used to denote a variety of clinical and histopathological changes of the mammary gland, which should be considered not so much as a disease but as a violation of physiological development, maturation, and involution (Dupont & Page, 1985).

With hormonal fluctuations, the main components of the mammary gland (stroma, ducts, and lobules of the mammary gland) are prone to fibrocystic changes. In the reproductive age, the glandular tissue of the mammary gland is directly related to cyclical jumps in the level of estradiol and progesterone in the plasma (Malherbe et al., 2023).

Depending on the pathological picture, fibrocystic changes are divided into nonproliferative and proliferative. The main histopathological changes include cyst formation, apocrine metaplasia, epithelial hyperplasia, fibrosis, chronic inflammation, gross calcification (with calcium phosphate or oxalates), and fibroadenomatoid changes (most common). There is big variability in the macroscopic and microscopic manifestations of mastopathy. Nonproliferative changes (cyst formation, apocrine metaplasia, fibrosis, intraductal hyperplasia, calcification, development of fibroadenoma, and associated lesions) usually do not pose a risk of mammary carcinoma.

Proliferative changes without atypia (floral ductal hyperplasia, sclerosing adenosis, and intraductal papillomatosis) and with atypia (atypical ductal or lobular hyperplasia) predict an increase in the risk of tumor malignancy, 2× and 4–5×, respectively, which is an important feature of mastopathy (Yadav et al., 2020).

An increase in the risk of mammary cancer against the background of proliferative forms of mastopathy with atypia (squamous atypia, atypical ductal hyperplasia, and atypical lobular hyperplasia) is also confirmed by the results of studies (Stachs et al., 2019).

Mysak et al. (2021) substantiate the possible direct involvement of fibrocystic disease in carcinogenesis by the high percentage of detection of the proliferative form (40%), as well as the presence of signs of its transformation and microfocal growth of the tumor.

The involvement of fibrocystic disease in increasing the risk of developing malignant mammary neoplasia has two aspects: it can be either a marker of predisposed tissue or a precancerous histological defect.

The probability of transformation of a benign proliferative lesion into a carcinoma is based on the fact that the initiation of carcinogenesis requires several stages of proliferation. Clinical confirmation of this theory is the fact of simultaneous pathomorphological verification in 17% of cases of tumor lesions of the mammary gland, cancer, and mastopathy (Habor et al., 2010).

On the other hand, Soysal et al. (2019) did not find significant somatic mutations in fibrocystic mammary tissue but only questionable shared mutations between benign and associated cancer tissue.

Therefore, further studies at the level of gene expression are needed to clarify the role of these benign changes in the development of mammary cancer.

Recently, the problem of mastopathy has become more relevant, which is due to the increase in the number of dogs with BCS, against the background of the proven role of mastopathy in the mechanisms of carcinogenesis and the debatable pathogenetic mechanisms of the disease.

The purpose of the study was to determine the influence of increased body conditions on the risk of developing mastopathy in bitches.

Materials and Methods

The research was carried out in the conditions of the Department of Veterinary Surgery and Reproductology of the Dnipro state Agrarian and Economic University and veterinary hospitals of the city of Dnipro during 2020–2022. During conducting research, we used client bases of separate units of the Dnipro City State Hospital of Veterinary Medicine, private veterinary clinics in the city of Dnipro: "Dobry Doctor", "Vetservice", "Biosvit", "Vet Life Clinic".

The conducted research was agreed upon and approved by the Bioethics Committee of the Faculty of Veterinary Medicine of the Dnipro State Agrarian and Economic University (meeting minutes No. 4 of September 2, 2020).

Informed consent of the owner of the patient to adhere to a high standard (best practice) of veterinary care was not required because the studies did not involve determining the effectiveness of treatment measures and the use of painful manipulations. Their basis was the establishment of a correlation between body weight (methods of its measurement were used) and the risk of mastopathy (statistical analysis).

In general, the medical histories of bitches were analyzed: with fibrocystic disease (391 dogs), benign tumors (568 dogs), and malignant neoplasia (602 bitches). The age of the bitches was from 2 to 8 years.

Mastopathy and neoplasms of the mammary gland were diagnosed on the basis of generally accepted histological studies of functional mammary tissue biopsies using the classification of Goldschmidt et al. (2011).

The biopsy required general anesthesia; propofol was used (Fresenius Kabi Austria, code ATX N01A X10) at a dose of 4–6 mg/kg intravenously.

Preliminary preparation of the operating field was carried out by hair removal and skin treatment with antiseptic Cutasept G (BODE Chemie, Germany, code ATS D08AX 53).

The biopsy was performed by inserting a sterile Biomedical BD14G 10 cm (Italy) soft tissue guillotine needle into the mammary tissue with a spring needle. Immediately before the protocol, the skin was moved to the side, avoiding the through channel formation in the mammary gland (after removal of the needle, the skin returned to its original position, closing the biopsy channel). After procedure, Dermabond protective glue (Ethicon, part of Johnson & Johnson, Bridgewater, New Jersey USA) was applied to the skin injection site. The depth of insertion depended on the amount of functional mammary tissue. For its exact determination, the needle is marked in centimeters.

To minimize the risk of false–positive results, biopsy samples were taken in three areas at different angles.

Taking into account the observance of aseptic/antiseptic rules, minor damage to mammary tissue, and the need to prevent antibiotic resistance of bitches after biopsy, antimicrobial therapy was not prescribed.

The method of Lyashenko et al. (2007) was used to study samples of pathological material. Consecutive stages of histological examination included fixation with Bouin's liquid (2–24 hours with 20–30°C degrees); washing (60 minutes); dehydration with 100% anhydrous acetone, at room temperature (first for 20 minutes, then again for 15 minutes); pouring into a mixture of paraffin (90%) + voscolite (10%) (first for 30 minutes, then again for 20 minutes) at a temperature of 56.5°C; cooling with water, during 10 minutes, at a temperature of 10–15°C; block formation; slicing on a Leica HistoCore Multicut microtome (Germany); straightening with distilled water (42°C), pasting and drying sections; deparaffinization with O-xylene (0.5–1.0 minutes at room temperature); replacement of O-xylene with 96–100% ethanol (0.5–1.0 minutes at room temperature); replacing ethanol with water (at room temperature); first staining with Ehrlich's hematoxylin (7–15 minutes at room temperature); washing with water (1 minute at room temperature); restaining with 1% eosin solution (up to 2 minutes at room temperature); differentiation with 96–100% ethanol (as the dye is removed at room temperature); and lighting with O-xylene (0.5 minutes at room temperature). We used a Sigeta Biogenic 40×–2000× LED Trino Infinity microscope (China) to study the prepared samples.

Body mass index (BMI) was determined using the standardized method of Muller et al. (2008). It is based on the mathematical processing of morphometric indicators (body weight and height) using the formula:

$$\text{BMI} = \frac{\text{Body weight (kg)}}{[\text{height (m)}]^2}$$

Height was measured with a tape measure, the starting point being the base of the neck (atlantooccipital joint), then along the upper contour of the spine to the last sacral vertebra and down the back surface of the pelvic limb.

In order to correctly estimate the BMI, in some cases, mathematical corrections were made. The obtained values for dogs with a body weight of less than 10 kg were increased by 10%, more than 25 kg were decreased by 20%. The assessment of body mass index is given in Table 1.

Statistical processing of the results was performed using the Statistica 10 program (StatSoft Inc., USA, 2011). Analysis of variance with Bonferroni correction was used to determine the difference between samples. Mean BMI values in the table are reported as means (x) and their standard deviations. Categorical variables of other indicators were presented in numbers, and its proportions are expressed in percentage and 95% CI.

Table 1.
Interpretation of the Obtained Data, Calculated According to the Formula of Muller et al. (2008)

Body Mass Index		
Insufficient	Optimal	Excessive
<11.7	11.8–15	>15

Results and Discussion

According to the results of pathohistological studies of biopsy samples in bitches (classification by Goldschmidt et al., 2011), the following oncological lesions of the mammary gland were verified (Table 2–4). Among malignant neoplasias, malignant epithelial neoplasms were diagnosed in the absolute majority of cases (*n* = 545, 90.5%, 95% CI: 86–97%). Among them, ductal carcinoma (*n* = 150, 25.0%, 95% CI: 22–28%), carcinoma simple: tubulopapillary (*n* = 66, 11.0%, 95% CI: 10–12%), and tubular (*n* = 60, 10.0%, 95% CI: 8–12%). Malignant epithelial neoplasms (special types) (*n* = 28, 4.7%, 95% CI: 4–6%) and malignant mesenchymal neoplasms (sarcomas) (*n* = 29, 4.8%, 95% CI: 4–6%) were registered much less frequently. In their structure, inflammatory carcinoma (*n* = 8, 1.4%, 95% CI: 1–2%), and fibrosarcoma (*n* = 8, 1.4%, 95% CI: 1–2%) occupy the largest share, respectively. Among benign neoplasms of the mammary gland, the most frequently diagnosed fibroadenoma (*n* = 117, 20.6%, 95% CI: 19–23%), benign mixed tumor (*n* = 102, 18.0%, 95% CI: 17–19%), intraductal papillary adenoma (*n* = 101, 17.8%, 95% CI: 16–20%). In relation to the histopathology of mastopathy, regular hyperplasia with fibrosis (interlobular fibrous connective tissue) (*n* = 94, 24.0%, 95% CI: 21–27%), duct ectasia (*n* = 89, 22.8%, 95% CI: 19–27%), and lobular hyperplasia (adenosis) (*n* = 66, 16.9%, 95% CI: 15–18%) were observed.

Table 2.
Pathohistological Types of Malignant Mammary Tumors in Bitches (n = *602)*

Pathohistological types		*n*	%	95% CI (%)
Malignant epithelial neoplasms (*n* = 545, 90.5%, 95% CI: 86–97)				
Carcinoma in situ		38	6.4	5–8
Carcinoma simple	Tubular	60	10.0	8–12
	Tubulopapillary	66	11.0	10–12
	Cystic papillary	24	4.0	3–5
	Cbriform	18	3.0	2–4
Carcinoma–micropapillary invasive		6	1.1	1–2
Carcinoma—solid		24	4.0	3–5
Comedocarcinoma		12	2.0	1–3
Carcinoma—anaplastic		12	2.0	1–3
Carcinoma arising in a complex adenoma/mixed tumor		48	8.0	7–9
Carcinoma—complex type		48	8.0	7–9
Carcinoma—mixed type		18	3.0	2–4
Ductal carcinoma		150	25.0	22–28
Intraductal papillary carcinoma		18	3.0	2–4
Malignant epithelial neoplasms – special types (*n* = 28, 4.7%, 95% CI: 4–6%)				
Adenosquamous carcinoma		5	0.8	0–2
Spindle cell carcinomas		4	0.7	0–2
Malignant myoepithelioma		3	0.4	0–1
Squamous cell carcinoma—spindle cell variant		4	0.7	0–2
Carcinoma—spindle cell variant		4	0.7	0–2
Inflammatory carcinoma		8	1.4	1-2
Malignant mesenchymal neoplasms—sarcomas (*n* = 29, 4.8%, 95% CI: 4–6%)				
Osteosarcoma		5	0.8	0–2
Chondrosarcoma		5	0.8	0–2
Fibrosarcoma		8	1.4	1–2
Other sarcomas		11	1.8	1–3

Table 3.
Benign Neoplasms of the Mammary Gland in Bitches (n = *568)*

Pathohistological Types	*n*	%	95% CI (%)
Adenoma simple	79	13.9	12–16
Intraductal papillary adenoma (duct papilloma)	101	17.8	16–20
Ductal adenoma (basaloid adenoma)	92	16.2	15–18
With squamous differentiation (keratohyaline granules)	23	4.0	3–5
Fibroadenoma	117	20.6	19–23
Complex adenoma (adenomyoepithelioma)	54	9.5	8–11
Benign mixed tumor	102	18.0	17–19

Examples of histopathological images associated with fibrocystic disease and benign and malignant mammary tumors based on the results of biopsy material are presented in Figures 1–4.

According to the analysis of medical histories (Table 5), the share of dogs with excessive body weight diagnosed with malignant mammary tumors was 52.7% (95% CI: 47–59%), benign—46.5% (95% CI: 40–54%), mastopathy—30.7% (95% CI: 25–36%); with the

Table 4.
Hyperplasia/Dysplasia of the Mammary Gland in Bitches (n = *391)*

Pathohistological types		*n*	%	95% CI (%)
Duct ectasia		89	22.8	19–27
Lobular hyperplasia (adenosis)		66	16.9	15–18
Regular hyperplasia	With secretory activity (lactational)	39	10.0	8–12
	With fibrosis—interlobular fibrous connective tissue	94	24.0	21–27
	With atypia	56	14.3	12–17
Epitheliosis		29	7.4	6–9
Intraductal papillomatosis		13	3.3	3–4
Fibroadenomatous change		5	1.3	1–2

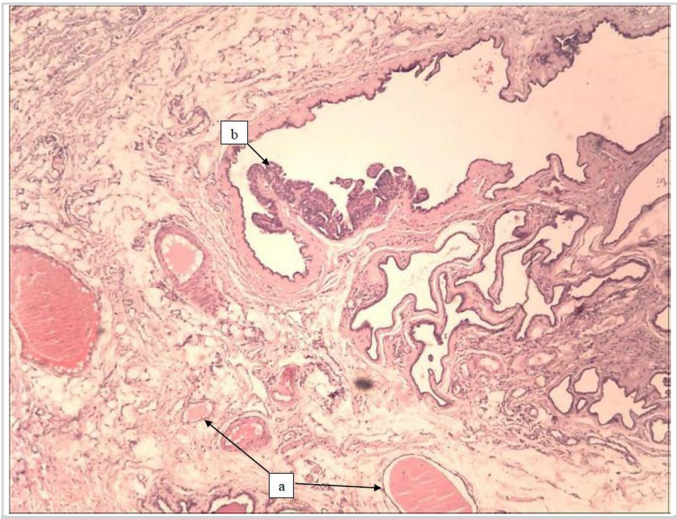

Figure 1.
Fibrocystic disease of nonproliferative form (a, vessels; b, intraductal papillomas with marked lymphoid and histiocytic infiltration of the walls). Staining with hematoxylin and eosin. ×100.

optimal—37.5% (95% CI: 33–43%), 44.5% (95% CI: 39–51%), 60.1% (95% CI: 53–70%), respectively. The number of cachexic animals with neoplastic changes in the functional tissue of the mammary gland varied between 9 and 10%. The increase in the number of obese bitches in the sequential chain "mastopathy-benign tumor-malignant neoplasia" serves as the basis for the conclusion that obesity creates conditions for the progression of pathological changes in the functional tissue of the mammary gland.

The analysis of average indicators of BMI (Table 6) made it possible to establish the following patterns. It was 9.3 ± 0.8 in dogs

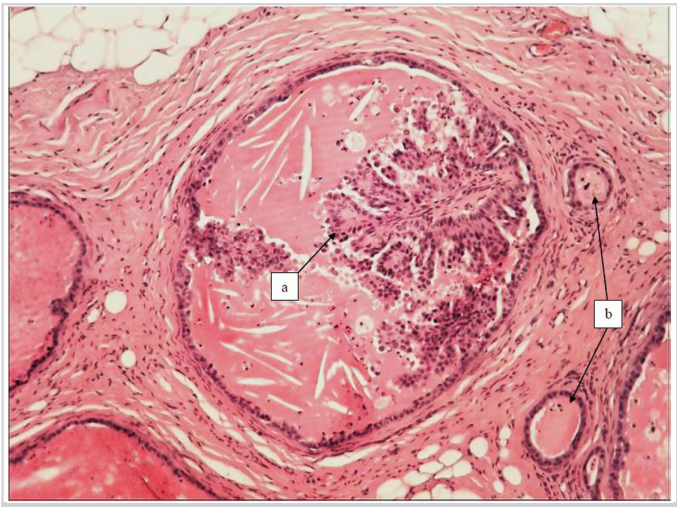

Figure 2.
Fibrocystic disease of a proliferative form with the formation of intraductal papillomas and cysts (a, epitheliosis of the mammary gland with intraductal proliferation of cells with chromatic nuclei; b, lobular hyperplasia with atypia and hyperchromic nuclei). Staining with hematoxylin and eosin. ×100.

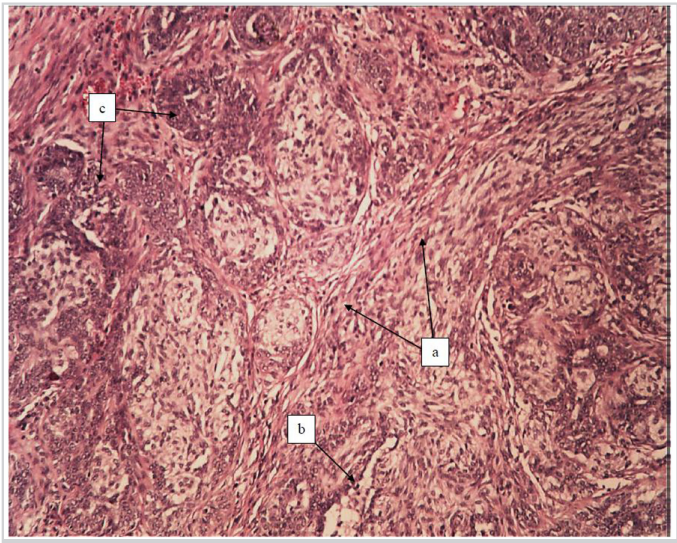

Figure 3.
Mixed adenoma of the mammary gland (a, hyalinosis of connective tissue; b, foci of proliferation of the myoepithelium of small ducts and alveoli; c, proliferation of the epithelium inside the interlobular duct). Staining with hematoxylin and eosin. ×100.

with insufficient BMI for mastopathy and 8.8 ± 0.5 for benign neoplasias of the mammary gland, which is significantly higher ($p < .05$) than in bitches with malignant neoplasms (6.5 ± 0.6). The values of BMI in overweight animals (24.6 ± 1.4 and 22.1 ± 1.1) determined for mastopathy and benign mammary neoplasms exceeded ($p < .001$) the corresponding values of dogs with malignant neoplasia (16.3 ± 0.9). The calculated average values of BMI confirmed that they are significantly higher ($p < .05$) in bitches with mastopathy (16.8 ± 1.0) and benign tumors of the mammary gland (16.7 ± 0.8), compared to malignant neoplasms (13.9 ± 0.7).

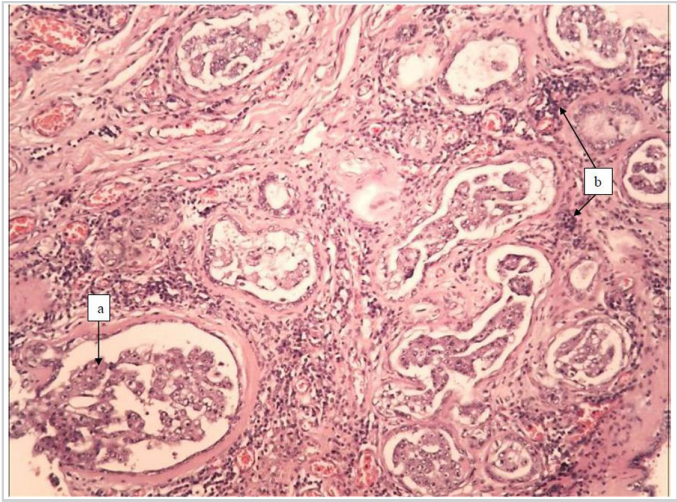

Figure 4.
Intraductal adenocarcinoma of the mammary gland (a, intraductal growth of cancer cells; b, multiple tumor emboli in vessels). Staining with hematoxylin and eosin. ×100.

Table 5.

Frequency of Pathological Changes of the Mammary Gland Depending on the Body Weight of Bitches

				Tumor Type					
	Mastopathy (*n* = 391)			Benign (*n* = 568)			Malignant (*n* = 568)		
Body Mass Index	***n***	**%**	**95% CI (%)**	***n***	**%**	**95% CI (%)**	***n***	**%**	**95% CI (%)**
Insufficient	36	9.2	8–11	51	9.0	8–11	59	9.8	9–12
Optimal	235	60.1	53–70	253	44.5	39–51	226	37.5	33–43
Excessive	120	30.7	25–36	264	46.5	40–54	317	52.7	47–59

A 3-year retrospective analysis of the incidence of mastopathy in bitches indicates a fairly high proportion of patients with increased body condition (Table 7). In total, 30.7% (95% CI: 25–36%) of animals diagnosed with mastopathy had excessive body weight. Important is the fact that during the last 3 years, among patients with mastopathy, the share of obese bitches has increased by 2.2 times: from 18.8% (95% CI: 16–22%) in 2020 to 41.0% (95% CI: 38–44%) in 2022, against the background of a 1.5-fold decrease in sick animals with optimal weight.

The analysis of the degree of risk of fibrocystic disease in bitches depending on body weight deviations in relation to optimal conditions proved the following facts (Table 8). An increase in the body condition of dogs was correlated with the probability of detecting mastopathy in them. In particular, in 20.8% (95% CI: 17–24%) of cases of mastopathy, an excess of the optimal weight within 20% was found, in 30.8% (95% CI: 23–38%) of bitches, an excess of conditions by 30–50% was registered, and in 48.4% (95% CI: 41–56%)—by more than 50%. That is, the presence of excess body weight correlates with the probability of developing mastopathy.

It has been established a direct correlation between the age of bitches with excess body weight and the risk of detecting fibrocystic disease of the mammary gland (Table 9). The minimum probability of detecting mastopathy is typical for young animals (up to 2 years) (2.5%, 95% CI: 2–3%) and the maximum for individuals older than 9 years (35.8%, 95% CI: 29–42%). Compared with young animals (up to 2 years), the frequency of mastopathy in 3-year-old bitches increases by 4.3 times (up to 10.8%, 95% CI: 7–14%) and in 6–8-year-olds by 7.3 times (up to 18.3%, 95% CI: 15–22%). The specified dynamics are consistent with the incidence rate of mammary neoplasms, which can be explained by the fact that mastopathy is considered a precancerous condition.

We considered the regional incidence of fibrocystic disease in bitches from a breed perspective (Table 10). Among the breeds

Table 6.

Mean Values of Body Mass Index of Bitches with Mastopathy and Mammary Gland Neoplasia (mean ± SD)

		Tumor Type	
Body Mass Index	**Mastopathy (*n* = 391)**	**Benign (*n* = 568)**	**Malignant (*n* = 602)**
Insufficient	9.3 ± 0.8*	8.8 ± 0.5*	6.5 ± 0.6
Optimal	13.9 ± 0.7	12.7 ± 0.4	12.5 ± 0.5
Excessive	24.6 ± 1.4***	22.1 ± 1.1***	16.3 ± 0.9
Average value	16.8 ± 1.0*	16.7 ± 0.8*	13.9 ± 0.7

Note: $p < .001$, relative to the rates of dogs with malignant tumors.
*$p < .05$.

Table 7.

Monitoring the Incidence of Mastopathy in Bitches in the Period from 2020 to 2022

Insufficient			**Optimal**			**Excessive**		
n	**%**	**95% CI (%)**	***n***	**%**	**95% CI (%)**	***n***	**%**	**95% CI (%)**
2020 (*n* = 101)								
9	8.9	7–11	73	72.3	69–76	19	18.8	16–22
2021 (*n* = 129)								
12	9.3	8–11	82	63.6	58–70	35	27.1	25–30
2022 (*n* = 161)								
15	9.3	8–11	80	49.7	45–55	66	41.0	38–44
Total (391)								
36	9.2	8–11	235	60.1	53–70	120	30.7	25–36

Table 8.

Correlation of the Incidence of Mastopathy with the Degree of Increase in Body Condition (n = *120)*

Body Weight /Norm, %	***n***	**%**	**95% CI (%)**
<20	25	20.8	17–24
30–50	37	30.8	23–38
> 50	58	48.4	41–56

Table 9.

The Structure of the Age-Related Incidence of Mastopathy in Bitches with Body Condition Score (n = *120)*

Age (years)	***n***	**%**	**95% CI (%)**
<2	3	2.5	2–3
3–5	13	10.8	7–14
6–8	22	18.3	15–22
9–11	43	35.8	29–42
>11	39	32.6	26–39

Table 10.
Breed Susceptibility of Bitches to Fibrocystic Disease (n = *120)*

Name of breed	*n*	%	95% CI (%)
German shepherd	15	12.5	11–14
Labrador retriever	12	10.0	9–11
Boxer	11	9.2	7–12
Poodle	10	8.3	7–10
Dachshund	10	8.3	7–10
English and American cocker spaniel	9	7.5	6–9
Pug	9	7.5	6–9
Yorkshire	7	5.8	5–8
Rottweiler	6	5.0	4–7
Pekingese	5	4.2	4–5
Central Asian shepherd dog	4	3.3	3–4
English bulldog	3	2.5	2–3
French bulldog	3	2.5	2–3
Mix breed	16	13.4	11–16

represented in the region, those most susceptible to mastopathy is German shepherd and Labrador retriever bitches: in the incidence structure, their share is 12.5% (95% CI: 11–14%) and 10.0% (95% CI: 9–11%), respectively. A fairly high risk of cystic fibrosis was observed in boxers (9.2%, 95% CI: 7–12%), poodles (8.3%, 95% CI: 7–10%), dachshunds (8.3%, 95% CI: 7–10%), English and American cocker spaniels (7.5%, 95% CI: 6–9%), pugs (7.5%, 95% CI: 6–9%). Among the breeds in which the incidence does not exceed 6% are Yorkshire terriers (5.8%, 95% CI: 5–8%), Rottweilers (5.0%, 95% CI: 4–7%), Pekingese (4.2%, 95% CI: 4–5%), Central Asian shepherds (3.3%, 95% CI: 3–4%), English and French bulldogs (2.5%, 95% CI: 2–3%). Among the patients, mix breeds made up 13.4% (95% CI: 11–16%). It should be noted that representatives of most of the mentioned breeds had a tendency to increase body conditions.

It should be noted that no correlation was established between the degree of obesity of bitches and histological changes in the functional tissue of the mammary gland. Excess body weight is a predictor of mastopathy, but the obtained results currently do not allow the use of BMI indicators to predict the further course of the disease.

A key factor in the disruption (due to obesity) of lipid metabolism, the antioxidant system, protein biosynthesis and catabolism, mucosal barrier function, and immunomodulation is the excessive consumption of energy-rich foods, particularly the use of high-fat diets (Lyu et al., 2022).

Obesity in domestic dogs is a serious and widespread problem in developed countries. Excess body fat has adverse metabolic consequences, including insulin resistance, altered secretion of adipokines, altered metabolic rate, abnormal lipid metabolism, and visceral fat accumulation. There is probably a link between obesity and diabetes in dogs. There is no system to identify obese pets that are at greatest risk of developing obesity-related metabolic diseases, and further research is needed in this area (Clark & Hoenig, 2016).

Obesity is not a cosmetic or social problem; it is an animal health problem that can lead to harmful long-term consequences. The metabolic effects of obesity on insulin resistance and the development of hyperlipidemia and the mechanical stress that excess weight places on the musculoskeletal system are well known in the literature. Mastopathy and tumors of the mammary gland, fatty liver disease, intestinal bacterial dysbiosis, and changes in the structure of the kidneys, as additional health risks associated with obesity, remain less studied (Weeth, 2016).

Canine obesity is associated with genetic, environmental, and behavioral factors, the latter of which include dog and owner behavior (Porsani et al., 2020).

In the risk group of oncological diseases of the mammary gland in bitches older than 2 years, it is advisable to include neutered dogs of middle or older age, which have a tendency to be overweight and obese (Chiang et al., 2022).

In addition to sterilization status and age, the risk factors for excessive weight gain and obesity include breed and keeping dogs in small towns and villages (compared to the city) (McGreevy et al., 2005). However, the mentioned correlative relationships are quite debatable.

Higher rates of dysplasia and mammary tumors in overweight bitches Nicchio et al. (Nicchio et al., 2020) are justified by hyperresistenemia, which is associated with metabolic, inflammatory, and neoplastic disorders and is directly proportional ($p = .0001$) to the proliferative potential of the tumor and excess fat.

The high incidence rate of mastopathy in bitches with an increased BMI was determined. It is probably due to an increased amount of circulating estrogen, including increased expression of adipokines in adipose tissue (Cleary & Grossmann, 2009).

In human medicine, studies using multiple in vivo models of obesity as well as human breast tumors have improved our understanding of how obesity alters the breast tumor microenvironment. Changes in the complement and function of adipocytes, stromal cells of adipose tissue, cells of the immune system, and endothelial cells, as well as remodeling of the extracellular matrix contribute to the rapid growth of mammary tumors in the context of obesity (Hillers-Ziemer et al., 2022). One of the possible explanations for the high risk of mastopathy in animals with excess body weight can be the published results of Lim et al. (2015), which indicate its effect on the development and behavior of mammary neoplasms through the interaction between the tumor and adipocytes and the increase in tumor growth associated with estrogen and progesterone receptors. In particular, the average age of onset of the disease for obesity was 8.7 ± 1.9 years (10.4 ± 2.7 years for "ideal" body weight) against the background of a high frequency of detection of poorly differentiated neoplasias and increased expression of aromatase and hormone receptors (were correlated, $p = .025$).

Overweight dogs, compared to lean and optimal weight dogs, more often showed signs of carcinoma invasion of lymphatic vessels. A decrease in the expression of adiponectin against the background of an increase in the number of macrophages in obese patients correlates with a high histological degree of neoplasia and lymphatic invasion, which justifies an unfavorable prognosis (Lim et al., 2015).

The etiological significance of the influence of feeding factors on the probability of developing mammary cancer requires further study. According to multiple logistic regression analysis, neither a high-fat diet nor obesity in the 1 year before diagnosis increased the risk of mammary cancer. The authors showed that the risk of neoplastic changes in functional tissue in 9–12-month-old dogs with reduced body weight was lower both in intact (odds ratio (OR) = 0.04 (95% CI 0.004–0.4)) and sterilized ((OR = 0.60 (95%, CI 0.2–1.9) females (Sonnenschein et al., 1991). This statement is consistent with the results presented by Sorenmo et al. (2011): the influence of obesity on mammary tumor risk is highest at an early age, body weight gain closer to the time of tumor diagnosis is insignificant, probably due to negative hormonal influence on functional tissue.

In addition, a multivariate analysis of the study found a link between diet and mammary cancer risk: dogs fed a diet high in red meat and dogs that were obese at age 1 were significantly more likely to develop dysplasia and mammary tumors, similar to the findings of Sorenmo et al. (2011).

Our studies did not confirm the regularity of the relationship between the frequency of dysplasia and mammary tumors in bitches with a diet (Perez Alenza et al., 1998).

The management of patients with oncological pathology can be problematic not only because of their complex multifaceted clinical picture of the course of the disease but also because of common misconceptions about the optimal management of feeding animals with neoplastic diseases in general (Mauldin, 2014).

Despite the fact that most publications have confirmed the connection between obesity and tumors, there are isolated reports that deny this fact. In particular, according to Weeth (2008), there is no direct evidence that obesity is a promoter of cancer in dogs, and current knowledge about connection between obesity and cancer in dogs is provocative.

The obtained results are consistent with the data of other scientists (Sorenmo et al., 2009) regarding the difference in clinical and histopathological changes in mastopathy and mammary neoplasia (benign and malignant), and also confirm the theory that malignant tumors develop from areas within preexisting benign lesions. In particular, for malignant breast neoplasms, the frequency of verification of necrotic areas significantly (Pearson's χ^2 test, $p = .00$) exceeds the corresponding indicators for benign tumors and mastopathy (Im et al., 2014).

Mysak et al. (2011) on the basis of the interpretation of echographic structural disorders, distinguish the following manifestations of mastopathy in bitches: fibroadenomatosis with a predominance of the glandular component (characterized by the presence of multiple hypoechoic structures in the parenchyma due to the expansion of the ducts and weak signs of fatty involution); fibroadenomatosis with a predominance of the fibrous component (manifested by a relative increase in thickness and a significant increase in the echogenicity of the glands parenchyma); fibroadenomatosis with a predominance of a cystic component (characterized by the presence of rounded anechoic formations with signs of a cyst against the background of a changed structure of the parenchyma). Although in clinical practice, ultrasound diagnosis of mastopathy and mammary gland tumors in bitches is not widely used.

Analysis of own data and publications of other scientists (Dyrstad et al., 2015; Hartmann et al., 2005) allows us to conclude that there is an urgent need to monitor cellular atypia during histopathological studies of mastopathy, in order to assess the risk of developing malignant neoplasms against the background of fibrocystic changes of the mammary gland in bitches.

Thus, obesity affects the development, progression, and prognosis of dysplastic and neoplastic changes in functional mammary tissue in humans and dogs, but currently, insufficiently documented information is available regarding the underlying mechanism of their development.

Against the background of the obtained results, the issue of the effectiveness of sterilization of bitches in the prevention of cancer becomes debatable: it acts as a risk factor for obesity, which in turn increases the risk of mastopathy and neoplasia of the mammary gland.

Conclusion

- With excessive body weight, compared to the optimal one, the share of bitches with mastopathy decreases by two times against the background of increasing the risk of developing malignant mammary gland neoplasia by 1.4 times.
- During 2020–2022, the incidence rate of mastopathy in bitches with increased body conditions increased by 1.3 times (from 30.7% to 41.0%), with optimal body weight decreased by 1.2 times (from 60.1% to 49.7%).
- For mastopathy, the average indicators of bitches with insufficient and excessive BMI significantly exceed the values of dogs with malignant neoplasia of the mammary gland ($p < .05$; $p < .001$, respectively).
- The maximum incidence of mastopathy in bitches with increased body condition is recorded in animals aged 9–-11 years (35.8%, 95% CI: 29–42%) and older than 11 years (32.6%, 95% CI: 26–39%).
- Among dogs with excess body weight, the greatest risk of developing mastopathy is in such breeds as German shepherds (12.5%, 95% CI: 11–14%), Labrador retrievers (10.0%, 95% CI: 9–11%), boxers (9.2%, 95% CI: 7–12%), poodle and Dachshund (8.3%, 95% CI: 7–10%).

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