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Carcinogenesis of malignant neoplasms in cats: Development factors

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Abstract:
An effective and timely prevention of diseases in animal companions is a major task faced by the modern veterinary science. This research featured the correlation between malignant neoplasms and ophthalmological diseases in cats. The authors studied the multifactorial effect on the neoplastic proliferation and cancer-related ophthalmopathy to develop a general scheme of neoplastic proliferation in cats.
The effect of exogenous and endogenous factors on neoplastic proliferation was described based on experimental studies of numerous samples taken from 192 cats, including 67 cancer patients.
The comprehensive methodological approach included anamnestic data sampling, clinical examination, examination of the pathological area, hematology, cytomorphology, and chemical-toxicological tests.
The cats with various ophthalmopathies were simultaneously diagnosed with one or more of the following cancer types: carcinoma (37.13%), squamous cell carcinoma (32.83%), lymphoma (29.85%), sarcoma (20.89%), melanoma (2.98%), and mastocytoma (1.49%).
The main factors of neoplastic proliferation included diet, care, living conditions, physical activity, stress, chronic inflammation, repeated cases, the rate of increase/decrease in clinical signs, previous therapies, etc. In most cases, the cancer-related ophthalmopathy developed as a result of tumor metabolites or as a side-effect of chemotherapy. The incidence of cancer-related ophthalmopathy increased with age.
Cancer was found to correlate with the amounts of zinc, iron, and lead in the fur. Another correlation occurred between carcinomas, especially mammary tumors, and the high copper content in the fur.

Keywords: *Felis catus,* hematology, cytomorphology, visual diagnostics, oncological study, ophthalmological study, biochemistry, microelement, microelement

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INTRODUCTION

Carcinogenesis is a popular and multifaceted research problem, but all attempts to trace the chain of processes that cause cell degeneration down to its cause have failed so far. The nature of neoplastic proliferation remains a scientific mystery [1–3]. Cancer is one of the main causes of morbidity and mortality in domestic cats. A correct understanding of the oncogenome for each particular cancer type is critically important because it affects all aspects of patient care, from diagnosis and prognosis to targeted therapy [4]. However, the frequency of tumor formation means that cell neotransformation is not unique, i.e., it needs no exceptional phenomena to occur. Yet, the current trend towards the autonomous assessment of oncogenesis factors and the ultra-detailed biology of tumor cells hinders any attempts of synchronous perception and prevents antitumor resistance [5].

Carcinogenesis is a complex multi-stage process that involves exogenous factors (environment, lifestyle, etc.), endogenous factors (heredity, hormones, immune issues, etc.), and their combinations. These factors change the genetic material of cells and disturb the immune system [6–8]. Depending on the nature and severity of risk factors, the carcinogenesis progresses, accelerates, or decelerates [9].

Local veterinary centers provide assistance to animal companions that share the same ecosystem with humans. These centers prevent and treat new and recurring diseases in pets, as well as conduct research on relevant issues.

Cancer-associated ophthalmopathy is a major problem in veterinary and human medicine [10–16]. Poor knowledge of the fundamental principles of carcinogenesis in ophthalmopathy prevents early diagnostics. This research project aimed at solving this problem.

A comprehensive review of medical publications made it possible to outline some important research results [15–27].

Liu *et al.* [17] described a case series of paraneoplastic neuromyelitis optica, including two new histological types of cancer and their histological rationale.

Recurrent optic neuritis and extensive longitudinal and transverse myelitis seem to dominate the clinical picture [18]. In most cases, paraneoplastic neuromyelitis optica is associated with autoantibodies that target the aquaporin-4 (AQP-4) water channel. Neuromyelitis optica spectrum disorder (NMOSD) in senior-age patients is associated with paraneoplastic etiology because NMOSD usually affects the young. NMOSD cases could be associated with squamous cell carcinoma of the lung or with anti-AQP-4 in the serum and cerebrospinal fluid. However, the method of immunohistological staining revealed no AQP-4 on the surface of tumor cells [18].

Cohen *et al.* [19] analyzed neuro-ophthalmologic data and macrophotography in a large cohort of CRMP-5 IgG-positive patients to describe their clinical phenotype and treatment response. They linked the response of collapsing response-mediator protein-5 immunoglobulin G (CRMP-5) with paraneoplastic optic neuritis, vitritis, retinitis, or a combination of those. However, such findings are scarce in scientific literature.

Garibaldi *et al.* [20] reported extensive clinical, serological, and morphological data on middle-aged male patients with isolated bilateral ptosis and external ophthalmoplegia caused by immune checkpoint inhibitors.

Gordon & Dinkin [21] described different paraneoplastic syndromes with neuro-ophthalmologic manifestations, their diagnostics, and therapeutic options.

Graus & Dalmau [22] featured paraneoplastic neurological syndromes, i.e., disorders that affect any part of the nervous system in cancer patients, usually as a result of autoimmune reactions caused by ectopic expression of neuronal proteins in cancer cells.

Paraneoplastic neurological syndromes are rare. However, the method of immune checkpoint inhibitors (ICIs) in cancer treatment algorithms triggered the scientific interest in paraneoplastic neurological syndromes. Immune checkpoint inhibitors demonstrate a much higher incidence of immunological toxicity than conventional cancer therapy, e.g., immune-related neurological adverse events (IRAEs) that may manifest as paraneoplastic neurological syndromes [22]. In theory, immune checkpoint inhibitors may increase the risk of paraneoplastic neurological syndromes, especially in patients with some particular types of cancer, e.g., small-cell lung cancer. A prompt diagnosis and early treatment of paraneoplastic neurological syndromes may prevent irreversible neurological deficits [21]. To diagnose these disorders in the context of immune checkpoint inhibition, the authors also reviewed paraneoplastic neurological syndromes with underlying syndromes, types of neuronal autoantibodies, and associated immunological mechanisms. They studied scenarios when immune-nerelated neurological adverse events met the criteria for paraneoplastic neurological syndromes, as well as examined their incidence and clinical manifestations. The research yielded a set of recommendations for the prevention and treatment of paraneoplastic neurological syndromes that may arise during immune checkpoint blockade therapy.

Becquart *et al.* [23] reported that immune checkpoint inhibitors improved the prognosis of metastatic melanoma and other cancer types. While studying the side effect of myasthenia, they described 34 cases of myasthenia associated with anti-programmed cell death protein 1 checkpoint inhibitor and melanoma.

Scientific publications [15–26] are scarce on clinical ophthalmopathy in animals and feature no clinical forms of the course of pathological changes.

The morphological picture of regeneration mechanisms also remains understudied. We found neither statistics nor risk factor analysis for immune-mediated paraneoplastic ophthalmopathy in dogs, cats, or horses. Other understudied areas include clinical differential diagnostic criteria for immune-mediated paraneoplastic ophthalmopathy, classification of clinical forms, diagnostically substantiated criteria, clinical risk factors for blindness in various animal species, etc. Treatment methods for ophthalmopathy need further development.

Tumor metabolism, chemotherapeutic drugs, and internal protective factors affect the damage and regeneration of retina, choroid, iris, ciliary body. Ophthalmopathy protocols cannot be applied to cancer patients without establishing the cause of the vision loss associated with a long-term effect of chemotherapeutic drugs. In this regard, new ways of early diagnosis of cancer-related ophthalmopathy are a relevant research task.

Our review of domestic and foreign publications proved that this research direction is fundamental, relevant, and understudied. This research contributes to effective prevention and treatment of diseases in cats as animal companions that share the same ecosystem with humans. We studied the ophthalmology-related neoplastic proliferation in cats to analyze the effect of all factors on ocular carcinogenesis and develop a general scheme of neoplastic proliferation in animals.

STUDY OBJECTS AND METHODS

The research was conducted at the laboratory of Ophthalmology, Oncology, and Animal Biochemistry, Russian Biotechnological University, Moscow, Russia. The exogenous and endogenous factors of neoplastic proliferation were studied experimentally. The experiments involved samples obtained from 192 cats, including animals with various oncological diseases (n = 67).

The comprehensive methodological approach covered data sampling, clinical examination, examination of pathological area, hematological and cytomorphological studies, visual diagnostics, and a complete oncological and ophthalmological examination.

The final diagnosis relied on such methods as magnetic resonance imaging, computed tomography, hematological blood indices, and morphological conclusions.

The autopsy samples and antemortem materials were subjected to standard histological processing.

After extraction, the eyeballs or their fragments were immediately placed in labeled sealed containers with 10% neutral buffered formalin. The fixation lasted at least seven days with a single solution change. The material-to-formalin ratio was ≥ 1:10. After fixation, the pathological material was excised for macroscopy. In every case, we obtained 1–2 sections for each eyeball, a total of 2–4 sections, and four sections of organ tissue.

After the histological examination, the tissues were embedded in paraffin and subjected to microtomy, during which we stained 5-µm-thick sections with hematoxylin and eosin in line with the official protocol.

A sample of wool (1–3 g) was taken from a 1-cm^2 area on the back, below the projection of the shoulder blades. The accumulation levels of zinc, copper, iron, lead, cadmium, and arsenic were studied using an AQUILON AAS A2 atomic absorption spectrometer.

The cats were grouped based on their diagnosis and further subdivided into severity cohorts. The monitoring relied on the medical histories of the most common oncological diseases in cats. The monitoring made it possible to calculate the share of animals with cancer accompanied by visual impairment in the anamnesis against the total number of cancer patients.

The anamnestic data included the following criteria: breed, age, sex, living conditions, bad habits of the owners, oncological heredity, chronic diseases, long-term drug treatment, e.g., immunosuppressants, hormone replacement therapy, etc.

The statistic processing revealed the arithmetic mean values (M), average errors (m), and standard deviations (δ). The nonparametric Shapiro-Wilk criterion W made it possible to identify reliable differences between the groups, the contingency between the features, and the nature of the compatibility data distribution.

To verify the differences between two samples, we used Student's test and Fisher's criterion; to verify the difference between several independent samples for one feature, we applied the one-way variance analysis and the nonparametric variance analysis based on the Kruskal-Wallis test. The regression analysis and Spearman's rank correlation coefficient clarified the correlation between two or more samples.

The statistical significance level was 0.05 for all statistical analyses. The databases were compiled in Microsoft Office Excel 2010 and Statistica 10.0.

RESULTS AND DISCUSSION

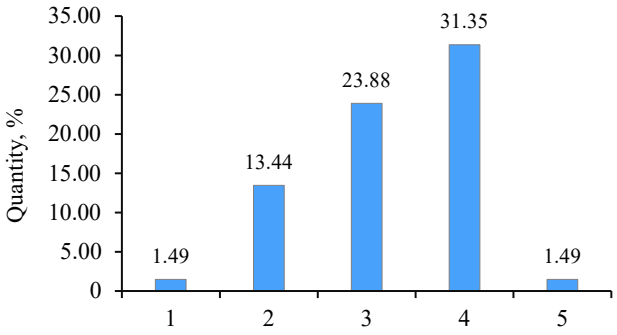
Etiology. About 34.9% of cats aged 3–15 y.o. had cancer at different stages, the most common localization being the oral cavity and phalanges. According to the morphological studies, the most common cases included carcinoma (31.35%), squamous cell carcinoma (28.35%), lymphoma (23.88%), and sarcoma (13.44%) (Fig. 1).

Other malignant tumors were much less common: melanoma and mastocytoma were responsible for 1.49% of all cases (Fig. 1). Benign tumors accounted for 11.9% of all tumors and tumor-like lesions. These results correlated with the data published by Ludwig *et al.* [4].

Some sporadic cases of sarcoma are associated with implants and injections in humans and animals [24–28]. However, cats appear to have a unique predilection for trauma and/or inflammation-related sarcoma. Injection-site sarcoma is a well-known phenomenon in cats, often associated with vaccination. In the USA and the UK, the estimates range from one case per 1,000–12,500 vaccinated cats [29, 30]. Most post-injection or post-traumatic sarcomas in cats are fibrosarcoma. Its histologic features include multinucleated giant cells, myofibroblast differentiation, and inflammatory infiltrates (lymphocytes and macrophages), which are typically absent from non-injection fibrosarcomas in cats [31–33]. Cats also may develop an intraocular sarcoma after an eye injury or an eye disease [34].

Researchers report no particular risk factors that could trigger a post-injection or post-traumatic sarcoma in cats. Potential chemopreventive strategies can probably be assessed in a relatively timely manner. Most cancers develop within three years after vaccination, although some researchers report a decade-long latency period [35–38].

Inflammation caused by post-traumatic and/or post-injection conditions is the main prerequisite for soft tissue sarcoma in cats. It develops in the withers, popliteal



1 – Melanoma, 2 – Sarcoma, 3 – Lymphoma, 4 – Carcinoma, 5 – Squamous cell carcinoma, 6 – Mastocytoma

Figure 1 Classification of neoplasms in cats

folds (injection sites), in the eye, and other soft tissues (trauma sites). Post-injection and post-traumatic sarcomas usually occur 2–10 months after the event. Ophthalmologic neoplasms can be multimodal or monomodal.

Animals with poor genetic or individual medical history are at high risk of cancer. Other risk factors associated with paraneoplastic ophthalmopathy may include poor diet and care, low physical activity, high stress, chronic inflammation, etc. Some previous medical treatments also may become risk factors. Cancerous ophthalmopathy could be triggered by biologically active substances in the tumor or may develop as a complication after chemotherapy.

Genetic and individual anamnesis. Breed is an important carcinogenic risk factor. Cancer often affects Siamese, Japanese, Somali, and Abyssinian cats, as well as some other shorthair breeds [24]. In our sampling, 34.3% of cancer cases belonged to pets adopted from animal shelters; in 16.3%, the owners failed to specify the breed. The diseased cats were crossbreeds (50.7%), British (26.9%), Maine Coons (10.4%), and Persians (7.5%). Exotic breeds were responsible for as little as 4.5% (Fig. 2).

Cats with one first-degree diseased relative in family history (parents, siblings, offsprings) were reported to develop cancer twice as often [8].

In our case, the data analysis revealed a strong hereditary nature: 19.4% of cancer cats had relatives with neoplasms (carcinoma, squamous cell carcinoma, lymphoma, sarcoma, melanoma, mastocytoma). About 15.4% of this number had a certain connection between subsequent generations in the first line. However, we failed to establish the correlation between types of inherited tumors across lines.

Mammary cancer is known to be of hereditary nature in felines. It is associated with point mutations in the BRCA2 tumor suppressor gene, which contains eight BRC repeats in exon 11. The BRCA2 protein interacts through the BRC (mammary cancer) domain with RAD51. This cellular component is important for genome stability and repairing double-strand breaks [25–27]. Feline mammary carcinomas are molecularly heterogeneous. An RNA-Seq-based comparative transcriptome profiling identified recurrent and exceptional differentially expressed (DEGs) genes used as a cancer marker in cats [28].

Immune response. Inflammation can be a major risk factor for the development of several types of cancer in animals [30]. Probably, the immune response to injection or trauma in cats is insufficient and excessive [30]. Eventually, it leads to chronic inflammation, causing proliferation and malignant transformation in fibroblasts. Chronic inflammation often leads to sarcoma, e.g., Kaposi's sarcoma, which is often associated with an inflammatory infiltrate [29]. Herpesvirus proteins associated with Kaposi's sarcoma activate such factors as Th2 lymphocytes, cyclooxygenase 2, and nuclear factor kappa B, which develop a pro-tumor inflammatory microenvironment [29].

According to Oh & Cho [29], injection-site sarcoma in cats may serve as a general model of inflammation-associated tumorigenesis due to the pathways shared by many different tumor histologies. Of course, not every vaccinated cat develops injection-site sarcoma. In the US and the UK, it occurs only in 0.1–0.01% of vaccinated cats. A strict control of living conditions, environment, diet, etc., may help reduce the risk. Biochemical and genomic screening is required to study the development of injection-site sarcoma and other tumors in cats. A recent example of best care for a cat with injection-site sarcoma is the approval of feline recombinant canarypox virus interleukin-2 (Oncept Il-2). It reduces local recurrence after standard therapy [29].

We attempted to identify cancer markers in cats using a clinical blood analysis and white blood cell count (Tables 1 and 2).

The white blood cell counts obtained from the cancer cats revealed a reliable 3.58-time decrease in eosinophils (Table 2) while the general clinical analysis showed a reliable ($p < 0.05$) increase in monocytes (2.94 times).

High monocyte count (monocytosis) is a marker of infectious diseases of viral, fungal, rickettsial, or protozoal nature; blood parasitic diseases, e.g., piroplasmosis; granulomatosis, e.g., tuberculosis, brucellosis, ulcerative colitis, enteritis; and tissue inflammation. In addition, monocytes may increase after surgery.

We detected low eosinophil and lymphocyte counts and high neutrophils; the red blood cell count exceeded the standard by 0.8%. High neutrophil counts (neutrophilia) accompany various bacterial infections, tissue inflammation or necrosis, progressive tumors with necrosis, acute and chronic leukemia, intoxication, etc.

The neutrophil-to-lymphocyte ratio may be a useful prognostic predictor for various types of cancer. However, it is seldom used for pre-surgery prognosis in feline cancer [30].

Biochemistry of blood serum. In addition to the clinical and leukocyte blood tests (Tables 1 and 2), we examined some key serum biochemical parameters (Table 3).

The biochemistry of blood serum reflects the state of metabolism in animals, i.e., the functional activity of individual organs and systems, as well as the general homeostasis. The biochemical analysis of blood serum shows the severity of the disease and the treatment effecti-

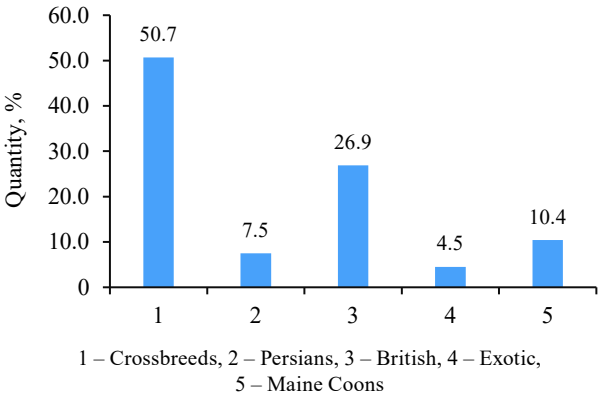


Figure 2 Paraneoplastic ophthalmopathy in cats by breed

Table 1 General clinical blood analysis of cats' blood samples (M ± SD)

Group	Neutrophils, %	Eosinophils, %	Basophils, %	Monocytes, %	Leukocyte count, $\times 10^9$/L	Lymphocytes, %	Red blood cell count, $\times 10^9$/L
Cancer patients (n = 67)	71.98 ± 9.63*	1.47 ± 0.35	0.34 ± 0.74	11.29 ± 2.55*	9.40 ± 6.08	20.03 ± 12.61	10.05 ± 1.39
Healthy cats (n = 125)	65.87 ± 14.52*	4.57 ± 0.46	0.48 ± 0.63	3.84 ± 1.13*	11.95 ± 3.64	42.18 ± 6.53	6.55 ± 1.70
Standard (reference data) [39]	60–75	2–8	0–1	1–4	5.5–13	36–51	5.28–9.97

* Significant differences between cancer and healthy patients are marked with an asterisk ($p < 0.05$), M – mean values, SD – standard deviations

Table 2 Leukocyte formula of cats' blood samples (M ± SD)

Group	Leukocytes, thousand/mcL	Lymphocytes, $\times 10^9$/L	Monocytes, $\times 10^9$/L	Neutrophils, $\times 10^9$/L	Eosinophils, $\times 10^9$/L	Basophils, $\times 10^9$/L
Cancer patients (n = 67)	9.40 ± 4.99	1.58 ± 0.98	0.52 ± 0.37	7.35 ± 4.49	0.12 ± 0.15*	0.01 ± 0.01
Healthy cats (n = 125)	8.61 ± 1.87	3.35 ± 1.28	0.01 ± 0.01	4.82 ± 1.95	0.43 ± 0.11*	0.00 ± 0.01
Standard (reference data) [39]	5.0–19.5	1.5–7.0	0–0.85	2.5–12.5	0–1.5	–

* Significant differences between cancer and healthy patients are marked with an asterisk ($p < 0.05$), M – mean values, SD – standard deviations

Table 3 Key biochemical parameters of cats' blood serum

Parameters	Group		Standard [39]
	Cancer patients	Healthy cats (control)	
Total protein, g/L	67.52 ± 9.72	55.96 ± 9.35	54–77
Indirect bilirubin, µmol/L	22.60 ± 29.02*	5.27 ± 1.35*	3–12
Direct bilirubin, µmol/L	12.92 ± 20.02*	5.13 ± 1.64*	0–5.5
Globulins, g/L	34.73 ± 8.67	23.43 ± 7.25	–
Alanine aminotransferase, m/L	123.34 ± 111.89*	55.27 ± 11.37*	17–79
Aspartate aminotransferase, m/L	83.73 ± 80.91*	14.84 ± 3.23*	9–29
Lactate dehydrogenase, m/L	145.04 ± 60.40	57.28 ± 20.37	55–155
Amylase, m/L	1505.26 ± 257.66	1387.32 ± 136.92	780–1720
Alkaline phosphatase, m/L	73.88 ± 61.11*	43.28 ± 23.48*	39–55
Urea, µmol/L	10.28 ± 2.80	5.85 ± 1.28	2–8
Creatinine, µmol/L	128.37 ± 34.07	103.28 ± 22.84	70–165
Glucose, µmol/L	6.16 ± 1.71	4.28 ± 2.01	3.2–6.4
Alanine aminotransferase vs. aspartate aminotransferase, RU	0.78 ± 0.39*	3.72 ± 0.45*	–
Calcium, mmol/L	2.84 ± 0.52	2.21 ± 0.33	2–2.7
Phosphorus, mmol/L	1.51 ± 0.23	1.34 ± 0.32	1.1–2.3
Sodium, mmol/L	154.01 ± 3.56	144.26 ± 23.74	143–165
Potassium, mmol/L	4.43 ± 0.38	5.01 ± 0.45	3.8–5.4

* Significant differences between cancer patients and control are marked with an asterisk ($p < 0.05$)

veness. In some cases, the biochemical parameters of blood serum may clarify the diagnosis made using other research methods.

The data obtained showed high total protein (by 20.7%) and globulin contents (by 48.2%). The increase in the synthesis of proteins and, especially, globulins, is a factor of immune response, which is typical for cancer patients. These data were confirmed by the content of bilirubin fractions in the blood samples. The direct bilirubin increased 2.51 times whereas the indirect bilirubin rose 4.28 times. The accelerated protein metabolism was manifested in the excretion of its derivatives, i.e., bilirubin.

A bilirubin molecule can bind with two molecules of glucuronic acid to form a water-soluble conjugate, i.e., direct bilirubin. Bilirubin enters bile mainly in its indirect form. Bilirubin count shows liver function and hemolytic processes. High bilirubin in blood plasma, especially its direct fraction, means a liver cell damage.

In this research, the cancer patients had the urea level increased by 75.7% compared to the control. The total amount of residual nitrogen and individual substances is another diagnostic tool. Low residual nitrogen in the plasma indicates poor liver function while high residual nitrogen means poor kidney function. Some diseases affect the total amount of residual nitrogen in the blood

plasma and its individual components. Poor excretory function of the kidneys results in a sharp increase in urea, i.e., uremia. In adult animals, high total nitrogen in the blood plasma is associated with increased breakdown of tissue proteins.

Creatine is important for energy metabolism as it provides for the synthesis of creatine phosphate in muscles and brain cells. As a result of dephosphorylation, creatine phosphate converts into creatinine. The standard amount of creatinine is 103.28 ± 22.8 μM for healthy cats. In the cancer patients, the amount of creatinine increased by 24.3% to reach 128.37 ± 34.1 μM. Since the level of creatine phosphate is proportional to the muscle tissue, the level of creatine in the blood plasma of young animals is always higher than that of creatinine.

The glucose content increased as well (by 43.9%) but remained within the standard range (3.2–6.4 mM). A carbohydrate diet boosts the concentration of glucose in the blood. The glucokinase (hexokinase) of the liver develops glucose-6-phosphate, the level of which depends on glucagon and insulin. High blood glucose inhibits glucagon synthesis and boosts insulin. This hormonal ratio is a direct allosteric effect of glucose.

We also detected an increase in the total amount of alanine aminotransferase and aspartate aminotransferase. These enzymes participate in the metabolism of amino acids, as well as intracellular metabolic processes. Membrane permeability, necrosis, and cellular lysis may increase the level of enzymes.

In this research, the main biochemical parameters of cat blood serum deviated from the standard values in cancer patients.

Oncological ophthalmopathy was established in 7.5% of all clinical cases. Approximately 16.4% demonstrated secondary inflammatory processes, manifested as serous and fibrinous posterior uveitis. About 1.5% had malignant neoplasms in the following forms: the invasion of surrounding tissues, lysis of bone structures, displacement or lysis of eye structures, invasion into the retrobulbar space, an inflammatory component, etc.

We also detected random cases of multimodal tissue damage of various organ systems, namely lung cancer and iris melanocytoma. There, the ophthalmopathy was of a primary long-term homogeneous limited nature with no inflammation.

We enucleated the eyeballs and removed the retrobulbar tissues, as well as sampled the damaged organs (Fig. 3a, b). The sclera, limbus, and damaged organs were macrophotographed (Fig. 3c, d).

The case below had a combined lesion of the eyeball choroid (melanocytoma), lung (sarcoma), and lymphatic system (lymphoma) (Table 4).

The micromorphological examination of iris melanocytoma revealed its thickness and changes in the layer ratio. The focal thickening was the morphological equivalent of the lesion. It was a well-defined, highly cellular mass that consisted of round and polygonal melanocytes with strongly pigmented cytoplasm (Fig. 4b). The nuclear details of the cells were partially invisible because of pigmentation. However, the signs of nuclear atypia were minor (Fig. 4a), with a mild scleral infiltration.

Old age was one of the most significant cancer risks. About 90% of all new cancer cases occur in ten-plusers. In our research, the average age of tumor onset in cats was 12.7 ± 6.1 years. This result exceeded the average age of oncology development in cats in Portugal [40] and Mexico City [41] by 3 years.

Pérez-Enriquez *et al.* [41] reported a late first development of benign tumors compared to malignant ones.

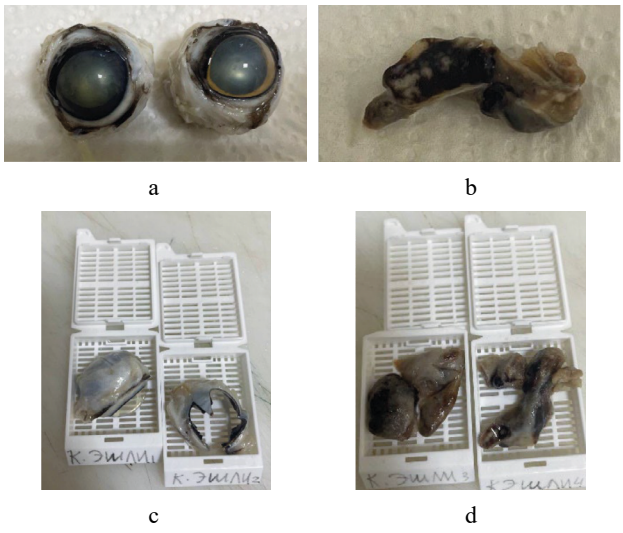


Figure 3 Macrophotographs: (a) eyeballs, (b) lung and sections, (c) sclera and limbus, and (d) lung

Table 4 Histopathology of feline eyeballs

Structure	Histopathology
Cornea	The corneal wall is deformed (artifact); the thickness was not measured. The corneal wall consists of 5–8 epithelium layers with no significant histological changes. The corneal stroma consists of keratinocytes with no histological changes. Descemet's membrane and corneal endothelium demonstrate no histological changes
Choroid	The anterior part is represented by clusters of melanocytes with no histological changes. The blood vessels are not dilated. The ciliary body demonstrates no histological changes. The pectineal ligament is indistinguishable
Tapetum	Not available
Iris	The iris is focally thickened by a round well-defined highly cellular mass that consists of round and polygonal melanocytes with pigmented cytoplasm. The nuclear details being partly obscured by pigmentation, the cells show only mild nuclear atypia. Mild scleral infiltration is observed
Retina	The vessels are not dilated, with no histological changes
Optic nerve	Not available

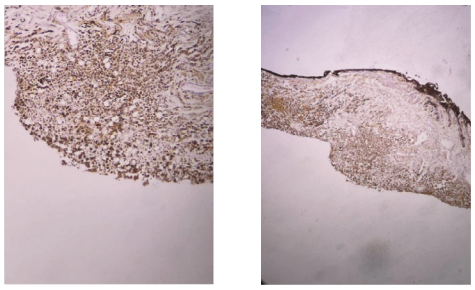


Figure 4 Microphotography of the iris: (a) nuclear details partially obscured by pigmentation (400× magnification), (b) focal thickening (100× magnification) after hematoxylin and eosin staining

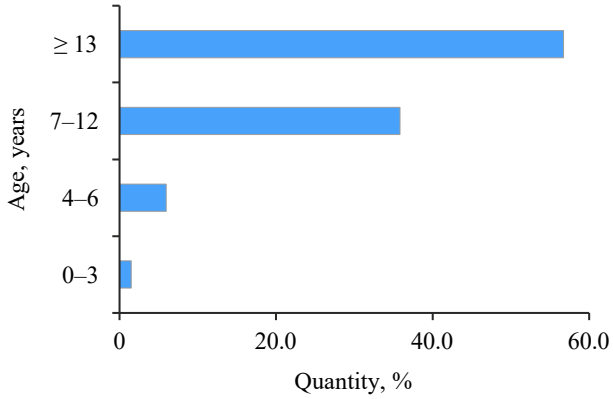


Figure 5 Age profile of cats

They calculated the correlation between the histological type and age, as well as summarized the age-related features of hematopoietic and lymphoreticular tumors. The authors statistically confirmed a high risk of lymphoma in young cats. Cancer patients of 7–12 y.o. and 13-plusers developed ophthalmopathy more often than other age groups. The frequency was 35.82 and 56.72% of all cases, respectively (Fig. 2). In cats under 3 y.o. and between 4 and 6 y.o., ophthalmopathy was the least common: 1.49 and 5.97% of all cases, respectively.

Our data confirmed other reports on the correlation between age and the overall incidence of malignant tumors in animals [8, 24, 34]. However, our data on the high incidence of neoplasms in adult and old cats were by 8.28% lower than those in Mexico City [41]. The main group demonstrated a significant increase in tumor incidence by 21.02%; the geriatric and young groups showed a decrease of 6.23 and 3.91%, respectively. The research included a quantitative sample of animals and studies based on animal shelters.

Domestic cats can serve as models for various non-neoplastic diseases and are particularly valuable for studying inherited ophthalmologic diseases. Cats and humans demonstrate a significant homology for certain genes [29]. Natural tumors in domestic cats make it possible to model cancer development in humans because they share some characteristics. Such studies include spontaneous cancers that develop in immunocompetent animals living in the same environment as humans. In addition, the relatively short lifespans facilitate research completion and data collection. A lot of cancer types have no treatment standards that could provide evaluation of treatment methods.

Feline oral squamous cell carcinoma is common and shares some clinical and molecular characteristics with human head and neck cancer. These similarities make it an attractive model for new treatment trials. Feline mammary tumors are typically malignant and aggressive, with a triple negative phenotype being more common than in humans. They also provide an opportunity to explore potential targets and treatments. Feline injection-site sarcoma may be a model for inflammatory tumorigenesis, although no definitive results are available for humans. However, there are good prospects for studying individual differences in treatment susceptibility, as well as developing preventive and therapeutic strategies [29].

If we interpret the age of cats to human age, these data correlate with the results of studies of neoplastic proliferation in middle-aged people.

In 65-plusers, the colorectal cancer risk is approximately three times as high as in people aged 50–64 y.o. and approximately 30 times as high as in people aged 25–49 y.o. For cats, the correlating age is 13, 9–12, and 2.5–8 y.o., respectively [31]. The average age of diagnosis is 68 and 72 for men and women, respectively, and 13–14 for male and female cats, respectively (Fig. 5).

The age-related character of colorectal cancer is especially obvious in developed countries, where the incidence of colorectal cancer is the highest. There, the incidence of colorectal cancer is associated, among other things, with a longer life expectancy, resulting in a higher proportion of senior citizens in the population [31].

However, some recent studies demonstrated an increase in the incidence of colorectal cancer in young people aged 20–49 y.o. in the USA and Europe (i.e., 2–8 years on the cats' age scale) [33]. The current recommendation is to conduct the first colorectal cancer screening at 50 y.o. (9 y.o. for cats). If the trend perseveres, these screening recommendations will have to be revised.

The sex dimorphism shows that male cats are more likely to get cancer, i.e., 57.14% of the total number of oncological diseases. However, most researchers deny the effect of sex on cancer development in cats [40]. Females are more likely to develop mammary cancer: its incidence is 17 times higher in females than in males, i.e., 25.40 vs. 1.50%. These data confirm other reports [24]. Moreover, males have a worse survival prognosis and an almost 40.00% higher mortality [8]. On the other hand, females have a higher proportion of right-sided tumors, which are often diagnosed at a late stage and tend to be more aggressive than left-sided tumors.

This sex-related difference remains a mystery. It may be related to the differences in the risk factors, diet, and

sex hormones [8]. In our research, castrated males were more common than sterilized females. The castrated males with cancer developed ophthalmopathy in 47.62% while for uncastrated males it was only 9.52%. Unsterilized females with oncological diseases and ophthalmopathy were more common than sterilized ones: 33.33 and 9.53%, respectively.

Early ovariohysterectomy (≤ 2 y.o.) significantly reduces the risk of mammary tumors, its effect depending on the timing [24].

The type of neoplasm was found to correlate with the vascular tract inflammation. Our morphological research made it possible to identify the most common malignant neoplasms with ophthalmopathy in cats. The cats with an ophthalmopathy were simultaneously diagnosed with one or more of the following diseases: carcinoma (25 cats; 37.13%), squamous cell carcinoma (22 cats; 32.83%), lymphoma (20 cats; 29.85%), and sarcoma (14 cats; 20.89%). Other malignant tumors were much less common: melanoma (2.98%) and mastocytoma (1.49%). In other words, cats with two or three types of tumors were rather common.

Considering the ratio of inflammation of the anterior uveal tract (Table 5), the acute fibrinous or hemorrhagic iridocyclitis and chorioretinitis in cats were much less frequent than, e.g., in dogs.

Cancerous ophthalmopathy manifested itself as separate neoplasms and metastases under the effect of substances that accumulated in the vessels or nerves. They triggered an inflammatory or degenerative reaction on the part of the vascular or nervous tissue of the choroid.

Figure 6 illustrates the course of anterior uveitis. Mydriasis and hyperpigmentation of the iris were present in 74.6 and 85.1%, respectively. The cornea was transparent (97.0%), the conjunctiva was pigmented (85.1%). The fluid of the anterior chamber was opalescent (47.8%).

Figure 7 shows chronic lesions of the posterior uveal tract in cats: they occurred more often in the chronic form of serofibrinous (52.2%) or hemorrhagic (31.3%) chorioretinitis, as well as hemorrhagic irido-cyclitis (7.5%).

About 6.0% of posterior uveal tract lesions were fibrinous (52.2%) or hemorrhagic (31.3%) inflammations, as well as retinal detachment (Fig. 8). Chronic chorioretinitis paired with vitreous adhesions (26.9%), posterior capsular false cataract (68.7%), posterior synechiae (7.5%), or posterior margin ruptures (7.5%).

Lymphomas usually have a multifactorial etiology. Chronic viral diseases, poor immune system, or immunodeficiency may be prerequisites for the development of some lymphomas in cats [6].

The cats with lymphoma were more likely to acquire chronic issues of the posterior uveal tract, i.e., fibrinous and hemorrhagic chorioretinitis (Table 5).

Carcinoma in cats is usually triggered by hormonal imbalance, genetic predisposition, or carcinogens [8]. In the six-plusers, mammary tumors were the most common, followed by skin neoplasms. Carcinoma was most often accompanied by chronic damage to the posterior uveal tract, i.e., fibrinous or hemorrhagic chorioretinitis. Chronic inflammation in the posterior uveal tract led to irreversible morphological changes.

Table 5 Clinical forms of inflammation in the uveal tract in cats with neoplasms

Clinical forms	Cats, %			
	Sarcoma (n = 9)	Lymphoma (n = 16)	Squamous cell carcinoma (n = 19)	Carcinoma (n = 21)
Fibrinous iridocyclitis	–	12.50	5.26	9.52
Hemorrhagic iridocyclitis	11.11	6.25	10.53	4.76
Fibrinous chorioretinitis	66.67	50.00	52.63	47.62
Hemorrhagic chorioretinitis	22.22	31.25	31.58	38.10

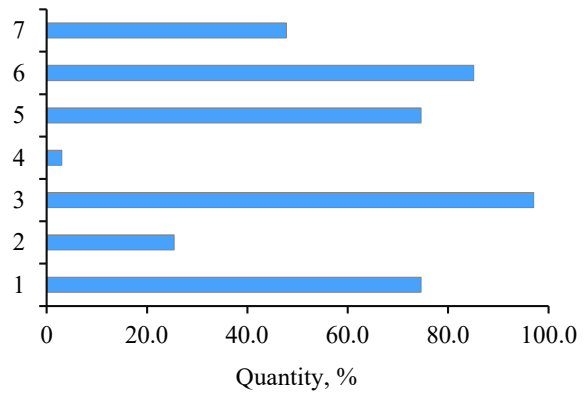
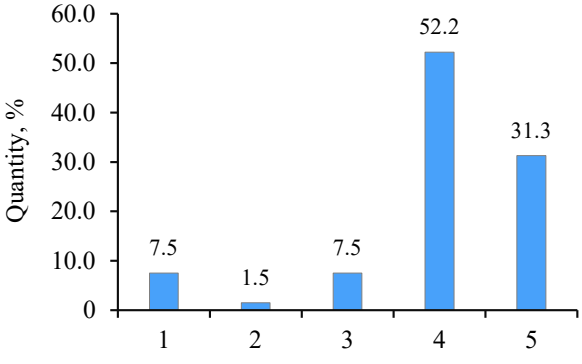
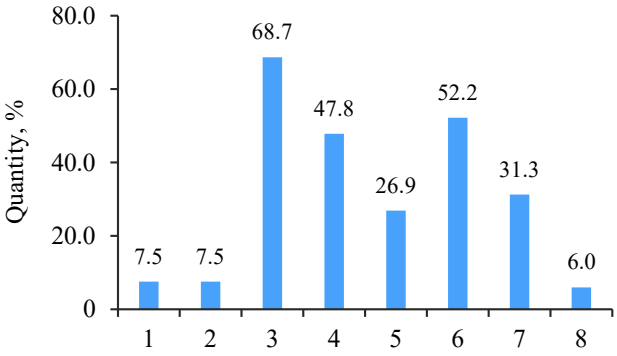


Figure 6 Clinical course of anterior uveal tract lesions in cats: conjunctiva (1 – pigmentation, 2 – no pigmentation), cornea (3 – transparent, 4 – posterior keratitis), iris (5 – mydriasis, 6 – iris hyperpigmentation), and anterior chamber fluid (7 – opalescence)



1 – Fibrinous iridocyclitis, 2 – Chorioretinitis, 3 – Hemorrhagic iridocyclitis, 4 – Fibrinous chorioretinitis, 5 – Hemorrhagic chorioretinitis

Figure 7 Clinical forms of inflammation in the posterior uveal tract in cats



1 – Posterior synechiae, 2 – Pupillary ruptures, 3 – Posterior capsular false cataract, 4 – Vitreous opalescence, 5 – Vitreous adhesions, 6 – Fibrinous inflammation, 7 – Hemorrhagic inflammation, 8 – Retinal detachment

Figure 8 Clinical course of posterior uveal tract lesions in cats

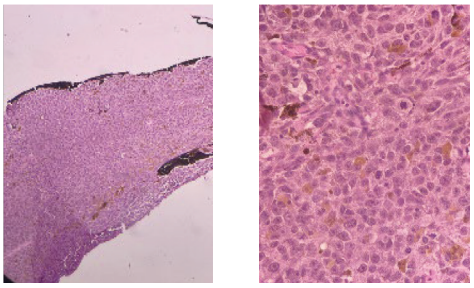
a b

Figure 9 Chorioretinitis in cats with preretinal opacification of the vitreous body: fundus and vitreous body (a), anterior segment of the eyeball unchanged (b)

Posterior uveal tract inflammation dominated in the cases of uveal inflammation in paraneoplastic ophthalmopathy: fibrinous inflammation (47.62% carcinoma, 66.67% sarcoma) and hemorrhagic inflammation (22.22% sarcoma, 47.62% carcinoma) in all cases of cancer.

Posterior uveal tract inflammation proved to be a quite common form of uveal inflammation in the cats with paraneoplastic ophthalmopathy.

Figure 9 describes the chronic chorioretinitis. The eyelids were of normal size; the palpebral fissure was normal; the conjunctiva was pale pink; the cornea was shiny, transparent, spherical, and moist; the anterior chamber was deep; the aqueous humor of the anterior chamber was transparent. The iris was yellow-green, with a normal pupillary edge. The ophthalmoscopy showed that the lens was unaffected, but the vitreous body demonstrated some opacity; the optic disc and retinal vessels were normal.



a b

Figure 10 Microphotography of neoplasm after hematoxylin and eosin staining: (a) neoplasm (10× lens, 20× ocular lens), (b) mitotic activity and cells with melanin (10× lens, 40× ocular lens)

In the case illustrated in Fig. 9, the oncological lesion of the iris (melanocytoma) was not accompanied by neoplasms in other organs (Table 6). Unlike multimodal lesions, monolesions of the iris were more likely to occur together with severe anisocytosis and anisokaryosis.

The microarchitecture of iris melanoma demonstrated focal proliferation caused by the abundant cellularity of the tumor. It consisted of polygonal and rounded cells with moderate eosinophilic cytoplasm and melanin. The nuclei were round and irregular, of medium and large in size, with pronounced karyomegaly, coarse-grained chromatin, and 1–3 clearly visible large nucleoli. The mitoses were abundant, with severe anisocytosis and anisokaryosis. The tumor slightly infiltrated the underlying sclera (Fig. 10).

We revealed a significant correlation between cancer and the accumulation of zinc, iron, and lead (Table 7).

Table 6 Pathohistological changes in cats' eyeballs

Eyeball structure	Histology
Cornea	The corneal wall is deformed (artifact); the thickness was not measured. The corneal wall consists of 5–8 epithelium layers with no significant histological changes. The corneal stroma consists of keratinocytes with no histological changes. Descemet's membrane and corneal endothelium demonstrate no histological changes
Choroid	The anterior part is represented by clusters of melanocytes with no histological changes. The blood vessels are not dilated. The ciliary body demonstrates no histological changes. The pectineal ligament is indistinguishable
Tapetum	Not available
Iris	The iris is focally thickened by a highly cellular mass that consists of round and polygonal melanocytes. The cells have a moderately eosinophilic cytoplasm; most cells in the cytoplasm are rich in black granular pigment (melanin). The nuclei are round and irregular, of medium and large size, with pronounced karyomegaly, coarse-grained chromatin, and 1–3 clearly visible large nucleoli. The mitoses are abundant (≤ 20 per 10×400). The anisocytosis and anisokaryosis are pronounced, with a weak infiltrative growth of the tumor into the underlying sclera. The tumor demonstrated no necrosis
Retina	The vessels are not dilated, with no histological changes
Optic nerve	Not available

Table 7 Macro- and microelements in cats with different health status, μg/g

Health status	Macro- and microelements					
	Zn	Cu	Fe	Pb	Cd	As
Paraneoplastic ophthalmopathy	43.78 ± 9.85*	23.84 ± 8.54*	254.84 ± 98.42	5.961 ± 2.513	0.174 ± 0.027	1.521 ± 0.242
Healthy	191.67 ± 47.43*	12.71 ± 1.83*	157.82 ± 38.74	4.580 ± 1.554	0.140 ± 0.058	0.991 ± 0.692

* Reliable differences in the level of macro- and microelements in cancer patients and healthy animals were marked with an asterisk ($p < 0.05$)

The animals with paraneoplastic ophthalmopathy demonstrated a statistically significant increase ($p < 0.05$) in the copper level (Table 11), which confirmed the data published elsewhere [35–37]. The high copper concentration in the fur was associated with a low zinc content. This correlation may be due to carcinoma and mammary tumors, which predominated in the sample [38, 42–44].

Due to the small sampling for each particular type of cancer, we revealed no correlations between other macronutrients and paraneoplastic ophthalmopathy.

Although scientists associate cancer with high lead content, our study did not confirm the well-established cancerogenic effect of lead [45]. The low zinc levels in paraneoplastic ophthalmopathies may be associated with its need for optimal metabolism of retinal cells, modification of plasma membranes of photoreceptors, regulation of the light-rhodopsin reaction, modulation of synaptic transmission, and maintenance of taurine in the retina [3]. The elevated copper levels are associated with the proliferation and metastasis of cancer cells, which need copper [3].

CONCLUSION

In this research, the cats with ophthalmopathy were simultaneously diagnosed with one or more of the following cancers: carcinoma (37.13%), squamous cell carcinoma (32.83%), lymphoma (29.85%), sarcoma (20.89%), melanoma (2.98%), mastocytoma (1.49%). Evidently, cats with two or three types of cancer are a common veterinarian case.

The main factors of neoplastic proliferation included the diet, care, living conditions, physical activity, stress, chronic inflammation, repeated cases, the rate of increase/decrease in clinical signs, previous therapeutic measure, etc. Cancer-related ophthalmopathy could be triggered by biologically active substances in the tumor or chemotherapeutic drugs, i.e., as a therapy complication. The incidence of cancer-related ophthalmopathy increased with age. Cancer correlated with the accumulation of zinc, iron, and lead in the fur. Carcinomas, especially mammary tumors, correlated with high copper concentration in the fur.

CONTRIBUTION

A.P. Kaledin, M.V. Stepanova, L.F. Sotnikova, and S.Yu. Zaytsev developed the research concept; M.V. Stepanova, S.Yu. Zaytsev, and L.F. Sotnikova designed the methodology; A.S. Kuryndina, D.A. Vilmis, and Yu.N. Melikova worked with the software; A.S. Kuryndina, D.A. Vilmis, Yu.N. Melikova, M.V. Stepanova, and L.F. Sotnikova were responsible for the data validation; A.S. Kuryndina, D.A. Vilmis, Yu.N. Melikova, L.F. Sotnikova, and S.Yu. Zaytsev provided the formal analysis; M.V. Stepanova, S.Yu. Zaytsev, and L.F. Sotnikova wrote the review; A.S. Kuryndina, D.A. Vilmis, Yu.N. Melikova, S.Yu. Zaitsev, and L.F. Sotnikova performed the data curation; M.V. Stepanova and S.Yu. Zaitsev drafted the article; M.V. Stepanova, S.Yu. Zaitsev, and L. F. Sotnikova proofread the manuscript; M.V. Stepanova, S.Yu. Zaitsev, and L.F. Sotnikova supervised the project; M.V. Stepanova, S.Yu. Zaitsev, and L.F. Sotnikova were responsible for the project administration; L.F. Sotnikova acquired the funding. All authors approve of the final version of the manuscript.

CONFLICT OF INTEREST

The authors declared no conflict of interest regarding the publication of this article.

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