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# Estudio retrospectivo de los grados histopatológicos de las neoplasias mamarias en perras domésticas

*Retrospective study of histopathological grades of mammary neoplasms in domestic bitches*

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**Palabras claves:**
Tumor maligno, tumor benigno, esterilización, raza, mortalidad.

**Resumen**

Las características epidemiológicas y clínico-patológicas de las neoplasias mamarias en perras domésticas es información valiosa para analizar el comportamiento de la enfermedad y son un recurso potencial para promover avances en las neoplasias mamarias. El objetivo de este trabajo investigativo fue valorar y analizar la clasificación de los grados histopatológicos en las diversas neoplasias mamarias en las perras domésticas e identificar los factores potenciales de riesgo como la edad, raza, nutrición y la falta de esterilización y como estos factores influyen en la aparición de las neoplasias mamarias y el tiempo de sobrevida de los pacientes. Los tumores más frecuentes fueron el Adenoma complejo, el Tumor mixto benigno, el Carcinoma complejo y el Carcinoma tipo mixto. Las razas afectadas con mayor frecuencia fueron el Poodle, Cocker Spaniel, Yorkshire Terrier, Pastor Alemán y sólo el Cocker, el Labrador mostraron mayor riesgo. En general, los datos indican que las neoplasias mamarias afectan sobre todo a hembras enteras, adultas mayores de 8 años de diversas razas; cursa con mortalidad alta y sobrevida corta en pacientes con tumor maligno de gran tamaño; sin embargo, las razas más afectadas no necesariamente son las más predispuestas. Además los factores de la alimentación y no esterilización temprana juegan un papel importante en la presencia de las neoplasias mamarias en perras domésticas.

**Keywords:**
Malignant tumor, benign tumor, sterilization, race, mortality.

**Abstract**

The epidemiological and clinicopathological characteristics of mammary neoplasms in domestic bitches are valuable information to analyze the behavior of the disease and are a potential resource to promote advances in mammary neoplasms. The objective of this research work was to evaluate and analyze the classification of histopathological grades in the various mammary neoplasms in domestic bitches and to identify possible risk factors such as age, breed, nutrition and lack of sterilization and how these factors influence the appearance of mammary neoplasms and the survival time of the patients. The most frequent tumors were complex adenoma, benign mixed tumor, complex carcinoma, and mixed-type carcinoma. The most frequently affected breeds were the Poodle, Cocker Spaniel, Yorkshire Terrier, German Shepherd and only the Cocker, with the Labrador showing the highest risk. In

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general, the data indicate that mammary neoplasms mainly affect all females, adults older than 8 years of different races; It presents with high mortality and short survival in patients with a large malignant tumor; However, the most affected breeds are not necessarily the most predisposed. Furthermore, feeding factors and early sterilization do not play an important role in the presence of mammary neoplasms in domestic bitches.

## Introduction

The most common and used methods to detect the presence of neoplastic cells in an individual are cytology and histopathology (1). Cytology is one of the most widely used diagnostic tools in Veterinary Pathology due to the easy sampling, minimal invasiveness, rapid diagnosis and easy availability (1).

Histopathology represents an examination of the morphological, structural and cellular characteristics of the tissue, thus allowing to know the biological behavior of the different types of tumors, their histological grade, neoplastic invasion, providing valuable information on the degree of invasion of neoplastic cells, stage of neoplastic proliferation, degree of malignancy and an approximate morphological classification to have a better prognosis and the most appropriate treatment (1).

Mammary neoplasias are most frequently diagnosed in female dogs and are therefore an important clinical problem. They are known for their great biological and histomorphological heterogeneity; they are made up of cell populations of epithelial, myoepithelial and/or mesenchymal origin. Furthermore, although these neoplasias may be benign, approximately 50% are malignant. Although in most cases they are tumors of epithelial origin or carcinomas, there are also other neoplasias that are less prevalent and are not known in depth (2).

The etiology of mammary neoplasias in female dogs is multifactorial, with the main risk factors being hormonal influence, with this risk increasing from 0.5% to 8% and up to 26%, depending on whether the ovariohysterectomy is performed in the first, second or any subsequent estrus, respectively; and age, with the average age of onset being 9-11 years in female dogs with malignant mammary tumors compared to 7-9 years in female dogs with benign tumors. In addition, other risk factors also include breed and dietary factors. Previous studies have shown that some breeds (e.g. Poodle, Yorkshire Terrier, German Shepherd, Cocker Spaniel, Labrador among others) have a genetic predisposition

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to suffer mammary tumors, although this predisposition varies according to geographic location (2).

Likewise, other studies have determined that dogs fed a diet rich in red meat or that are obese have a higher risk of developing mammary dysplasia or neoplasia (2).

Various studies indicate that 60% of breast neoplasms are located in the fourth and fifth mammary gland, probably due to the greater volume of breast tissue susceptible to tumor transformation. More than 50% of cases of breast neoplasms were multiple (3).

**Goals**

General objective

- Retrospective study of the histopathological grades of mammary neoplasias in domestic dogs.

Specific objectives

- To assess the classification of histopathological grades in the various breast neoplasms.
- Identify predisposing factors: age, race and nutrition, which influence the presentation of neoplasias.
- To determine how the lack of sterilization influences the presence of mammary neoplasia.

## Materials and methods

The objective of this bibliographical review is to bring us closer to the retrospective study of the histopathological grades of mammary neoplasias in domestic dogs. This work aims to generate current information that compiles reports or clinical cases, synthesizing the results of multiple primary investigations and serve as a source of reference for future analysis.

The search, selection and compilation in the PubMed, Scielo and Redalyc databases was carried out using keywords and connectors present in each of the databases. It began with a general search at the Latin American level and then proceeded to a more detailed search by country. Keywords such as “mammary tumors in dogs” and “histopathological grades of breast tumors” were used for the general search, as well as for the rest of the countries belonging to Latin America.

The selection of studies for inclusion was performed using a two-step approach. During the first stage, articles, scientific journals and official pages were selected from the search

results based on titles and abstracts, excluding those considered irrelevant to the topic (all those that were outside the search year range).

The bibliographies of the reviewed articles were scanned for additional older literature. The corresponding studies on the research questions were assessed in the second stage with the full text, including the studies for which inclusion was done on the basis of title or abstract. All retained articles and scientific journals after the first step were reviewed and verified to meet the criteria.

**Discussion**

Mammary neoplasias account for approximately 42-50% of all types of neoplasia. The incidence of mammary neoplasia in bitches is higher than in other domestic species and three times higher than in humans (4).

The average age at which mammary gland neoplasias occur is 10-11 years, with an interval of 2-16 years (4). It has been observed that there is a continuous transformation of breast tissue known as histiogenic transformation, which takes place through hyperplasia, dysplasia, benign neoplasia and malignant neoplasia (4).

These neoplasms are usually multicentric, the caudal glands are more affected than the cranial ones, they can be hard in consistency, with circumscribed or indefinite edges, indicating malignant behavior due to infiltration into adjacent tissues. Some may be encapsulated. They are palpable when they measure at least 1 cm in diameter (4). When breast neoplasm is present and malignancy is suspected, it is recommended to evaluate the regional lymph nodes to rule out metastasis. This is done through cytological evaluation of one or more samples obtained by aspiration or fine needle puncture (FNA or FNA) (4).

Cytological differentiation between benign and malignant is also difficult to predict, the correlation is approximately 20%. Histopathology is the best method for diagnosis because it allows us to determine the type of tumor, the benign versus malignant character, histological grade and establish a more accurate prognosis. The most important criterion for differentiating benign from malignant breast tumors is based on H&E stains (5).

Histological grade is an important prognostic factor. Recent studies indicate that the median survival time for grade I breast neoplasms is more than 37 months, for grade II it is 32 months and for grade III it is 18 months. The median 2-year survival rate is 100%, 80% and 30%, respectively. The risk of recurrence/metastasis and mortality associated with the neoplasm varies between 3.4% for grade I, 15.8% for grade II and 58.8% for grade III (5).

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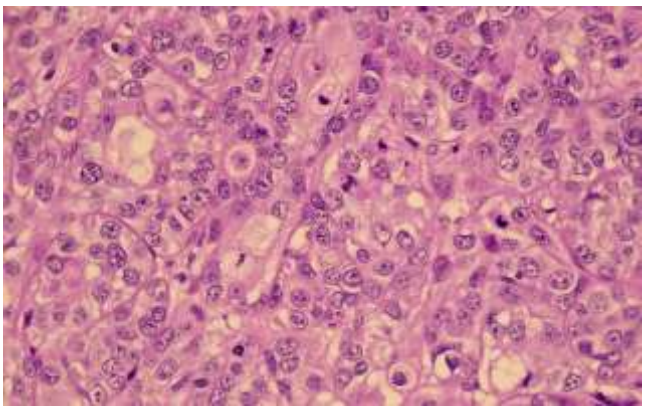
**Table 1.**

*Histological grades of mammary neoplasias in domestic dogs*

| Score | Formation of tubules | Nuclear pleomorphism | Mitosis in 10 fields/HPF |
|---|---|---|---|
| **1** | Greater than 75% | Small uniform or regular nucleus and occasional nucleolus | 0-9 |
| **2** | Moderate tubule formation (10-75%) | Moderate degree of nuclear variation in size and shape, hyperchromatic nucleus and presence of nucleolus | 10-19 |
| **3** | Minimal or no training (more than 10%) | Marked variation in the sizes of the nuclei, they are hyperchromatic with 1 or more prominent nucleoli | Over 20 |

**Figure 1.**

*Histopathological plate breast neoplasia*



Mammary neoplasias account for 50% of all neoplasias affecting intact bitches and 41 to 53% of these are malignant. In the present study, 58.4% of the tumors were found to be benign and 41.6% malignant. In this study, 47.8% of the mammary tumors were benign, 47.5% were malignant and 4.7% were non-neoplastic mammary lesions (hyperplasia, dysplasia or mastitis) (6).

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Histological type is another important independent factor for predicting breast neoplasia. Ductal carcinomas (62.5%) and other adenocarcinomas (27.4%: solid, papillary, tubular, simple and complex carcinoma) were found to be associated with fatal outcomes. Recurrence and metastasis were also evaluated: for complex carcinomas, recurrence was 3.8% and metastasis rate, 43.4%; for simple carcinomas the numbers were 4% and 52%, respectively, and for ductal carcinoma, 4.3% and 59.6%, respectively (6).

The metastasis rate for Carcinosarcoma is 100%. In the present study, the worst prognoses, in decreasing order of survival, were for solid Carcinomas and Carcinosarcomas. On the other hand, the least aggressive types were simple Carcinomas, mixed Carcinomas and complex Carcinomas; the latter showed the longest survival time. This criterion showed that complex Carcinomas exhibited a low rate of local invasion and lymphatic permeation (6).

Based on histological analysis of the total neoplastic masses, benign mammary neoplasms were more frequent than malignant ones; however, the majority of bitches presented multiple tumors, both benign and malignant (6).

On the other hand, when analyzing the frequency of breast neoplasms according to the tissue of origin that composes it, a similar distribution was evident between mixed type and epithelial ones; when discriminating according to their biological behavior, in benign neoplasms mixed type neoplasms were more frequent (67%), while malignant ones tended to be epithelial (51%) (6).

**Figure 2.**

*Frequency of benign mammary neoplasias in female dogs according to morphological classification*

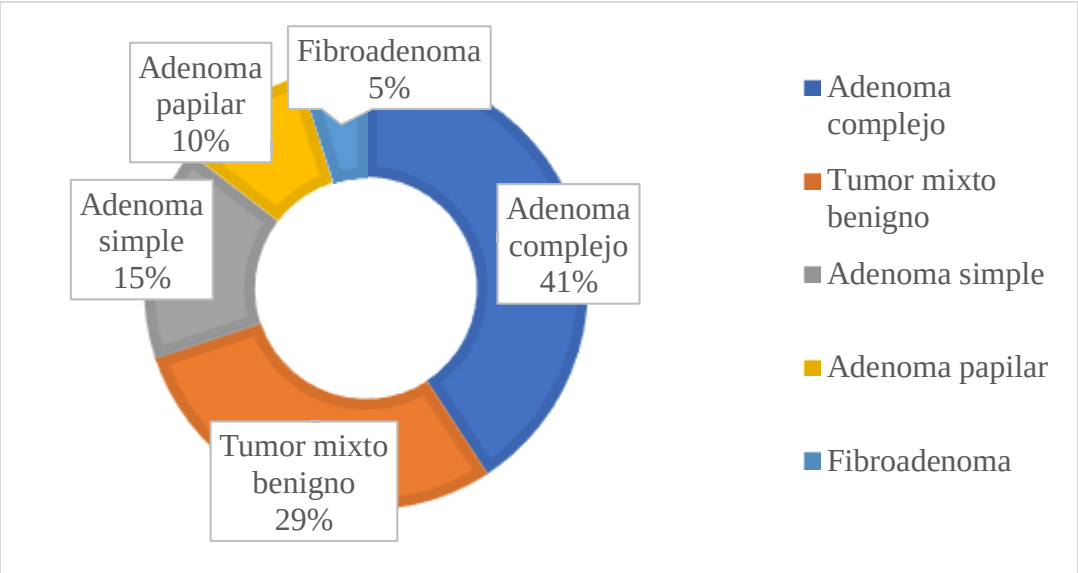

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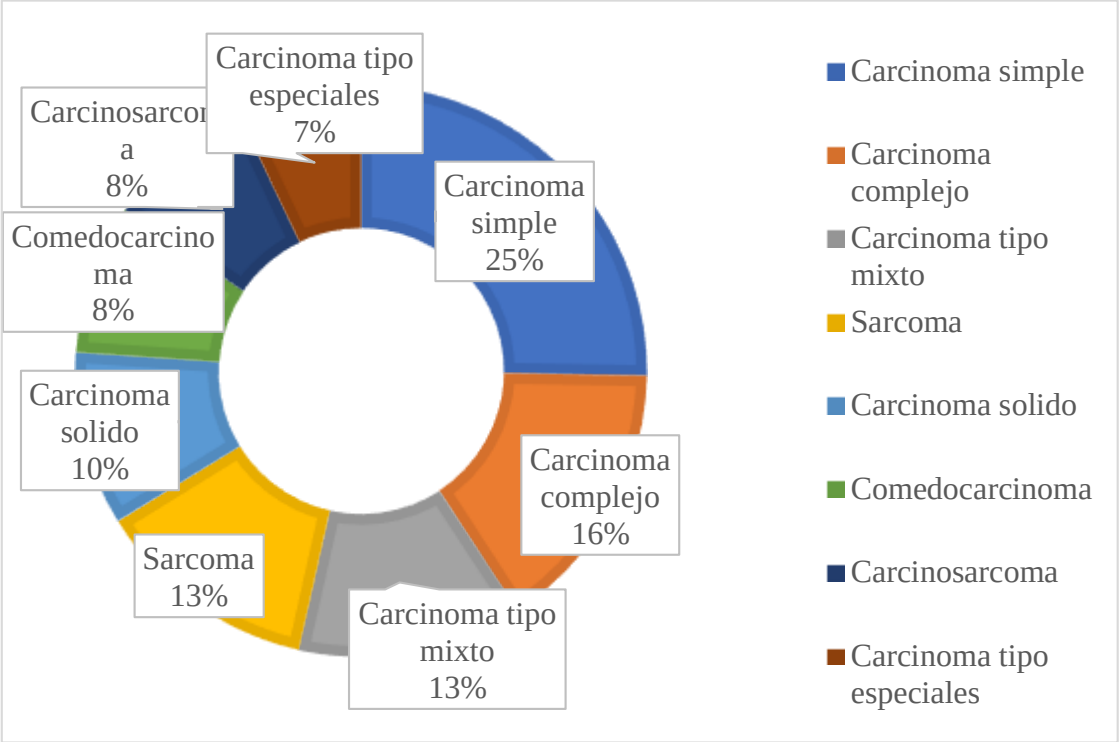
**Figure 3.**

*Frequency of malignant mammary neoplasms in bitches according to morphological classification*




Three epidemiological studies have been conducted in female dogs in which dietary and body conformation risk factors for mammary neoplasia have been analyzed. The results of these studies demonstrated that the fat content of the diet had no significant relationship with the incidence of neoplasia, although obesity increased the relative risk of mammary carcinoma (7).

Interestingly, one study showed that as dietary protein concentration increased, the relative risk of mammary neoplasia decreased, while a second study showed an increased relative risk of mammary neoplasia in dogs fed raw meat as the primary source of caloric intake.(7).

For many years it was thought that all patients with tumor cachexia had elevated basal metabolic rates due to increased metabolism in the cancerous tissue. However, numerous studies in humans, and now in veterinary medicine, have shown that the basal metabolic rate does not change after tumor removal. Furthermore, the basal metabolic rate can be extremely variable and is not usually associated with cachectic syndrome. Until recently, it was thought that excessive muscle loss was due to increased amino acid breakdown to

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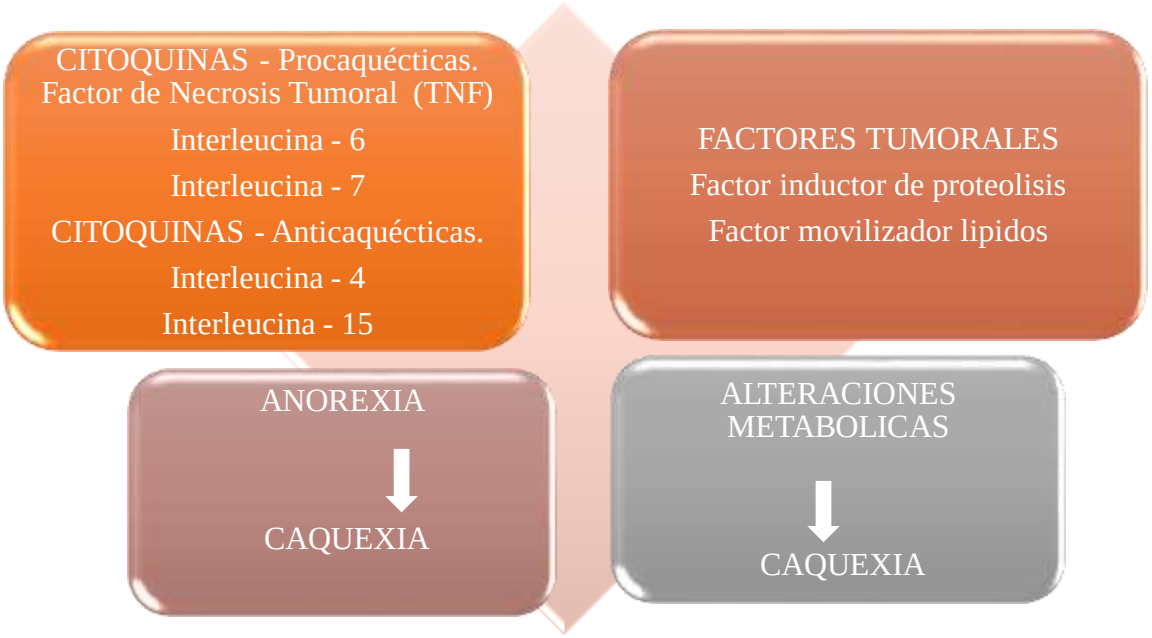
support tumor growth and that without adequate intake, the body would catabolize skeletal muscle to meet this demand. (7)

**Figure 4.**

*Humoral and tumor factors associated with anorexia and cachexia in cancer*




Several investigations indicate that unspayed female dogs may have seven times more risk of developing mammary neoplasia than animals that have been ovariectomized early in their life. The development of mammary neoplasia appears to be dependent on ovarian hormones (8).

Early ovariohysterectomy decreasedThe risk of breast neoplasia would be increased, but the protective effect would decrease over time under the influence of hormones. Apparently, important changes occur between the first and fourth estrous cycle, which become clinically evident years later (8).

**Conclusions**

- According to the degree of histopathological assessment of mammary neoplasias in domestic dogs, we can say that malignant neoplasias are assessed in histopathological score grade 3 and in the case of benign neoplasias they are assessed in histopathological score grade 1. This allows us to determine the patient's survival time and the possible treatments that the Veterinary Medical professional should execute.
- The most frequent ages of appearance of malignant or benign mammary neoplasms in female dogs are between 8 and 12 years.

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- The present retrospective study indicates that the breeds most susceptible to developing mammary neoplasia are Poodle, Cocker Spaniel, Yorkshire, Boxer and Labrador.
- Obesity, high-fat diets and high-crude protein diets are predisposing factors for the presence of mammary neoplasia in domestic dogs.
- The prevention of mammary neoplasia in domestic dogs is sterilization, before the first heat, which reduces the appearance of mammary tumors by 99.5%, as well as the prevention of reproductive problems: pseudopregnancies (psychological pregnancy), uterine infections (pyometra), metritis, neoplasia (ovarian, uterine or vaginal), ovarian cysts, vaginal hyperplasia and prolapse.

## Conflict of interest

The authors declare that they have no conflict of interest.

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