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Comparative epidemiological studies: approach of cancer registries and the study of human and canine mammary gland tumors in Portugal

Paulo Tiago Carvalho

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COMPARATIVE EPIDEMIOLOGICAL STUDIES: APPROACH OF CANCER REGISTRIES AND THE STUDY OF HUMAN AND CANINE MAMMARY GLAND TUMORS IN PORTUGAL

Dissertação de Candidatura ao grau de **Mestre em Oncologia – Especialização em Oncologia Clínica** – submetida ao Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto

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Oral Communications

II Congresso Científico de Estudantes de Saúde – apresentação de uma sessão temática "Oncologia Comparada", 9 de outubro de 2022, Escola Superior de Enfermagem do Porto.

4º ENJIO - Encontro Nacional de Jovens Investigadores em Oncologia – Resumo, 24 de setembro de 2022, Liga Portuguesa Contra o Cancro - Núcleo Regional do Norte.

5th ASPIC International Congress – poster "Comparative epidemiological studies: approach of cancer registries and the study of human and canine mammary tumors in Portugal", 30 de junho a 1 de julho, 2022, Instituto Português de Oncologia do Porto (IPO-Porto).

6th Symposium of Master in Oncology, 14 e 15 fevereiro de 2022, Instituto Português de Oncologia do Porto (IPO-Porto).

Publications

Pinello, K., Pires, I., Castro, A. F., Carvalho, P. T., Santos, A., de Matos, A., Queiroga, F., Canadas-Sousa, A., Dias Pereira, P., Catarino, J., Faísca, P., Branco, S., Lopes, C., Marcos, F., Peleteiro, M. C., Pissarra, H., Ruivo, P., Magalhães, R., Severo, M., & Niza-Ribeiro, J. (2022). Cross Species Analysis and Comparison of Tumors in Dogs and Cats, by Age, Sex, Topography and Main Morphologies. Data from Vet-OncoNet. Veterinary sciences, 9(4), 167. https://doi.org/ 10.3390/vetsci9040167 2022 DOI: 10.3390/vetsci9020072

Pinello, K., Pires, I., Castro, A. F., Carvalho, P. T., Santos, A., de Matos, A., Queiroga, F., & Niza-Ribeiro, J. (2022). Vet-OncoNet: Developing a Network of Veterinary Oncology and Reporting a Pioneering Portuguese Experience. Veterinary sciences, 9(2), 72. https://doi.org/10.3390/vetsci9020072.

Acknowledgments

I would like to express my gratitude to all that provided support to this work. I have been extremely lucky to have the opportunity to complete my Master Thesis under the supervision of Professor Katia Pinello. A true inspiration on this academic journey. Thanks Professor Katia Pinello for giving me the chance to grow and for constantly showing that I deserved your trust. This work results from your unequivocal support.

I wish to express my sincere thanks to Professor João Niza Ribeiro, co-supervisor of this Thesis, for the valuable guidance and continuous encouragement during this journey. His knowledge was crucial for this work.

I owe a special gratitude to Professor Carmen Jerónimo for all the wisdom and for having welcomed me so well at IPO-Porto.

I am also grateful to Professor Maria José Bento and all her Epidemiology Service staff, namely, Rita Silva Calisto and Jéssica Rocha Rodrigues, for providing me with facilities for the research and all the accessibility of the data.

To all veterinary laboratory partners that referred to Vet-OncoNet (DNATech, Laboratory of Veterinary Pathology at the University of Porto, Laboratory of Veterinary Pathology at the University of Lisbon, VetPat, Segalab and Cedivet), this work was only possible with your precious contribution.

I am extremely thankful and indebted to Professor Milton Severo for all the support regarding the statistical analysis.

This Master Thesis is dedicated to my wife Ana, who always supports my goals and gives all the love and care. Thank you for being close to me in the happy and in the more difficult times of this journey.

Para ser grande, sê inteiro: nada
teu exagera ou exclui. Sê todo
em cada coisa. Põe quanto és
no mínimo que fazes. Assim, em
cada lago a lua toda brilha,
porque alta vive.

Ricardo Reis, in "Odes" Heterónimo de Fernando Pessoa

Abbreviations and symbols

ACR – Animal Cancer Registry

AJCC – American Joint Committee on Cancer

BC – breast cancer

BRCA – breast cancer gene

CI – confidence interval

CMH – cancro da mama humano

CMM – cancro da mama da mulher

COR – Clinical Oncology Registry

CT – computed tomography

DCIS – ductal carcinoma *in situ*

ER – oestrogen receptor

GHIPOFG – Grupo Hospitalar Instituto Português de Oncologia Francisco Gentil

GIVCS – Global Initiative for Veterinary Cancer Surveillance

HBC – human breast cancer

HER2 – human epidermal growth factor receptor 2

IARC – International Agency for Research on Cancer

INE – Instituto Nacional de Estatística

ICD-O – International Classification of Diseases for Oncology

IHC – immunohistochemistry

cIR – crude incidence risk

MBC – men breast cancer

MGT – mammary gland tumors

mMGT – malignant mammary gland tumors

MRI – magnetic resonance imaging

NOS – not otherwise specified

PET – positron emission tomography

PHS – patient health system

PBCR – population-based cancer registry

PR – progesterone receptor

RFR – Risk Factors Registry

RIC – Repositório Integrado do Conhecimento

RON – Registo Oncológico Nacional

RORENO – Registo Oncológico Regional do Norte

RR – relative risk

SD – standard deviation

SIAC – Portuguese Companion Animal Information System

SPMS – Serviços Partilhados do Ministério da Saúde

TGM – tumor da glândula mamária

TNM – tumour, node, metastasis

VLP – veterinary laboratory partners

WBC – women breast cancer

WHO – World Health Organization

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Resumo

O cancro é uma das causas mais comuns de morte a nível mundial, particularmente nos países mais desenvolvidos. Nos animais de companhia a oncologia apresenta um crescente valor clínico e epidemiológico com mais de 4.2 milhões de cães, nos EUA, diagnosticados com cancro anualmente. Avanços recentes em oncologia comparada destacaram que os cães podem ser um modelo valioso para o desenvolvimento do cancro esporádico em humanos. Nesse contexto, o objetivo deste estudo foi (1) realizar uma análise comparativa dos registos do cancro humano e animal em Portugal, RON e Vet-OncoNet, respetivamente, identificando as suas principais características e funcionalidades; e (2) uma análise comparativa entre o cancro de mama humano e canino, com a descrição das características epidemiológicas, identificando as suas semelhanças e associação geográfica nos municípios do distrito do Porto. A existência de um registo do cancro decorre da necessidade de identificar e prever tendências e tomar decisões baseadas na prevenção, diagnóstico e tratamento de doenças oncológicas. Essa é a premissa fundamental dos registos humano e animal. Para adquirir as informações sobre os registos oncológicos foram aplicadas técnicas qualitativas de observação e entrevistas semiestruturadas. Ambos os registos apresentam um objetivo comum mas com diferenças significativas que incluem, o alcance dos sistemas utilizados, a obrigatoriedade de notificação e as variáveis recolhidas. Com as diferenças identificadas entre estes dois sistemas, algumas medidas poderão ser tomadas para melhorar ambos os registos, nomeadamente, a automatização do fluxo de informação, mais investimento e sensibilização para o registo do cancro em particular nos animais de companhia. Mais do que um banco de dados, os registos do cancro humano e animal devem servir para gerar evidência e conhecimento acessível a toda a rede colaborativa de oncologia.

Os cães desenvolvem tumores da glândula mamária (TGM) espontaneamente e apresentam características epidemiológicas e clínicas semelhantes ao cancro da mama humano (CMH). Neste estudo foram utilizados casos de CMH diagnosticados entre 2010 e 2015, obtidos do Registo Oncológico Regional do Norte (RORENO). Os casos caninos de TGM foram diagnosticados e recolhidos entre 2019 e 2022 na plataforma Vet-OncoNet. A partir de ferramentas como os sistemas de classificação de neoplasias, o ICD-O-3.2 e o atual equivalente veterinário, Vet-ICD-O-canine-1, foi possível realizar uma análise comparativa que mostrou semelhanças na distribuição por sexo, sendo predominante na mulher e na cadela e, quanto à idade, observou-se um padrão muito semelhante. Em relação à morfologia tumoral, verificou-se que existem algumas diferenças entre as duas espécies. Na TGM houve uma predominância de tumores benignos e algumas raças apresentaram um maior risco relativo ou um efeito protetor para o desenvolvimento de

neoplasias mamárias. Este estudo destaca a elevada correlação entre o risco bruto de incidência de cancro da mama na mulher (CMM) e TGM malignos nas cadelas nos municípios do distrito do Porto (R= 0,85, *p-value* < 0,001), suportando o valor hipotético do cão como sentinela da epidemiologia oncológica humana. Este trabalho é pioneiro no contexto *One Health*, contribuindo notavelmente para o campo da oncologia comparada.

Abstract

Cancer is one of the most common causes of death worldwide, particularly in high-income countries. Oncology in companion animals is growing in a clinical and epidemiological value with over 4.2 million dogs in the USA being diagnosed with cancer annually. Recent advances in comparative oncology have highlighted that dogs can be a valuable model for the spontaneous development of cancer in humans. In this context, the aims of this study was to (1) perform a comparative analysis of human and animal cancer registries in Portugal, RON and Vet-OncoNet, respectively, identifying their main characteristics and functionalities; and (2) a comparative analysis between human and canine mammary cancer, with the description of the epidemiological characteristics, identification of similarities and geographical association in the municipalities of the district of Porto.

The existence of a cancer registry stems from the need to identify and predict trends and make decisions based on the prevention, diagnosis and treatment of oncological diseases. That is the underlying premise in human and animal records. To acquire information about oncological records, qualitative techniques of observation and semi-structured interviews were applied. Both registers have a common objective but with significant differences that include the scope of the systems used, the compulsory notification and the existing variables collected. With the differences identified between these two systems, some measures can be taken to improve both records, namely, the automation of the flow of information, more investment and awareness for the registration of cancer, particularly in companion animals. More than a database, human and animal cancer registries should help to generate evidence and accessible knowledge to the entire oncology collaborative network.

Dogs develop mammary gland tumors (MGT) spontaneously and show a remarkable epidemiological and clinical features similar to human breast cancer (HBC). In this study, cases of HBC diagnosed between 2010 and 2015 were used, obtained from the North Regional Oncological Registry (RORENO). Canine MGT cases were collected on the Vet-OncoNet platform between 2019 and 2022. Using tools such as the neoplasm classification systems, ICD-O-3.2 and the current veterinary counterpart, Vet-ICD-O-canine-1, it was possible to carry out a comparative analysis that showed similarities in the distribution by sex, being predominant in women and female dogs and, regarding age, a very similar pattern was observed. Regarding tumor morphology, it was found that there are some differences between the two species. In MGT there was a predominance of benign tumors and some breeds had a higher relative risk or a protective effect for the development

of mammary neoplasms. This study highlights the high correlation between the crude risk of incidence of women breast cancer (WBC) and female dogs malignant MGT in the Porto district municipalities ($R= 0.85$, p-value < 0.001), supporting the hypothetical value of the dog as a sentinel in human oncological epidemiology. This is a pioneering work in the *One Health* context, making a remarkably contribution to the field of comparative oncology.

1. Introduction

Cancer registration is important to any cancer control and prevention strategy and have been widely used in epidemiological research (1, 2). The main purpose of a cancer registry is to record confirmed cases from within a given catchment area (3). Ideally, this can support estimation of cancer incidence rates if population-at-risk information is available, with the purpose of helping to assess and control the impact of malignancies on the community (2). Human cancer registries have been used in many countries and collaboration exists at both national and international levels (2). Veterinary cancer registries have as aim to assemble information on the risk and incidence of different cancer types within species, breeds and geographical regions (1, 4). While human cancer registries have advanced since the 1940s, veterinary cancer registries have existed in reduced number (4). Variations in cancer distribution between different geographic areas and correlations made between neoplasia in human and companion animals are important to study the development of cancer research (5).

Cancer is one of the most common causes of death worldwide, particularly in high-income countries (6). Oncology in companion animals is growing in a clinical and epidemiological value with over 4,2 million dogs in the USA being diagnosed with cancer annually (7-9). Recent advances in comparative oncology have highlighted that dogs can be a valuable model for the spontaneous development of cancer in humans empower the scientific community to develop prevention approaches (7, 9, 10). Naturally occurring canine MGT also share several similarities with their human counterpart, including incidence, relative age of onset, risk factors, biological behaviour, metastatic pattern, histological, molecular, and genetic features and therapy response (5, 11-13). Sharing their living environment intimately, humans and dogs are exposed to the same environmental hazards (14). Comparative spatial analysis of tumors in humans and dogs is an important tool to this approach (4). Therefore, in an epidemiological perspective, dogs can act as sentinels of human cancer (15, 16).

Within *One Health* context, this was the challenge, inspiration, and motto for the development of this pioneering project. Divided into two chapters, the first intends to describe the human and animal oncological registries in Portugal, analysing their main characteristics, differences and potentialities. In the second part, a descriptive analysis of HBC and canine MGT in Porto district is carried out, verifying the existence of common points, geographic distribution and potential associations.

2. Objectives

1: Perform a comparative study between human and companion animals cancer registries in Portugal.

Questions: How human and companion animals cancer registries work? Are human and veterinary cancer records similar? What sets them apart?

2: Descriptive analyses of HBC and canine MGT in Porto district: similarities, geographic distribution and potential associations.

Questions: Are human and canine mammary tumors similar in the epidemiological description in Porto district? Is there a geographic correlation between them?

CHAPTER I

3. Comparative analysis between human and companion animals cancer registries in Portugal

3.1. Introduction

Cancer registration is important to any cancer control and prevention strategy and have been widely used in epidemiological research (1, 2). The main purpose of a cancer registry is to record confirmed cases from within a given catchment area (3). Ideally, this can support estimation of cancer incidence rates if population-at-risk information is available (2). Information from cancer registries also can support studies of cause and prevention, as well as diagnosis, survival (post-diagnosis and/or treatment) and quality of life issues, with the purpose of helping to assess and control the impact of malignancies on the community (2). Only with accurate measures of disease occurrence, permits a valid comparisons between populations and over time (2). This is the basic function of a population-based cancer registry (PBCR) (3). PBCRs were initially concerned with describing cancer patterns and trends (17). Subsequently, many of them developed the necessary capability to follow up registered patients and calculate survival and prevalence (18). Over the past 20 years, the role of registries has expanded further to encompass the planning and assessment of cancer control activities, and the care of individual cancer patients (2, 18). Over these years, PBCRs compiled basic information targeted at ascertaining the incidence of different tumors, while hospital-based registries documented numerous variables (relating to diagnosis, prognostic factors and treatment) on a more limited number of cases. Currently, however, the development of electronic clinical records and robust linkage facilities means that this distinction is becoming increasingly archaic (18). Moreover, PBCRs are an essential component of cancer surveillance around which cancer surveillance programmes are built (18). Human cancer registries have been used in many countries and collaboration exists at both national and international levels (2). A central cancer registry is a resource which co-ordinates co-operating hospital registries in a specific geographical area, and which collects, combines, compares and assesses uniformly defined information on cancer patients (19).

The PBCR in the Portuguese territory historically emerged in Lourenço Marques, in Mozambique, at this time known as Maputo. In Portugal, the pioneer population-based registries were Viana do Castelo and Vila Nova de Gaia, created in 1976 and 1980, respectively (20). In 1988, three regional registries were formed and regulated by law: the Registries of the South Region, the North Region and the Central Region (21). In 2017, a new decree was established anticipating the implementation of a National Cancer Registry, covering all inhabitants in Portugal (Law 53/2017, issued 14 July 2017, in Diário da

República n. º 135/2017, Série I). The Portuguese National Cancer Registry (RON - acronym for the corresponding Portuguese designation Registo Oncológico Nacional) has been identified as a potentially interesting source of data for health technology assessment in oncology (21).

Veterinary cancer registries have as aim to assemble information on the risk and incidence of different cancer types within species, breeds and geographical regions, as well as to contribute to provide information on genetic and environmental risk factors, treatment evaluation and location of patients for clinical trials and case-control studies (1, 4). However, emerging fairly precise estimates of cancer morbidity and mortality rates in companion animals has proven challenging to achieve. While human cancer registries have advanced since the 1940s, veterinary cancer registries have existed in reduced number of countries and have often been short lived (22). Still, communication and collaboration between the registries is limited (4). Variations in cancer distribution between different geographic areas and correlations made between neoplasia in companion animals and humans are important to study the development of cancer research (5). The cancer registries for companion animals were first created in the 1960s in response to an increasing mortality from spontaneous tumors (23). The first proposals were from Kansas University between 1961 and 1972 (4); the California Animal Neoplasm Registry, operating from 1963 to 1966 (4); the Tulsa Registry of Canine and Feline Neoplasms in Oklahoma, from 1972 to 1977 (8); the Purdue Comparative Oncology Program, established in 1979; and the Cancer Registry and Surveillance System for Companion Animals from Cornell in New York State in 1980. The active cancer registries are The Veterinary Medical Database, established in 1964; the Norwegian Canine Cancer Registry, started in 1990 (4); the Danish Veterinary Cancer Registry, created in 2005 which is based on the Danish Cancer Registry for Humans (24); the VetCompass, established in 2007 and owned by the Royal Veterinary College (25); the SAVSNet, started in 2008 by the British Small Animal Veterinary Association and the University of Liverpool; and the C.H.A.R.G.E. (Canine Health and Registry Exchange) that was developed in the United States of America in 2022 to provide the veterinary community and dog owners with important data to help guide canine cancer diagnosis and treatment decisions (26). The former projects have been discontinued for different reasons, nevertheless the era of Big Data has begun and new technologies and tools to improve preventive and veterinary medicine are now available (27).

In Portugal it was created in 2019, the platform Vet-OncoNet. Vet-OncoNet, Veterinary Oncology Network, is an initiative of the School of Medicine and Biomedical Sciences (Instituto de Ciências Biomédicas Abel Salazar – ICBAS) of the University of Porto with the supportive collaboration of the Institute of Public Health of the University of Porto (Instituto de Saúde Pública da Universidade do Porto – ISPUP), which fits into the context

of the One Health activities in these institutions. One of the goals is to create a National Veterinary Oncology Registry (ROVN), carry out the collection and processing and dissemination of animal oncological data, promote the sharing of relevant information for users, promote and carry out training specialized in the field of oncology and promote epidemiological-based cancer studies and research (28).

The aim of this study is to describe the current solutions in the registry of human and companion animal cancer in Portugal and to compare its main features and functionalities. With an emphasis on determining the translational relevance of both records, it is also intended to understand the main differences and identify the opportunities for collective benefit, contributing to the improvement of comparative oncology.

3.2. Material and Methods

In order to perform this comparative study an intensive literature review was conducted. Two types of qualitative techniques were applied to acquire information about cancer registry systems (RON and Vet-OncoNet): observation and semi-structured interviews. Data were collected from the teams responsible for RON and Vet-OncoNet. The institution responsible for managing the RON at the time of the study was IPO-Porto. Two interviews lasting one hour each were carried out in November 2021 with those responsible for coordinating and processing the records of both systems. The main topics explored in the interviews were: main architecture and key functionalities; data integration, data quality and data use (29).

3.3. Results

The results are divided into the following subsections: description of the main architecture and key functionalities, data integration and data quality.

3.3.1. Registo Oncológico Nacional (RON)

Main architecture and key functionalities

RON is a centralized registry based on an electronic platform, whose purpose is to collect and analyse data from all cancer patients diagnosed and or treated in mainland Portugal and in the autonomous regions of Azores and Madeira. The registration is mandatory. This registry allows the monitoring of the activity carried out by the institutions, the effectiveness of organized screenings and therapeutic effectiveness, epidemiological surveillance, research and, in conjunction with INFARMED - Autoridade Nacional do

Medicamento e Produtos de Saúde, I. P. (INFARMED, I. P.), scrutinizing the effectiveness of medicines and medical devices (30).

The entity responsible for the administration of RON is the board of directors of Hospital Group of Portuguese Oncology Institute Francisco Gentil (GHIPOFG – Grupo Hospitalar Instituto Português de Oncologia Francisco Gentil). This board nominate a coordinator on a rotating basis for registry implementation, guaranteeing the technological support and the necessary maintenance (30).

RON is allocated on SPMS (acronym for the corresponding portuguese designation Serviços Partilhados do Ministério da Saúde) servers and is only accessible by the Health Informatics Network (RIS) which is a private multimedia network of the Ministry of Health that interconnects the local networks of its organizations and services. Access to RON is done through the attribution of access profiles by the entity responsible for its administration and treatment (30) (Table 1).

TABLE 1 List of the different profiles existing in RON and the respective task performed in the system.

Profile	Tasks
Local Register	Creation and modification of cases, tracking the respective cancer registry and extracting unidentified aggregated data reports.
Regional register	Creation, modification and deletion of cases, resolution of doubts or inconsistencies, follow the respective oncological record and extract unidentified aggregated data reports.
A person responsible for regional oncology data	Consultation, modification, and extraction of reports of unidentified aggregated data, monitorization of the quality of all data, their consolidation and the resolution of data conflicts.
A person responsible for the regional cancer screening programs	Consultation of data, referring to the oncological groups targeted by the screening program.
Health manager	Access to statistical information that can be obtained by searching the RON and that facilitates the carrying out of epidemiological studies integrated within its scope, namely with regard to cancer screenings, allowing the definition of health policies regional public.
RON coordinator	Consultation, extraction of reports of unidentified aggregated data and the export of anonymized data of all data contained in the RON, monitoring of data quality, its consolidation and conflict resolution of data.
Paediatric coordinator	Consultation, modification, and extraction of reports of unidentified aggregated data from all paediatric cases, monitoring the quality of these data, consolidating them and resolving data conflicts.
Administrator	Management, monitorization and development of the computer application, both in terms of access profiles and RON reference and administration table

The RON platform guarantees interconnection, through automatic interoperability mechanisms, with other databases (30) (Table 2).

TABLE 2 List of databases that contribute with information to RON platform.

Database	Description
National or Central Registries	The National User Registry
	The Integrated Surgery Enrolment Management System
	The National Database of Homogeneous Diagnostic Groups
	The Death Certificate Information System
	The Database of the National Network of Tumour Banks
	The Oncology Screening Database
	National Health Technology Assessment System
	The Contracting and Monitoring Information System
	The Information System that supports the validation of the production and billing of the contract-program of hospital institutions
	The Health Data Platform
Local information systems	Computer programs of the pathological anatomy services of hospital institutions
	Hospital drug prescription programs
	Computer systems of radiotherapy services
	Computer programs for administrative management of hospital institution
	Health Information Systems: SClinico and the Hospital Information Integrated System (SONHO)

This registry is mandatory and includes treatment data, diagnostic facilities data and the official territorial death registry. Additional data sources from ambulatory, private clinics, elderly care homes and general practitioners' networks are also included. Currently, this registry is based on record linkage that allows real time integration of data from clinical databases. It is possible to integrate information from various sources, including the pathological laboratory, the oncology department, the surgical procedure or radiotherapy department (21, 30) (Figure 1).

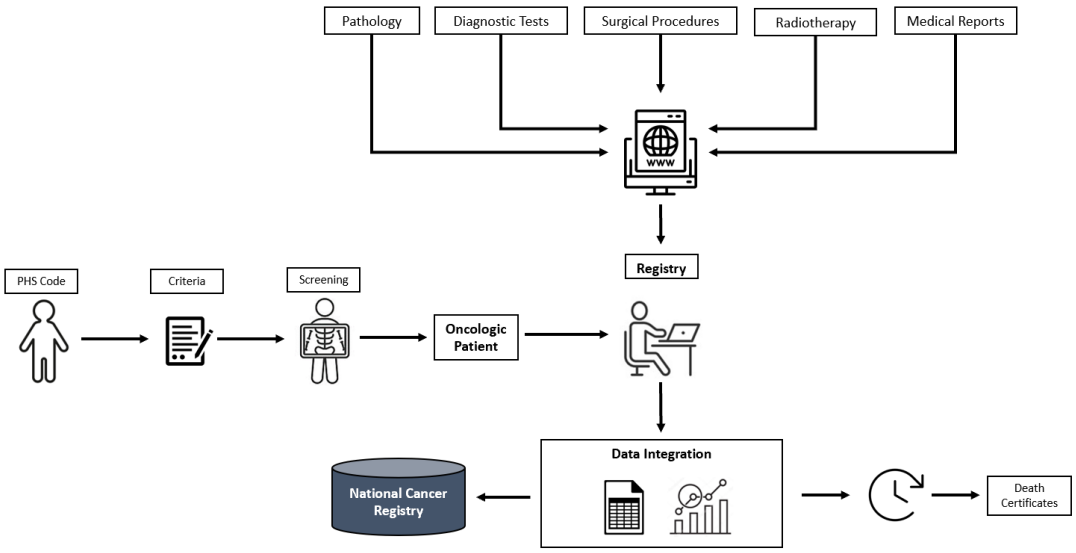

FIGURE 1 Structure and data sources of the Portuguese Cancer Registry (adapted)(21). *PHS* code, patient health system code.

Data integration

The registry is based on record linkage that allows real-time integration of data from clinical databases. This is a disease registry, so inclusion in the database is triggered by the identification of a new cancer case. The system was initially set up in the 1990s as a simulation of a network where the information was sent to the central database using encrypted information in packages to preserve the anonymity of individuals (21). In 2005, with the creation of the citizen's card, Portugal gained a competitive advantage over other European countries as this access enabled the creation of a unique patient record so a longitudinal follow-up of the individual who enters the National Health System exists. At this point in time the structure of the database was changed from a purely data entry format to a mixed system, where all data previously existing in data sources could be imported into an intermediate database and the registry would then have the possibility to upload and integrate them. Currently, there is the possibility to integrate information from various sources, including the pathological laboratory (biopsy result or surgical fragment), the oncology department (first appointment or chemotherapy treatment), the operating theatre (surgical procedure) or radiotherapy department (radiotherapy treatment) (21).

The main goal of this system is to aggregate cancer registries from different healthcare institutions in the country. However, to ensure the equilibrated contribution from all parts, and to motivate all stakeholders to pursue the collaboration into this common aim of increasing the knowledge of cancer and its treatment, it was always considered and

foreseen in this decree that the registry would be managed by one of the three oncology institutes in rotation periods of 3 years (21, 30).

Data quality

Because the population-based registry is, in fact, based on a collection of hospital-based registries for which exhaustive and rigorous information is needed and cannot be obtained in a totally automatic manner, one of the conditions for a successful registry is to ensure that there is a medical oncologist nominated as registry coordinator in each of the institutions. Data are registered in the RON database by each of the institutions involved. The duplication of cases is also evaluated semi-automatically, by evaluating cases with the same user card number and similar names, with the comparison variables being date of birth, address (district and municipality) and tumor location. To evaluate multiple tumors, the International Agency for Research on Cancer (IARC) criteria defined specifically for ICD-O-3.2 are used (31). To guarantee the quality of the data, they are submitted to computer processing in the form of a list of anonymous individual cases. The list of cases is introduced in the IARCcrgTools program (version 2.05) that checks and evaluates the consistency of the data, according to the IARC criteria. The cases in which errors and unlikely or rare combinations are detected are reviewed and, when necessary, corrected, being resubmitted to the IARCcrgTools program, until there were no errors and unlikely or rare combinations confirmed. This procedure allowed to improve the accuracy and comparability of the data (32)

One major problem reported by the RON team members interviewed is the need to have trained professionals to enter the data in the system, making the process more time consuming. The existence of a list of numerous tasks for resolving conflicts/errors was also a negative aspect mentioned by them. Another aspect, is the existence of some intercurrences in access to some statistics to carry out studies and research projects.

Data use

With the contribution of RON, national oncological records of all tumors in the population residing in Portugal are published (32), among other publications, such as MEMO - Measuring Effectiveness of Medication used in Oncology.

3.3.2. Repositório Integrado de Conhecimento (RIC)

Since 1988, IPO-Porto has been reporting cancer cases sent by different healthcare institutions of the north of Portugal. In 2005, this cancer centre acquired a software named

RORENO (acronym for the corresponding Portuguese designation Registo Oncológico Regional do Norte) that facilitates the communication with this network. From this, a new platform developed within the scope of the ODISSEIA project (Oncology Disease Information System) was applied. During this study, it was possible get in touch with RIC (acronym for the corresponding Portuguese designation Repositório Integrado do Conhecimento) that is the IPO-Porto Cancer Registry (33). RIC allows the registration of a wide range of data, of great value for clinical and epidemiological research, but also automatically integrates a set of exams and treatments performed at IPO-Porto and the pathological diagnosis.

RIC is the institutional cancer registry of IPO-Porto. It is hosted on a local server at this cancer center and is only accessible via the institution's intranet. This system reduce the registration time of each clinical file in the registry. With RIC, it is possible to consult the patients' pipeline of treatments and exams at the institution. RIC data are then uploaded into the RON. This particular system has a high potential, since it gives the possibility to add new variables to the system, unlike RON. Also allows a better data quality through the implementation of rules for this purpose, an integration with local systems from various institutions and National applications of the Ministry of Health and an unlimited capacity for exploration and visualization of oncology data. Despite also needing a trained team specialized in data coding, this new platform has a more appealing and simple design.

3.3.3. Vet-OncoNet

Main architecture and key functionalities

The project Vet-OncoNet - The Veterinary Oncology Network, was officially launched in December 2019 and its mission is to generate scientific evidence and knowledge on animal oncology, based on the perspective of One Health. Another crucial point is to offer streamlined communication in animal oncology to veterinary practitioners and pet owners (34). One of the most important features is the creation of a system of registries on animal oncology, with emphasis on the Portuguese Animal Cancer Registry (ACR) (35), similar to those existing in the other countries (4). The main activities of this network are the collection, processing, analysis and retrieving to several types of users, the information extracted out of the databases from veterinary laboratories and veterinary clinical practices/hospitals, compiling the information in one big source (34).

This network developed its information system, using SQL, R and business intelligence tools, to create three databases based on the source - Animal Cancer Registry (ACR), that includes pathology reports from Veterinary Pathological Laboratories; Clinical

Oncology Registry (COR), based on data from Veterinary Practices (Vet Practices), after oncology routine; and Risk Factors Registry (RFR), which is data introduced by owners of oncologic patients (28)(Figure 2). As showed in figure 2, every registry entering Vet-OncoNet ACR component represents a confirmed animal cancer diagnosis and is regarded as a pathology-based registry. The COR, which is independent from ACR, registers clinical information, including data/information of cancer diagnostics in clinical practice, method of diagnostic and therapeutic more frequently used, cancer staging and outcome of cases. For RFR, Vet-OncoNet created an interface where owners of oncologic pets can access information about their pet's disease from a reliable source. The platform called Pet-OncoNet also provides an interface where owners fill a questionnaire developed to collect potential cancer risk factors (36).

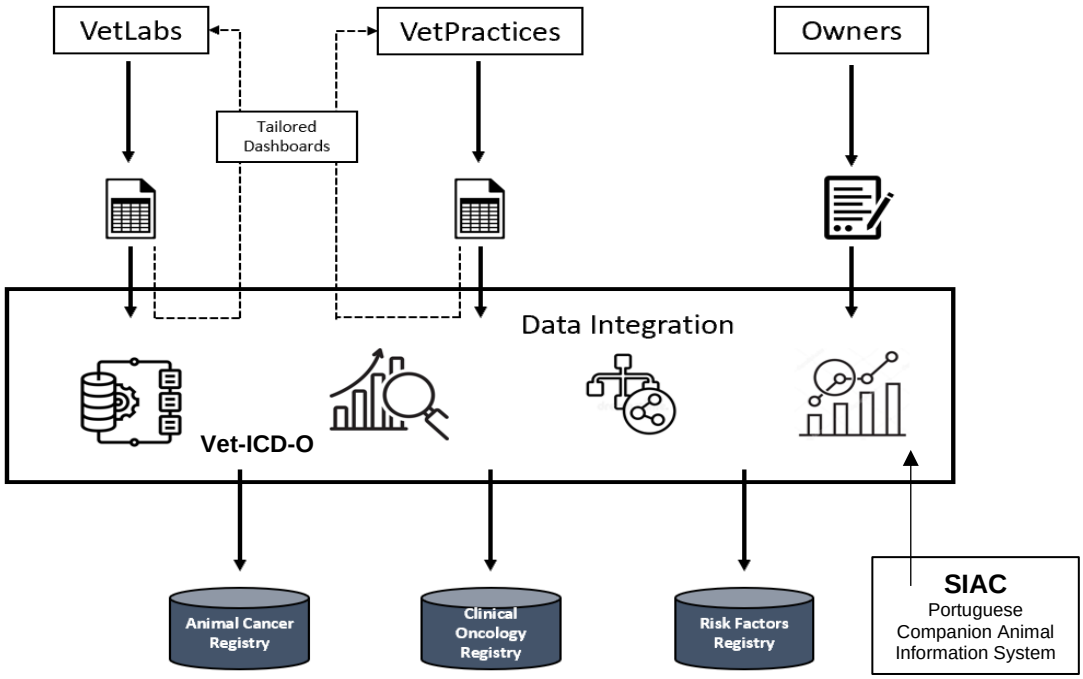

FIGURE 2 Structure and data sources of the Vet-OncoNet (adapted from Pinello, 2022).

Data integration

Data are provided by partners in an electronic format. Once in the system, data undergoes a first data cleaning and treatment that includes editing, validation, standardization of the terms and classification (37). All tumors are classified using Vet-ICD-O classification (37). This classification system is in continuous development and improvement by the Global Initiative for Veterinary Cancer Surveillance (GIVCS), an international group that includes members of Vet-OncoNet (28, 37). It's the animal

counterpart of the human classification ICD-O-3.2 which will allow comparability between veterinary and human cancer registries, important for comparative oncology. After this standardization, the data goes through an epidemiological analysis and the interactive reports (dashboards) are generated. These reports can be assessed by all Vet-OncoNet partners, via web service, and each partner can perform a dynamic visualization and analysis of their own data (28) (Figure 2).

Vet-OncoNet and Animal Census

Vet-OncoNet is a partner of the Portuguese Companion Animal Information System (SIAC), an official site for compulsive registry of pets that provides a national pet census. As a partner of SIAC since August 2021, Vet-OncoNet is responsible to perform the demographic treatment and analysis of the Portuguese pet population. The Portuguese pet census is available to Vet-OncoNet, after this partnership agreement, and allows calculating population-based cancer indicators. The use of the animal-based risk estimates will allow us to perform comparative studies of tumor risk incidence-based on human population and dog or cat cancer data.

Data quality

One of the limitations found on the Vet-OncoNet network was on the database COR, because of the high variability and heterogeneity in clinical records between Vet Practices. Other problem found was the lack of information provided. Also, another main difficulty was Vet Practices' lack of time in submitting data to Vet-OncoNet. By using the Vet-ICD-O classification system, the data obtained are more homogeneous (37). One major problem reported by the Vet-OncoNet researchers is the fact that the registration is not mandatory.

Data use

With the contribution of Vet-OncoNet, the animal oncology registry was published in 2020 (35) and publications are regularly carried out in leading scientific journals (38, 39).

3.3.4. Comparative analysis

Table 3 shows the results of a comparative analysis between human and animal cancer registries in Portugal. In this work, the variables that both registries collect include are: ID, diagnosis, tumor, treatment and outcome. An important point to mention is the existence of a PHS code (Patient Health System code) in the human registry, while in

companion animals, it is non-existent. With regard to the variable “tumor”, the human oncological registry provides a more complete description, addressing molecular aspects, tumor markers and genetic study. Concerning the variable “treatment”, it should be noted that in RON, the monitoring of therapeutic effectiveness is recorded for each type of situation.

TABLE 3 Variables recorded in RON and ACR.

Variables	Human Cancer Registry	Animal Cancer Registry
ID	Name, sex, date of birth, address, PHS code, institution identification, clinical file number, profession and place of birth of the patient	Vet-OncoNet code, report ID, name, species, age, sex, transponder number, date of diagnosis, species, breed, age, postal code and city (laboratories), reproductive status, age of animal when neutered, weight, body condition, size, vaccination status
Diagnosis	Start date of symptoms, date of first observation, date of first consultation, date of diagnostic exams, type of exam (mammography, histology, cytology, ultrasound, other)	Cytology, histopathology, immunohistochemistry, molecular biology, clinical, imaging (XRay/CT/ ultrasound), other
Tumor	Topography and morphology (ICD-O-3.2), laterality, staging at presentation, grade, TNM classification, clinical and pathological diameter, sentinel node, Performance Status (WHO), molecular and tumor markers, genetic study of the tumor (when applicable), tumor bank	Topography and morphology (Vet-ICD-O-1), grade, method of diagnosis (histopathology, cytology, necropsy)
Treatment	Surgery, chemotherapy, radiotherapy, hormone therapy, immunotherapy, bisphosphonates, clinical trials	Surgery, chemotherapy, radiotherapy, palliative, none, no information, anti-inflammatories, steroids, electrochemotherapy, other
Outcome	Vital state, follow-up	In surveillance, in treatment, resolved, euthanized, death from cancer, death from another cause, no information

Table 4 shows the main characteristics of human and animal oncological records, namely, compulsiveness, PHS code (Patient Health System code), post code, variables, staff, data standardization, data sources and financing.

TABLE 4 Main characteristics of human and animal oncological registries.

Characteristics	Human National Cancer Registry	Animal Animal Cancer Registry
Compulsiveness	Yes	No
PHS code	Yes	No
Post code	Patient	Vet Practices
Variables	Broader information	Narrower information
Staff	Trained professionals	Vet Practices/Vet Labs
Data standardization	Yes	Yes
Data sources	Multiple	Restricted
Financing	Public	Private

PHS code, patient health system code

3.4. Discussion

The existence of a cancer registry stems from the need to predict trends and make decisions based on prevention, diagnosis and treatment of oncological diseases. This will be the fundamental purpose across both human and animal registries. In this work it was possible to analyse the two registries, identifying their main characteristics and functionalities. In fact, they start from a same goal but with significant differences that include the systems used, the obligation and the existing variables. With the differences identified between these two registries, some measures could be taken to improve both systems, namely, the automation of information flow, more investment and awareness for cancer registration particularly in companion animals. More than a database, animal and human cancer registries should be a basis of accessible knowledge to the entire collaborative oncology network.

It is important to emphasize that the different value of human and animal life means that the type and complexity of existing interventions and systems are radically different from human ones. This fact explains the differences seen in the variables captured by the two systems, which start from the available (potentially) and existing ones. One of the main differences between the animal and human cancer registry is the fact that RON is mandatory, unlike the veterinary registry. Additionally, the human clinical processes that are specialized and take place in the context of the SNS are financed mainly by public money and clinical processes related to companion animals are private and financed by animal owners. The National Cancer Registry needs to have trained professionals to enter data into the system, in contrast to the veterinary registry that is done by Vet Practices and VetLabs. Given the size of the human registry system, there is a list of numerous tasks for conflict/error that needs to be resolved by team members on a daily basis which has hindered network dynamics and normal data access.

Bearing in mind that Vet-OncoNet is a tripartite network that includes different databases depending on the source (ACR, COR and RFR), it will be important to carry out a comparative analysis separately with RON. COR, which is independent from ACR, registers clinical information, including proportion of cancer diagnostics in clinical practice, method of diagnostic and therapeutic more frequently used, cancer staging and outcome of cases. Despite the type of variables recorded in both registries being very similar, it should be noted that in RON, its informative potential is superior. This fact may be associated with the limitations and availability of information that exist in veterinary clinical practice in Portugal, for example in diagnostic methods and cancer treatment. Another limitation of the COR is the lack of follow-up of the case, which makes it impossible to determine the most realistic outcome and clinical course. Since registration is not mandatory in companion

animals and associated with the fact that Vet Practices reveal a lack of time and a low perception of the importance of cancer registries, results in a lower submission of cases on the platform.

Every registry entering on ACR component represents a confirmed animal cancer diagnosis and is regarded as a pathology-based registry. In contrast to the human counterpart where the postal code corresponds to the patient, in the ACR corresponds to the Vet Practices. This fact may lead to a bias regarding the geographical location of the veterinary cases. Concerning diagnostic methods, in ACR, cytological diagnosis is often the only method used. Another crucial aspect between ACR and RON is data standardization. While in the human registry the classification is made using criteria defined in the ICD-O-3.2, in the ACR there is a high variability and heterogeneity in clinical records between Vet Practices as well as Vet Labs. The GIVCS, recognized to promote and coordinate animal cancer registration worldwide, created a comparative coding system for canine cancers (40). Vet-ICD-O-canine-1 is the human ICD-O-3.2 counterpart. By using the Vet-ICD-O classification system, the data achieved are more standardized and, as mentioned, allow comparison with human cancer. The standardization of pathologists' reports will be a factor that may, in the future, improve the consistency of ACR data. This could be one of the great advantages of this ACR (37). Indeed, it is an important contribution to the field of comparative oncology. The evaluation of incidence rates is also a greater value, especially for comparative oncology. To achieve this goal, it is necessary to determine the number of animals at risk, which will be close to reality since the placement of a transponder is mandatory in all companion animals, being an untransmissible number. As a partner of SIAC since August 2021, Vet-OncoNet is responsible to perform the demographic treatment and analysis of the Portuguese pet population. The Portuguese pet census promote the potential of this network allowing the calculation of population-based cancer indicators.

During this study, it was possible to get in touch with RIC, in the IPO-Porto Cancer Registry (33). This new platform allows the registration of a wide range of data, of great value for clinical and epidemiological research, but also automatically integrates a set of exams and treatments performed at IPO-Porto and the pathological diagnosis. This particular system has a high potential, since it gives the possibility to add new variables to the system an unlimited capacity for exploration and visualization of oncology data, unlike RON. Despite also needing a trained team specialized in data coding, this new platform has a more appealing and simple design. RON could benefit from the adoption of some features that this platform presents.

Given the intricacy that oncological registries present, efforts are being made to advance in this field. It is important that population-based studies continue to be made over time so increasing or decreasing tendencies for different types of tumors may be observed.

Therefore, if the target is to improve general data information and to sustain a registry with the minimum amount of bias and with the biggest number of reports possible, the cleverest choice is to automatize the process of retrieval and for that, the strategies used in the human cancer registry can be adopted. More investment and awareness for cancer registration in companion animals will be an important advance in the future.

3.5. Conclusion

Accurate cancer surveillance data are part of the basis to produce appropriate inferences about this cancer burden; to establish strategies for prevention and control; to design research to recognize causal associations between exposures and cancer risk. In this work it was possible to analyse the two cancer registries, RON and Vet-OncoNet, identifying their main characteristics, differences and potentialities. Substantial differences were identified that include the systems used, the obligation and the existing variables.

Some strategies could be taken to improve both systems, namely, the automation of information flow and awareness for cancer registration particularly in companion animals. Adding more investment and upgrading both networks, will contribute to the oncology research.

CHAPTER II

4. Descriptive analyses of human and canine mammary gland tumors in Porto district: similarities, geographical distribution and potential associations

4.1. Introduction

Cancer is one of the most common causes of death worldwide, particularly in high-income countries (6). It is known that the exposure to environmental carcinogens is considered responsible for 1.3 million new human cancer cases every year (41). The oncology focus in companion animals is growing in a clinical and epidemiological value with over 4.2 million dogs in the USA being diagnosed with cancer annually (7-9). Recent advances in comparative oncology have highlighted that dogs can be a valuable model for the spontaneous development of cancer in humans empower the scientific community to develop prevention approaches, diagnostic advances, as well efficacy and safety of innovative therapy options for both species (7, 9, 10). These models of cancer have numerous advantages namely, the evaluation of the animal's immune response to the tumor, the capacity to replicate interactions between the neoplastic cells and the microenvironment, and the ability to reproduce the metastatic behaviour (12, 42, 43). Furthermore, the shorter life span and faster progression of cancer in dogs permit an earlier data collection than in human neoplasms (44).

Naturally occurring canine mammary tumors also share several similarities with their human counterpart, including incidence, relative age of onset, risk factors, biological behaviour, metastatic pattern, histological, molecular and genetic features, and therapy response (5, 11-13). By sharing their living environment intimately, humans and dogs are exposed to the same environmental hazards (14). Therefore, in an epidemiological perspective, dogs can act as sentinels of human cancer (15, 16).

Changes in the canine cancer incidence ratios were described to precede by 2 years similar changes in human incidence rates, which might be useful for predicting changes in cancer patterns in humans (45). Comparative spatial analysis of tumors in humans and dogs is an important tool to this approach (4). However, spatial analyses are currently limited, mostly because canine cancer data sources are scarce and often incomplete(4). On other hand, existing canine cancer data sources are typically hospital-based thus impeding meaningful insight into risk factors for both species (22).

4.1.1. Human Breast Cancer

Worldwide, human breast cancer (HBC) is the most frequently diagnosed in women (46). In 2018 there was about 2.1 million newly diagnosed women breast cancer (WBC) cases, which represents one in four cancer cases among women, and approximately 630 000 women died of it (47). In Portugal, breast cancer was the most relevant tumor in women with an incidence rate of 139.14 per 100 000 woman (48). The incidence rate increased considerably with age until the age of 70, with about 60% of cases between 45 and 69 years (48).

Subtypes

Breast cancer (BC) is the common term for a set of breast tumor subtypes with distinct molecular and cellular origins and clinical behaviour (49). The two most frequent subtypes are invasive carcinoma of the breast, not otherwise specified (NOS), previously named ductal carcinoma representing 70%–75% of cases, and lobular carcinoma with 12%–15% of cases (49). There are another 18 rare subtypes known (from 0.5% to 5%), which exhibit specific morphological traits (50).

The different disease subtypes and molecular alterations that characterized them are, generally, associated with the presence or absence of oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) (49). For the pathological diagnosis, the World Health Organization (WHO) classification (50) and the eighth edition of the American Joint Committee on Cancer (AJCC) tumour, node, metastasis (TNM) staging system are used (51). This staging system provides anatomical and prognostic information related to tumor biology (tumor grade, ER, PR, HER2 and gene expression data, if available). Proliferation markers such as the Ki67 labelling index may supply additional useful information (52). Thereby, the final pathological report should include presence/absence of ductal carcinoma *in situ* (DCIS), the histological type, grade, immunohistochemistry (IHC) evaluation of ER status and, for invasive cancer, IHC evaluation of PR and HER2 expression or HER2 gene amplification (53). For prognostic and treatment purposes, tumors should be grouped into surrogate intrinsic subtypes, defined by routine histology and IHC data (54).

ICD-O Classification

The International Classification of Diseases for Oncology (ICD-O) has been used in the last 35 years, mainly for tumor or cancer registries, but also for coding the site

(topography) and the histology (morphology) of the neoplasm, important for the pathology report (55). This classification system consists of the use of four characters for topography, that run from C00.0 to C80.9 (37). It is based on the malignant neoplasm section of ICD-10 and the topography code remains the same for all neoplasms of that site (37) (Table 5). The decimal point (.) separates subdivisions of the three-character categories. For morphology terms, the classification introduces a five-digit code ranging from 8000/0 to 9992/3, in which the first four digits indicate the specific histologic term. The fifth digit, after the slash or stroke (/), represents the behaviour code, that indicates whether a tumor is malignant, benign, in situ, or uncertain about tumor malignancy (55). For BC, ICD-O topography code is under C50. The Table 5 summarizes the code according to topography.

TABLE 5. Breast Cancer topography codes and terms (adapted from ICD-O-3.2).

ICD-O-3	Term
C50.0	Nipple
C50.1	Central portion of breast
C50.2	Upper-inner quadrant of breast (UQI)
C50.3	Lower-inner quadrant of breast (LIQ)
C50.4	Upper-outer quadrant of breast (UOQ)
C50.5	Lower-outer quadrant of breast (LOQ)
C50.6	Axillary tail of breast
C50.8	Overlapping lesion of breast
C50.9	Breast, NOS (excludes Skin of breast C44.5); multi-focal neoplasm in more than one quadrant of breast

NOS: Not Otherwise Specified

Clinical presentation

Most of the early breast carcinomas are asymptomatic, especially if they are discovered during a breast-screening program (49). Although, the most common symptom is lump palpable by the patient (49). In cases where the patient has not noticed a lump, then signs and symptoms indicating the possible presence of BC may include change in breast size or shape, skin dimpling or skin changes (eg, thickening, swelling, or redness), recent nipple inversion or skin change or other nipple abnormalities (eg, ulceration, retraction, or spontaneous bloody discharge), nipple discharge and axillary lump (49). The physical examination is important for the diagnosis and must include an assessment of the breasts with the patient upright with arms raised. A complete examination includes assessment for lymphatic and distant metastases, particularly bone, lung, liver, and brain (56). Thus, the

physical examination should include the axillae and supraclavicular fossae, the chest and sites of skeletal pain, and abdominal and neurologic evaluation (49).

Diagnosis

The diagnosis of BC is based on clinical examination in combination with imaging and confirmed by pathological assessment (57). Generally, BC is diagnosed through either screening or a palpable lump that triggers a diagnostic exam. The advantaged of screening of healthy women is the detection of smaller tumors which are associated to lower odds of metastasis and more amenable to breast-conserving and limited axillary surgery (58).

In addition to physical examination, mammography and/or ultrasound is the gold standard for the diagnostic work-up of a patient with mammary lump (59). In some cases, magnetic resonance imaging (MRI) is recommended: younger patient, genetic mutation, multifocal disease suspected, or a mammogram or ultrasound yields indeterminate findings (60).

Other diagnostic procedures will be indicated according to the disease stage (61). A chest radiograph and routine laboratory blood tests are appropriate for staging patients with clinical stage I or II breast cancer and no specific symptoms for metastatic disease (61). When there is suspicion of advanced (stage IIIB/C or IV) disease, the recommendation of National Comprehensive Cancer Network guidelines is to perform chest, abdomen, and pelvis computed tomography (CT) scan or chest CT with abdomen and pelvis MRI as well as bone scan or sodium fluoride positron emission tomography (PET)/CT(61).

Treatment

Surgery is considered primary treatment for early-stage BC and many patients can be cured with surgery alone (49). The goal is to achieve the complete resection of the primary tumour with negative margins to reduce the risk of local recurrences and pathologic staging of the tumor and axillary lymph nodes to provide necessary prognostic information (49). In the situations which there is locally advanced breast cancer, preoperative (neoadjuvant) chemotherapy is used to reduce the tumour volume and allow definitive surgery (62). In patients with triple-negative or HER2-positive disease, response to neoadjuvant therapy can guide the selection of adjuvant therapy (62). Adjuvant treatment of BC aims to treat micrometastatic disease and involves radiation therapy and systemic therapy, including a variety of chemotherapeutic, hormonal and biologic agents (49).

4.1.2. Canine Mammary Gland Tumors

Mammary gland tumors (MGT) are very common in dogs and cats being the second most frequent tumor in dogs and the third in cats (39, 63, 64). The estimated annual incidence of canine mammary carcinomas is 192 cases per 100,000 female dogs (24, 65, 66). A Swedish study have found that the incidence increased with age, with an incidence of 1% at age 6 years, 6% at age 8 years and 13% at age 10 years (65). Another study found that the median age of canine MGT manifestation is 10 to 11 years of age, with rare occurrence in dogs younger than 4 years old (67).

Subtypes

According to the information submitted about histologic diagnosis provided by veterinary practices submitted for histologic diagnosis 41% to 53% of mammary tumors are malignant (68). Although histologic evidence of malignancy, it does not mean a malignant clinical course (69). Additionally, marked variation in histologic appearance can occur within the same tumor mass (69). The majority of malignant mammary tumors are classified as epithelial tumors or carcinoma and pure sarcomas represent a minority of cases (70) (71).

Some clinical signs (rapid growth, tumor size, ulceration, and fixation to skin and underlying tissues) may be indicative of malignancy, but it is very difficult to differentiate between benign and mMGT only by clinical history (72).

As mentioned above, in WBC, molecular subtypes are characterized by mapping the phenotypic diversity to a specific gene expression pattern (73). Recently there have been several studies that attempted to classify canine and feline mammary carcinomas according to their molecular subtypes (74-76). There were identified five phenotypes: luminal A, luminal B, basal-like type (triple negative), HER2-overexpressing and “normal” phenotype. The proportion of the luminal A subtype was 29.0% (76) to 44.8% (74), while for luminal B subtype was between 13.5% (74) to 49.0% (76). For basal-like subtype there was determined a proportion between 24.5% (75) to 29.2% (74) and for HER2-overexpressing subtypes between 0% (76) to 24.46% (75). Only one study determined the proportion for “normal-like” which was 3.1% (75). These molecular subtypes are correlated with histological type, grade, and survival in dogs (74). The basal subtype is associated to simple carcinomas, frequently solid carcinomas, while complex carcinomas are mostly luminal A. The basal-like phenotype is significantly associated with shorter overall survival and disease-free interval (77). However, the results between these studies were contradictory.

Thus, additional investigations using standardized protocols for IHC and interpretation of the IHC results need to be carry out.

Vet-ICD-O

Within the Global Initiative for Veterinary Cancer Surveillance (GIVCS) (40), established to foster and coordinate animal cancer registration worldwide, a group of veterinary pathologists and epidemiologists created a comparative coding system for canine tumors, the Vet-ICD-O-canine-1 (37). It is the canine counterpart of the human classification ICD-O-3.2 which will allow comparability between veterinary and human cancer registries.

In fact, most morphological terms and codes overlap fully, as expected given the well-described histologic similarities between human and canine neoplasms, important for comparative oncology (37). However, the new coding system considers the peculiarities of some canine tumors, resulting in 126 new codes for entities that cannot be reliably coded with the ICD-O-3.2 (37).

New veterinary topographic codes for each canine mammary gland cranial thoracic (C50.10), caudal thoracic (C50/20), cranial abdominal (C50.30), caudal abdominal (C50.40), and inguinal (C50.50) were created, since the distinction in portions and quadrants of the human breast is not equivalent to the number and site of canine mammary glands(37).

In the histological classification of mMGT, some entities are unique to dogs and are not registered in the human BC classification system. The authors introduced new specific veterinary codes for carcinoma arising in a complex adenoma/benign mixed tumor (8941.1/3) and complex carcinoma (8983.1/3) (37) which can be consulted in the list of MGT from Vet-ICD-O-canine-1(Table A1).

Clinical presentation

Clinically, mammary tumors can manifest as single or multiple nodules within the mammary gland, and may be associated with the nipple or, more often, the glandular tissue itself. Dogs have five pairs of glands, all of which can develop one or more benign or malignant tumors (69). Is it described that 65% to 70% of canine tumors occur in glands 4 and 5, probably because of the greater volume of mammary tissue in these glands (69). A characteristic of MGT is the common manifestation of multiple nodules at diagnosis, with benign and malignant tumours coexisting (78). This fact proposes that benign and mMGT might not be separate entities and they may be part of a continuum process in which the

malignant invasive carcinomas correspond to the advanced stages. Therefore canine mammary cancer offers an adequate model to study mammary gland carcinogenesis, with direct use in HBC research (79). Benign mammary tumors are usually small, well circumscribed, and firm on palpation. Physical examination is important for the diagnostic workup because it helps to detect whether local or loco-regional disease (69). Most dogs with mammary neoplasms do not present with any signs of systemic illness. At presentation, about 20–30% of mMGT cases present regional lymph node metastases, and less frequently, distant metastases, mainly in the lungs, but also in the liver, bone, and other organs(80). The clinical course differs notably according to different clinical and tumour features, including clinical staging, tumour histological type and grade, mode of growth, immunophenotype, and molecular and genetic features (12, 13, 80).

Diagnosis

For the definitive diagnosis is necessary to perform histopathology analyses since cytological differentiation between benign and malignant MGT has an approximately 20% accuracy (72). Histopathology evaluation includes the tumour type, malignancy features and grade (72).

Before treatment, staging is an important step (69). It requires the evaluation of the primary tumor, evaluation of the regional lymph nodes and the attempt to identify any distant metastatic sites. The most common sites of distant metastasis are the lungs, sublumbar, sternal, and prescapular lymph nodes, liver and, rarely, bone (69). Thoracic radiographs in both the right and left lateral and ventrodorsal planes should be taken before surgery to evaluate the lungs and sternal lymph node for possible metastasis (69). In dogs, where there is involvement of the two caudal glands, the sublumbar region should be evaluated for metastatic lymphadenopathy using caudal abdominal radiographs or ultrasonography (69).

Retrospective and prospective studies using univariate and multivariate analyses show that clinical staging based on the TNM system has good prognostic significance (81-86).

Treatment

Traditionally, surgery is the gold standard treatment for mammary tumors in dogs, except for inflammatory carcinoma (87) or distant metastasis (81, 88).The type of surgery will depend on the extent of disease (69). Recently, is has been emphasized that the focus should be placed in the completeness of surgical margins, as this factor is associated with

an improved survival of dogs with mMGT (89). The expansion of knowledge in malignant canine mammary tumors biology has still not been reflected on treatment changes of affected animals (90). On the contrary to HBC treatment, adjuvant chemotherapy has not been proven to have a clear benefit in dogs yet (89). Nevertheless, refinements in the management of female dogs with mMGT may be markedly influenced by the validation of prognostic factors (90).

4.1.3. Risk factors for HBC and canine MGT

Sex

Breast cancer is more common in women than in men which represent less than 1% of all human cancer cases (91). The same trend is observed in MGT in dogs. They are rare in male dogs, being 62 times less likely to develop MGT than in female dogs (39, 92).

Age

Age is the most important known risk factor for WBC and this risk increases significantly with age. It has been described a peak in the incidence at the age of menopause and then gradually decrease or remain constant (93, 94). In fact, less than 5% of cancers cases are diagnosed in humans from birth to 35 years and less than 10% from birth to 45 years (95).

The same pattern was found in dogs where less than 5 to 10% of cancer cases are diagnosed between birth and 3-5 years (96). The longevity of companion animals has increased which also amplified the number of cancer diagnosis (97). A Brazilian study found that the risk of canine mammary tumors increases 1.625 times annually (98). The relative ages of female dogs and cats with mammary tumors are similar to those described for women with breast cancer (99). As in women, the incidence in female dogs increases with age, with a peak of diagnosis at 11–13 years of age (65, 100) and a mean age at diagnosis of 9–11 years (79, 101).

Ethnicity and breed

Human breast cancer incidence and mortality rates differ widely according to geographic regions and racial and ethnic populations (102). One study has determined that African-American women have a lower incidence of BC compared to White women, but a higher overall mortality (103). For Asian and Hispanic/latino populations, the incidence and mortality also varies (104, 105). Hispanic women may have an overall incidence of breast

cancer lower than non-Hispanic white women, but their breast cancers are often diagnosed at a later stage (104).

The incidence of mammary tumors in dogs varies with breed. Although breeds reported to be at higher risk differ in different studies, and in different geographic locations (106). Poodles, Chihuahuas, Dachshunds, Yorkshire Terriers, Maltese and Cocker Spaniels are frequently listed as high-risk dog breeds in the small breed category (107). Some of the larger breeds are also at higher risk, including the English Springer Spaniel, English Setters, Brittany Spaniels, German Shepherds, Pointers, Doberman Pinschers, and Boxers (106).

Endocrine environment

In women, the age of menopause was associated with an increased risk for BC development (93). It is known that BC is more common in nulliparous women and multiparity is associated with a reduced risk. On the other hand, older age at first full-term pregnancy is associated a higher risk (93, 108). Different from dogs, the relationship between WBC and use of contraceptive pills is controversial. A case-control study showed that the use of oral contraceptives was associated to a higher risk in women (109). However another study conducted in women between 35 to 64 years old with current or previous use of contraceptive pills did not established a positive association (110). Considering postmenopausal hormone therapy, the risk of BC is higher in women with hormone replacement therapy use and the risk can decrease following discontinuation use and diminishes after 5 years (111).The endocrine environment, which is defined by the length of exposure to oestrogen and progesterone, has been implicated in the development of canine and feline mammary carcinomas (112-114). A study has shown that in female dogs, the risk to develop mammary tumors can be reduced to 0.5%, 8%, and 26% if the ovariohysterectomy or ovariectomy is performed before the first, before the second, or after the second estrus, respectively (115).

Another study has shown that non-neutered female dogs were 9.3 times more likely to have MGT compared with female dogs submitted to ovariohysterectomy (98). Female dogs neutered before six months and one year of age have a 91% and 86% risk reduction, respectively, for the development of the disease when compared to non-neutered (113). On the other hand, administration of progestogens to prevent estrus is linked to an increased risk of MGT development by a dose-related carcinogenic effect (112, 116). Also the pituitary hormones and growth hormone have been associated with HBC and canine and feline MGT (117-120).

Genetics and Epigenetics

For human breast cancer there is a well-established familial genetic predisposition, with different genes and gene mutations being associated with an increased risk for the disease (121, 122). Another study reported that women with a family history of BC, with negative BRCA mutations have a risk to develop breast cancer 11 times higher (123). Also in women, benign breast diseases are an important risk factor for BC and a cohort study proved an association between the two (124).

Consistent associations between certain types of cancer and dog breeds indicate the presence of risk alleles which can be linked to heritable risk for cancer development (125). A genetic predisposition to develop mammary tumors has been suggested in some canine and feline breeds. Additionally, a number of human cancer predisposition genes have been found in the constitutional DNA of dogs with cancer, including BRCA1/BRCA2 germline mutations (126, 127). Recently, 'human-like' mammary tumor phenotypes such as luminal A, luminal B and triple negative (basal-like) have been defined for dogs (128).

Epigenetic mechanisms can currently complete and give more information in cancer pathogeny, especially focusing on sporadic cases, when genetic risk cannot define a detailed heritability (129). The epigenetic influences may explain the mechanisms which are able to drive cells with the same genotype towards different phenotypic identities: this research trend represents one of the best promises in cancer investigation (129). A number of features of human BC involving genomic aberrations have been identified MGT (29, 130, 131). Liu et al. investigated the genetic differences between simple and complex carcinomas. Their findings indicated that canine simple carcinomas probably arise from genomic aberrations, whereas complex carcinomas originate from epigenomic alterations (131).

Currently, due to the known evidence on the heterogeneity in MGT, a pilot study that included synchronous multiple tumors from the same animals reported different clonal genetic profiles between tumors, providing preliminary evidence for a probable independent pathogenesis of the different tumors of dogs presented with multiple mammary tumors (29). In veterinary oncology, and specifically in MGT, there is a long path ahead and efforts should be followed to increase the knowledge on genetic and epigenetic changes and mechanisms involved in cancer development (29).

Overweight and obesity

Overweight and obesity are associated with a higher risk for HBC (132, 133). Obesity in women may affect the expression of progesterone receptors which interferes with the course of the disease and may influence the survival rate (134). Other hypothesis

is that obesity is associated with higher rates of conversion of androgenic precursors to oestrogen through peripheral aromatization in adipose tissue, which leads to high concentrations of oestrogen, increasing BC risk (134, 135). On the other hand, high levels of insulin and insulin-like factors in response linked to obesity can stimulate the growth of cancer cells (135).

Obesity has been also associated with MGT development, principally juvenile obesity, with female dogs with overweight or obesity at 9–12 months with a higher risk of mammary tumor development (136, 137). One study have shown that overweight female dogs had a risk 2.331 times superior for the development of mammary tumors compared with female dogs with normal weight (98). As in women, overweight or obese diseased female dogs tended to have more aggressive tumors comparing with lean or ideal weight dogs (138).

Diet

Considering HBC, the relationship between diet and cancer has been intensively study (139). In a case–control study, there was a relationship between nonvegetarian diet and risk of BC (94). Another study has shown that the risk of BC increases with the increase in total consumption of meat and nonprocessed meat (140). A European prospective study on cancer and nutrition found that satured fat consumption is significantly associated with the risk of developing BC (141).

Some studies have been evaluating the hypothesis that diet composition can influence the development of canine cancer and its course, but there are little research data for evidence-based guidelines on diet to prevent or manage canine cancer (136, 137). An American study in dogs with mammary carcinoma evaluated the dietary macronutrient composition of various cohorts with their survival times. The highest median survival time of 3.2 years was found in a subgroup of dogs that consumed diets higher in protein and carbohydrate and lower in fat, concluding that feeding a high-protein/low-fat/high-carbohydrate diet might increase survival time in dogs with BC (136). This same study and a Spanish one have determined diet composition of dogs with MGT (136, 137).

In the American study, the dogs with mammary tumors *versus* the controls, on average, consumed less fat and more carbohydrates, but in the Spanish study the opposite was seen. There was another discrepancy between the two studies regarding the type of food: commercial dog food *versus* homemade or table food, with American dogs with mammary tumors with a lower proportion of table food and the Spanish dogs counterparts with higher proportion of homemade food (136, 137). However, the two studies referred did identify a uniform risk factor related to weight, namely juvenile overweight (136, 137). The

American one showed that the risk of breast cancer in dogs were lower in dogs thin at 1 year of age (136). The Spanish one concluded that obesity at 1 year of age was associated with higher risk of cancer. This same study found a positively association between mammary tumor risk with the intake of red meat, with this risk factor emerging as an emerged as an independent factor associated with the risk in the multivariate analysis (137).

Pollutants

A study on the relationship between air pollution and the incidence rate of BC in postmenopausal European women has shown a positive correlation (142). This report evaluated 15 cohort studies from nine European countries and found that there is an association between air pollution and the incidence rate of postmenopausal BC in European women (142).

Dogs live in the same general environment as humans whilst escaping the influence of certain carcinogens which are already formally recognized in humans, such as active smoking, alcoholic beverages or professional exposures (143). During the last decades, regarding an increased environmental chemical pollution, we assist to an increased incidence of breast cancer in industrialized countries.

Geographical variations, time trends, and studies of populations migrating from low to high-risk areas (with migrants approaching the risk of the host country in one or two generations) clearly supports the importance of environmental factors in the aetiology of the disease. The same pattern was observed in mammary cancer in pets and many spontaneous canine cancers are similar to their human counterparts, regarding phenotypic but also molecular aspects (43, 144, 145). It is known that persistent organic pollutants (POPs) are able to interact with hormonal receptors by penetrating cellular membranes (146-150), and they were found in human as in dog blood and adipose tissues (151-153).

The resemblance between spontaneous tumors of companion animals and their human counterparts, due to epidemiological and clinicopathological similarities, make companion animals valuable models in human cancer research. Because of the faster progression of cancer in cats and dogs, in comparison with humans, their shorter life span and exposure to the same risk factors, the study of cancer in companion animals can provide important data to comparative oncology (44). Thus, the main aim of this study is to perform a descriptive analysis of human and canine mammary tumors in the district of Porto, evaluating the similarities, geographical distribution and potential associations.

4.2. Material and Methods

4.2.1. Cancer cases

Human Breast Cancer

Human breast cancer cases diagnosed between 2010 and 2015, referring to the district of Porto, obtained in RORENO, upon official request and data protection were collected. The data included gender, age group, municipality, date of the diagnosis, tumor topography (C50), morphology and biologic behaviour (code 3), using the ICD-O-3.2 (55).

Canine Mammary Gland Tumors

Canine MGT cases were collected in the Vet-OncoNet platform between 2019 and 2022. The veterinary laboratory partners (VLP) that referred to Vet-OncoNet were DNATech, Laboratory of Veterinary Pathology at the University of Porto, Laboratory of Veterinary Pathology at the University of Lisbon, VetPat, Segalab and Cedivet. Data included age, sex, breed, postal code of the veterinary centres, date of diagnosis, tumor topography (C50), morphology and biologic behaviour. Each record was classified accordingly to the Vet-ICD-O-canine-1 classification system (37). Dogs were also categorized according to the Fédération Cynologique Internationale (FCI) criteria (154).

4.2.2. Population data

Human population

The data of the human population were available by INE (Instituto Nacional de Estatística), referring to the 2021 census (155).

Animal population

The data source for the canine population was from the Portuguese Companion Animal Information System (SIAC), which included live dogs, aged up to 20 years. Vet-OncoNet is a partner of this Portuguese official site for compulsive registry of domestic animal, providing the pet national census. As a partner of SIAC since August 2021, Vet-OncoNet is responsible to perform the demographic treatment and analysis of the Portuguese pet population. The Portuguese pet census is available to Vet-OncoNet, after this partnership agreement, and allows calculating *population-based* cancer indicators (28). Using SIAC population data, it was possible to calculate the Relative Risk (RR) per breeds and per biologic behaviour.

4.2.3. Study design

Descriptive and exploratory analysis

Descriptive analyses were performed with the data referred in the item 4.2.1. and includes sex, age, morphology and topography. For the canine MGT, descriptive analysis of tumor cases by sex, age, breed, FCI breed groups, topography and morphology. For the comparative study, only canine malignant MGT were considered, and a descriptive analysis was performed.

Comparative Study between species

A comparative cross-sectional study between HBC cases (2010-2015) and female dogs mMGT (2019-2022) was performed taking into consideration, age, sex, topography, morphology and geographic distribution. To allow comparisons, the crude Incidence Risk ($_{c}$IR) was calculated as described in Table 6.

TABLE 6. Crude Incidence Risk formula.

Cases	Formula
WBC	(Number of cases per municipality/population per municipality INE 2021) / 6 *10.000
Female dogs mMGT	(Number of cases per municipality/population per municipality SIAC 2022) / 3 *10.000

Geographic analysis

Choropleth maps of $_{c}$IR per municipalities were performed using the QGis® Software.

4.2.4. Statistical analysis

The descriptive analysis was performed in Excel®. For categorical variables analysis included frequencies and percentages, and for continuous variables central tendency and dispersion measures were calculated. Comparisons between groups were performed, using independent samples and ANOVA or Kruskal Wallis tests for continuous or categorical variables, respectively. Chi-squared and Fisher's exact tests were used to evaluate the association between two categorical variables.

Relative Risk and their 95% confidence intervals (95%CI) were calculated as a measure of the risk of having mammary gland tumors in breed dogs compared to the no-breed dogs.

To explore the relationship between categorical variables, Correspondence Analysis (CA)(156), a multivariate graphical technique, was performed on R (library ca).

The Z-Score was calculated to allow a comparative analysis between the ages of WBC cases and the female dogs mMGT. For women whose ages were given at intervals of 5 years, the medians of the respective intervals were considered. Then, for both women and female dogs, the Z-score was calculated for each data set according to the formula: $z = (x - \mu) / \sigma$ where x is your data point, μ is the mean, and σ is the standard deviation. Then, an F test to compare tests was performed to verify variance and the non-parametric Wilcoxon rank sum test for difference in medians. Also, a two samples-Kolmogorov-Smirnov (K-S) test were performed on SPSS® (IBM SPSS Statistics Version 28.0.1.0) to assess differences between human and dog age distributions.

Associations between human and canine mammary tumors were assessed at the municipality level using Pearson's correlations. Statistical analysis was performed in R and a *p-value* less than 0.05 were considered statistically significant in all tests.

4.3. Results

4.3.1. Characteristics of HBC cases in Porto district

A total of 7674 HBC cases were included in this analysis with diagnosis between January 2010 to December 2015, referring to the district of Porto.

Regarding sex distribution, Figure 3 shows a substantial predominance of women (n=7584, 98.8%) with men representing 1.2% of cases (n=90).

Concerning age distribution, 69.2% of WBC cases were diagnosed between 40 and 69 years of age, 23.3% between 70 and over 85 years and 7.5% between 20 and 39 years of age (Figure 3). In male breast cancer (MBC), although not very representative, the age group between 60 and 64 years old represents 20% of the total cases (Table A2).

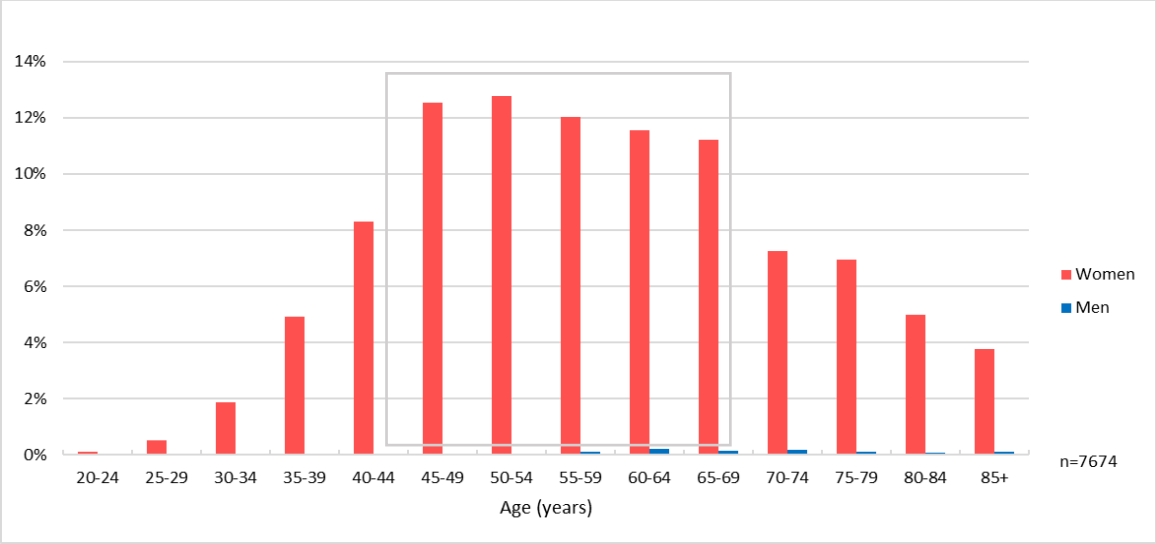

FIGURE 3 Distribution by age and sex of HBC cases in Porto district, between 2010 and 2015.

4.3.1.1. Tumors description

The most frequent WBC topographies recorded were Overlapping lesion (C50.8) (n=2069, 26.96%), Breast, NOS (C50.9) (n=2028, 26.43%) and Upper-outer quadrant (C50.4) (n=1901, 24.77%) (Figure 4). Concerning MBC topographies, the most frequent were (50.9) (n=59, 0.77%), (50.1) (n=14, 0.18%) and (50.8) (n=9, 0.12%), which correspond to the breast, NOS, central portion and overlapping lesion (Figure 4).

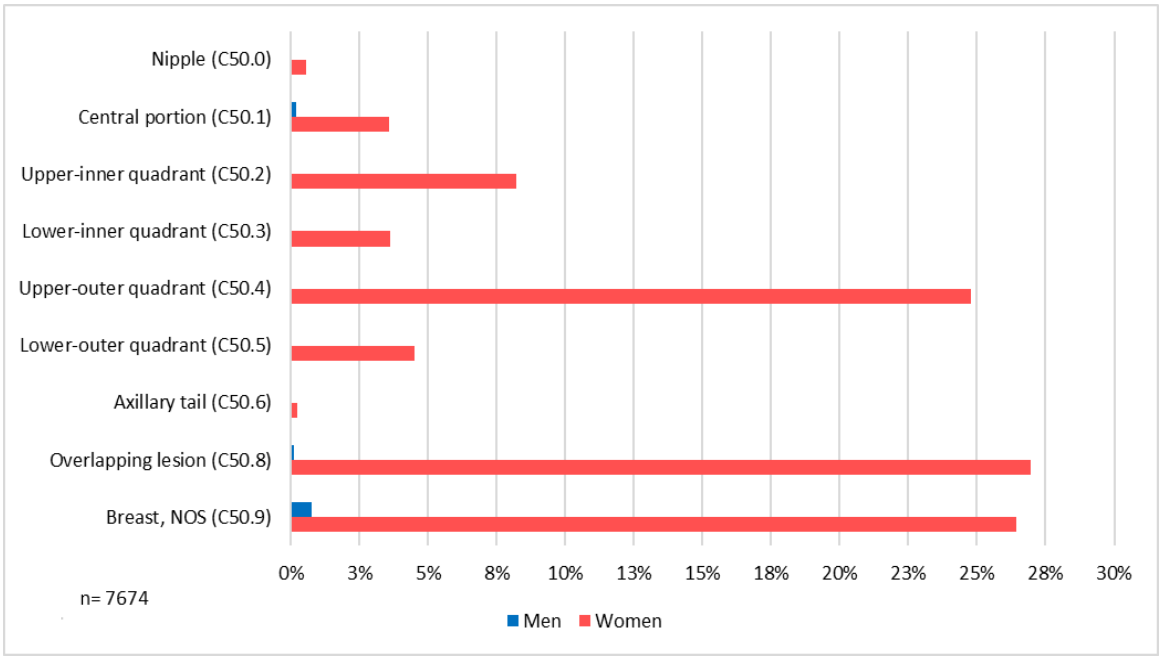

FIGURE 4 Distribution of HBC cases by topography in Porto district, between 2010 and 2015.

Regarding the distribution by morphology (Figure 5 and Table A3), infiltrating duct carcinoma, NOS was the most observed in HBC cases, with 5679 cases (74%) followed by lobular carcinoma, NOS with 707 cases (9%) .

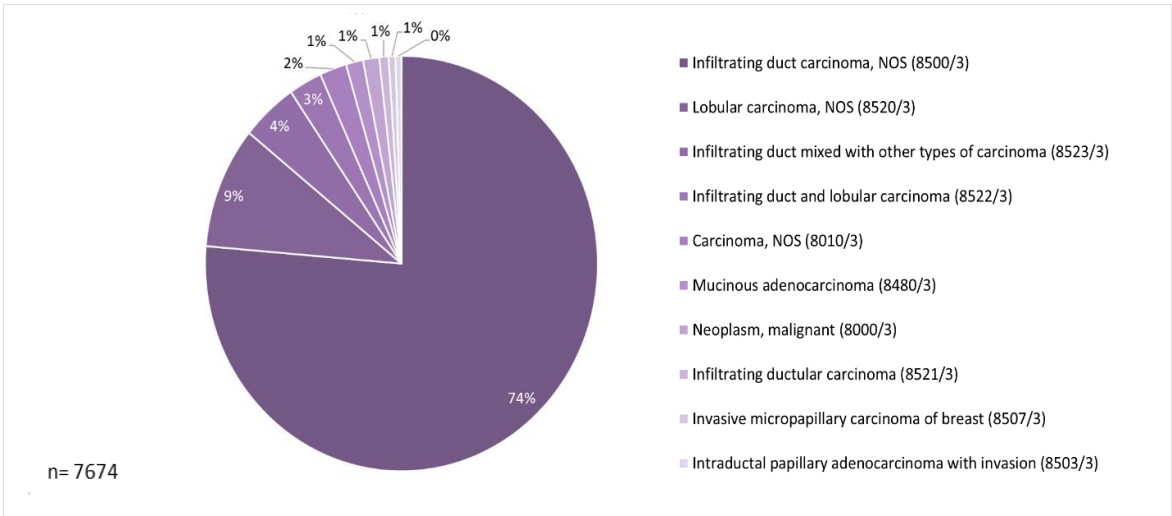

FIGURE 5 Distribution of the ten main morphologies of HBC cases, in the district of Porto.

4.3.1.2. Distribution by municipalities

The distribution of HBC by municipalities, is represented in Figure 6 with the corresponding population and its annual incidence risk per 10,000 (IR). Vila Nova de Gaia,

Matosinhos, Gondomar and Maia showed the highest number of HBC cases. It is noted that the IR is higher in the municipalities of Porto, Vila Nova de Gaia, Matosinhos, Gondomar and Maia.

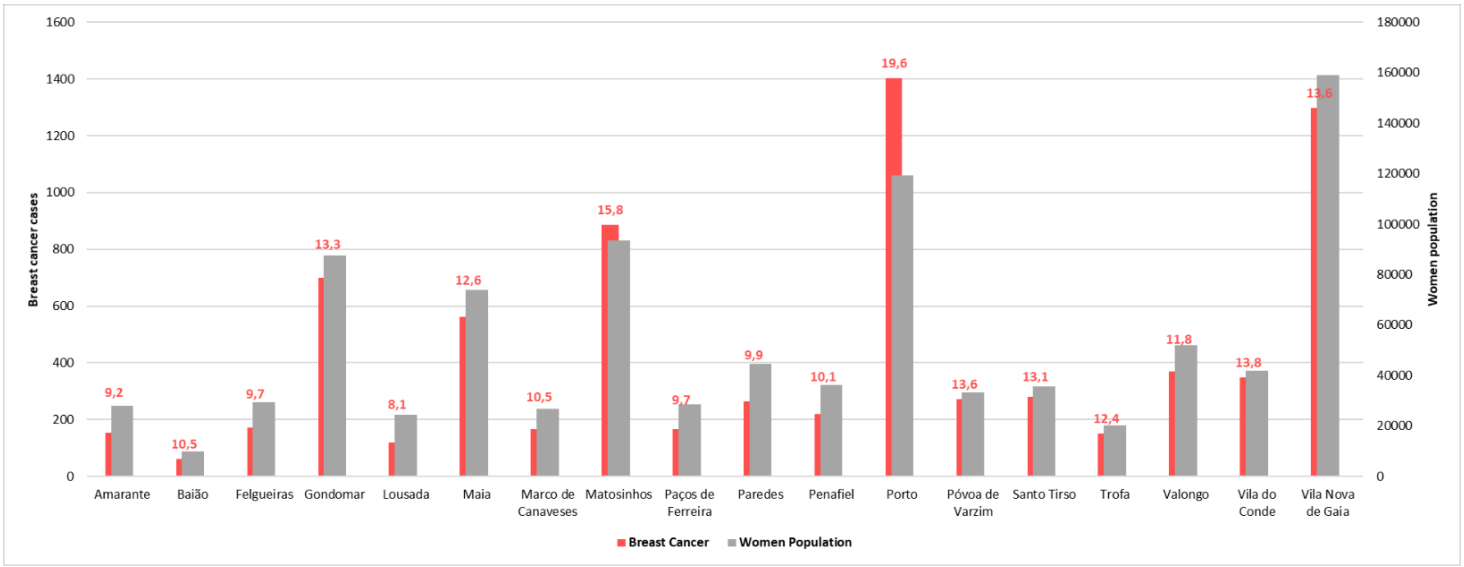

FIGURE 6 Distribution of HBC by municipalities registered in RORENO between 2010 and 2015 (on left) and women population (on right) in Porto district. The labels represent the HBC annual incidence rate per 10,000 (IR).

4.3.1.3. Distribution by main morphologies

Concerning the morphologies' distribution of the of HBC by municipalities in the district of Porto, the infiltrating duct carcinoma, NOS was the most frequent in all of them (Table 7) with a higher frequency in the municipality of Trofa (n=122, 80.3%). The municipality of Matosinhos showed more cases of lobular carcinoma, NOS (n=118, 13.1%), Amarante with infiltrating duct mixed with other types of carcinoma (n=13, 8.3%) and Baiao had more cases of infiltrating duct and lobular carcinoma (n=4, 6.6%) (Table 7).

TABLE 7 Distribution of the four main HBC morphologies by the municipalities of Porto.

	Infiltrating duct carcinoma, NOS (8500/3)		Lobular carcinoma, NOS (8520/3)		Infiltrating duct mixed with other types of carcinomas (8523/3)		Infiltrating duct and lobular carcinoma (8522/3)	
Municipalities	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Amarante	112	71,8%	10	6,4%	13	8,3%	7	4,5%
Baião	46	75,4%	3	4,9%	2	3,3%	4	6,6%
Felgueiras	133	76,9%	11	6,4%	9	5,2%	5	2,9%
Gondomar	518	73,5%	53	7,5%	45	6,4%	27	3,8%
Lousada	80	66,7%	10	8,3%	7	5,8%	3	2,5%
Maia	412	72,7%	58	10,2%	23	4,1%	22	3,9%
Marco de Canaveses	131	78,0%	10	6,0%	9	5,4%	7	4,2%
Matosinhos	666	74,1%	118	13,1%	21	2,3%	15	1,7%
Paços de Ferreira	124	74,3%	16	9,6%	9	5,4%	5	3,0%

Paredes	200	75,5%	25	9,4%	12	4,5%	10	3,8%
Penafiel	160	71,8%	15	6,7%	14	6,3%	11	4,9%
Porto	1021	72,1%	148	10,5%	59	4,2%	38	2,7%
Póvoa de Varzim	212	75,2%	25	8,9%	14	5,0%	2	0,7%
Santo Tirso	198	69,7%	27	9,5%	9	3,2%	6	2,1%
Trofa	122	80,3%	9	5,9%	4	2,6%	1	0,7%
Valongo	273	73,6%	32	8,6%	26	7,0%	5	1,4%
Vila do Conde	278	78,1%	23	6,5%	19	5,3%	4	1,1%
Vila Nova de Gaia	993	75,9%	114	8,7%	50	3,8%	32	2,4%
Total	5679	74,00%	707	9,2%	345	4,5%	204	2,7%

To allow a better evaluation of the patterns of the different proportions of the subtypes by municipalities, a correspondence analysis (CA) was carried out (Figure 7). The CA was performed with the variables showed in table 7 (Porto district municipalities x the four main HBC morphologies). In CA graphic (figure 7), Dimension 1 is represented by the horizontal axis and Dimension 2, the vertical axis. The distance between any row points or column points gives a measure of their similarity (or dissimilarity). Along Dimension 1, it is possible to see on the map that Matosinhos and Gondomar are furthest away from the origin and therefore have the most dissimilarity. Also, in Lobular Carcinoma, NOS and Infiltrating duct carcinoma. Dimension 2 shows that Vila do Conde shows the most dissimilarity from Maia profile. The other correspondences being closer to the origin imply that the deviations from the expected proportions are relatively small (156). Categories that are closer together indicate that they are more closely associated. And these associations can, in this study, describe oncological profiles.

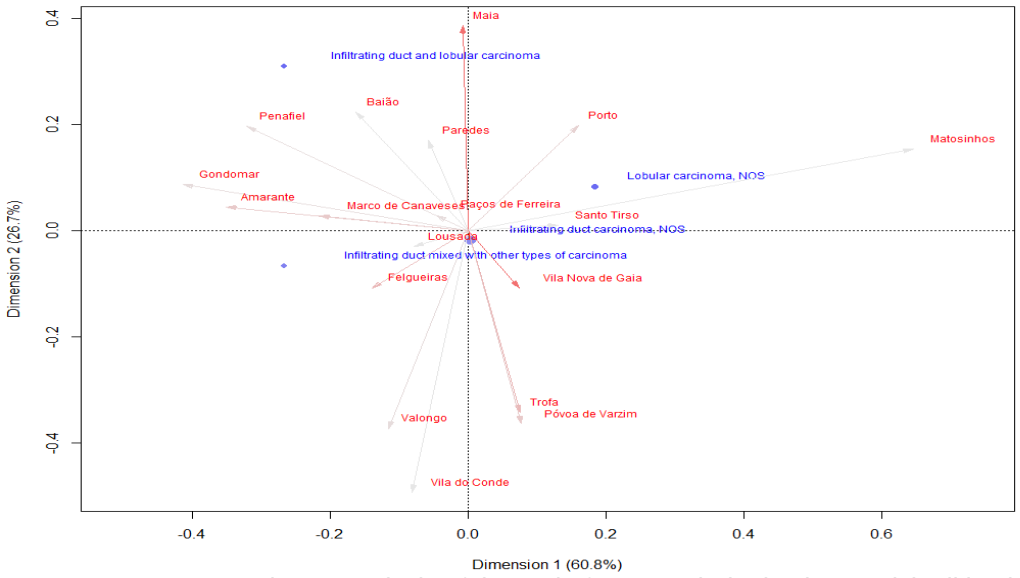

FIGURE 7 Correspondence analysis of the main four morphologies by municipalities in Porto district.

4.3.2. Characteristics of the canine MGT cases in Porto district

A total of 1155 canine MGT cases diagnosed between January 2019 to May 2022 were included in this study (Table A4). Regarding sex, there was a significant predominance of female dogs (n= 1130, 97.8%) with male dogs representing 2.2% of cases (n=25). Figure 8 shows the distribution of MGT cases by age and sex in years. 53.9% of MGT cases were diagnosed between 9 and 12 years of age (Figure 8). The average age was 9.7 (SD=2.6) for females and 7.9 years (SD=4.0) for males being statically different ($p<0.001$).

Information about the reproduction status (spayed) was not considered in the study since many registries lacks this information. Only in 1.5% cases (n= 17) the information was available.

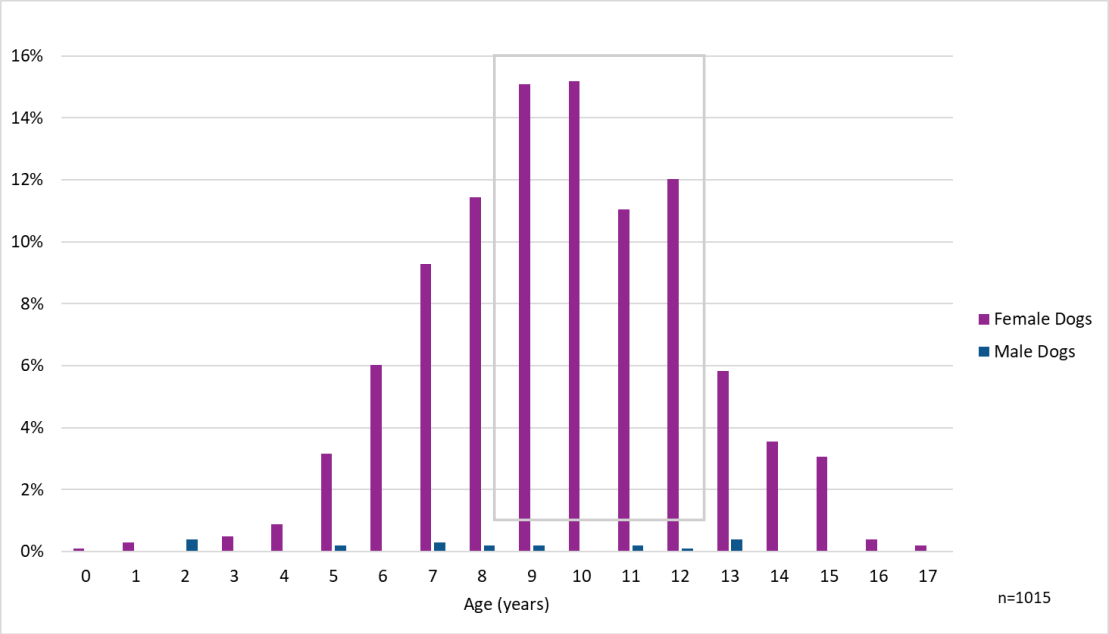

FIGURE 8 Distribution by age and sex of canine MGT in Porto district, between 2019 and 2022.

4.3.2.1. Distribution by breed

Regarding the breed distribution (Figure 9), no-breed dogs were the most affected (n=571, 50.1%), followed by Labrador retrievers (n=103, 9%), Yorkshire terrier (n=88, 7.7%) and German shepherd (n=86, 7.6%).

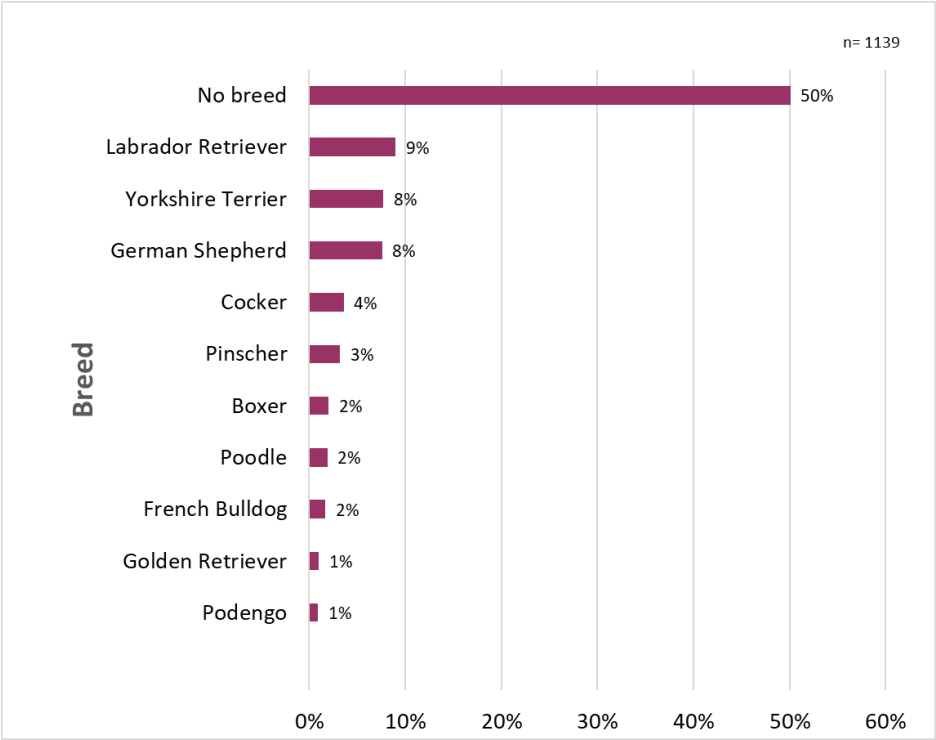

FIGURE 9 Distribution of the canine MGT by breed, in Porto district (only breeds with n > 10 were listed).

Regarding the age distribution analysis (Table 8 and Figure 10), Labrador retriever showed the highest statistically significant mean age (10.4 years, SD=2.5) in opposition with French bulldog (7.2 years, SD=2.3). No-breed, Labrador, Cocker and Poodle showed higher mean age than other breeds.

TABLE 8 Age distribution of canine MGT by breed (only breeds with n>10)

Breed	n (%)	Mean (SD)	Median (IQR)
No-breed	503 (55.3)	9.9 (2.8) [bc]	10.0 (4.0)
Labrador retriever	100 (11.0)	10.4 (2.5) [b]	10.0 (3.0)
Yorkshire terrier	78 (8.6)	9.3 (2.1) [ab]	9.0 (2.7)
German shepherd	78 (8.6)	9.1 (2.3) [ac]	9.0 (4.0)
Cocker	37 (4.1)	9.6 (2.4) [bc]	10.0 (3.0)
Pinscher	33 (3.6)	9.4 (2.5) [ab]	10.0 (3.0)
Boxer	22 (2.4)	8.5 (2.3) [ab]	8.0 (2.7)
Poodle	21 (2.3)	10.0 (2.4) [bc]	9.0 (2.0)
French bulldog	18 (2.0)	7.2 (2.3) [a]	7.0 (2.7)
Golden retriever	10 (1.1)	9.9 (2.3) [ab]	9.5 (3.7)
Podengo	10 (1.1)	8.1 (3.1) [ab]	8.0 (2.5)
Total	910 (100.0)		

Letters indicates the results of ANOVA followed by Tukey test, p<0.05. Age missing data.

Figure 10 show that Boxer has a higher density of MGT at 8 years of age. French bulldogs present a distribution at a younger age and no-breed dogs present many outliers, indicating a greater variability of the distribution by age in this group.

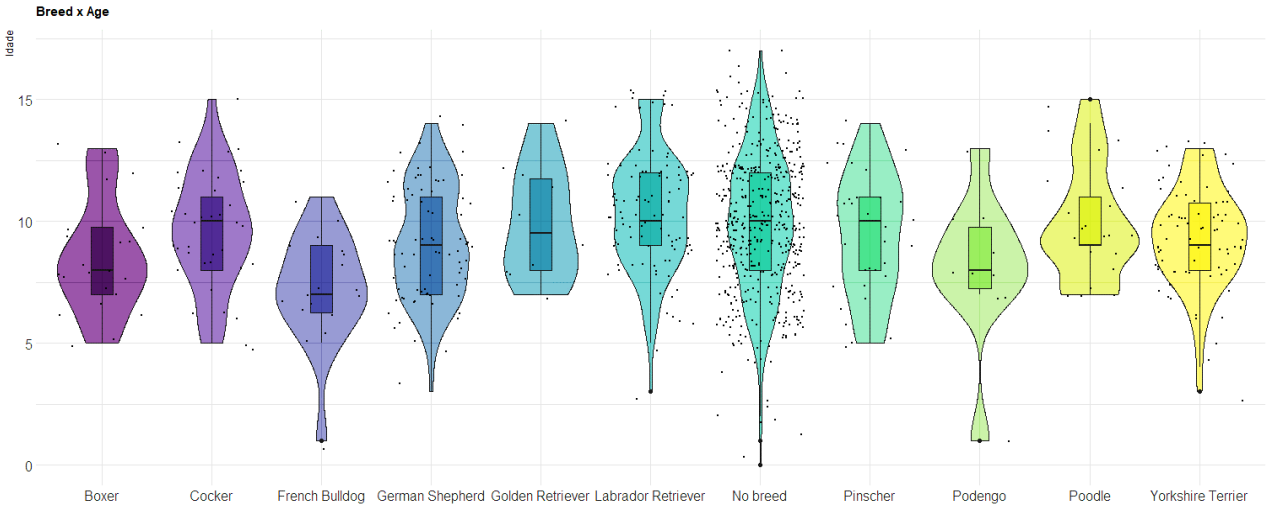

FIGURE 10 Violin chart of the age distribution at diagnosis of the canine MGT by the main breeds (n>10).

Regarding the malignancy proportion (MP) (Table 9), the results shows that no-breed dogs have a higher MP of 48.3% when compared to purebred dogs (45.7%). French Bulldog and German Shepherd presented the highest MP in contrast with Pinscher and Yorkshire Terriers. Using SIAC population data, it was possible to calculate the relative risk (RR) for each breed per benign, malignant and for all MGT. Table 9 and Figure 11 show relative risks from malignant and benign tumors of the breeds that showed 10 or more tumor cases on the database. It can be seen from both, Table and Figure, that the risk profile of benign and malign tumors is different among breeds. Cocker has the 3-fold higher risk of having MGT when compared to no-breed dogs (RR=3.2, 95%CI 2.27-4.24). What concerns to benign MGT, Cocker (RR=3.9, 95%CI 2.61-5.78, p-value<0.001) and Yorkshire Terrier (RR=2.0, 95%CI 1.47-2.60, p-value<0.001) have the highest RRs (Figure 11). As for malignant MGT, Cockers and German shepherd have the highest RR (RR=2.4, 95%CI 1.40-3.98, p-value=0.001, RR=1.4, 95%CI 1.05-1.92, p-value<0.05, respectively). Pinschers have a protective effect against the development of malignant MGT (RR=0.4, 95%CI 10.22-0.75, p-value=0.002). It should also be noted that pure breed dogs have a protective factor for the development of both malignant and benign MGT. Podengo dogs (a Portuguese breed) have a RR of 0.1 for the development of MGT.

TABLE 9 Distribution of benign and malignant MGT and respective Relative Risks (RR) by the most frequent breeds (n>10).

Breeds	Number of cases			Benign MGT			Malignant MGT			All MGT		
	Benign	Malignant	Population (SIAC)	RR	95% CI	p-value	RR	95% CI	p-value	RR	95% CI	p-value
No-breed	295 (51.7)	276 (48.3)	64425	Ref.	-	-	Ref.	-	-	Ref.	-	-
Labrador Retriever	55 (53.4)	53 (46.6)	11593	1,0	0.76-1.36	0,908	1,0	0.78-1.40	0,790	1,0	0.84-1.26	0,788
Yorkshire Terrier	56 (63.6)	32 (36.4)	6228	**2,0**	1.47-2.60	<0,001	1,2	0.84-1.73	0,308	**1,6**	1.27-1.98	<0,001
German Shepherd	39 (45.3)	47(54.7)	7858	1,1	0.78-1.51	0,637	**1,4**	1.05-1.92	0,023	1,2	1.00-1.56	0,053
Cocker	26 (63.4)	15 (36.6)	1444	**3,9**	2.61-5.78	<0,001	**2,4**	1.40-3.98	0,001	**3,2**	2.27-4.24	<0,001
Pinscher	26 (70.3)	11 (29.7)	6135	0,9	0.62-1.38	0,706	**0,4**	0.22-0.75	0,002	0,7	0.48-0.94	0,019
Boxer	12 (52.2)	11 (47.8)	2002	1,3	0.73-2.34	0,360	1,3	0.68-2.29	0,466	1,3	0.84-1.95	0,246
Poodle	11 (50.0)	11 (50.0)	2174	1,1	0.61-2.01	0,744	1,2	0.63-2.11	0,646	1,1	0.74-1.72	0,581
French Bulldog	8 (42.1)	11 (57.9)	3289	0,5	0.26-1.07	0,073	0,8	0.42-1.39	0,374	0,6	0.41-1.02	0,057
Golden Retriever	6 (54.5)	5 (45.5)	1436	0,9	0.41-2.05	0,981	0,8	0.33-1.92	0,606	0,9	0.47-1.55	0,604
Podengo	5 (50.0)	5 (50.0)	14834	**0,1**	0.03-0.18	<0,001	**0,1**	0.03-0.19	<0,001	**0,1**	0.04-0.14	<0,001
All breeds*	308 (54.2)	260 (45.7)	88608	**0,8**	0.65-0.89	<0,001	**0,7**	0.59-0.82	<0,001	**0,7**	0.36-0.82	<0,001

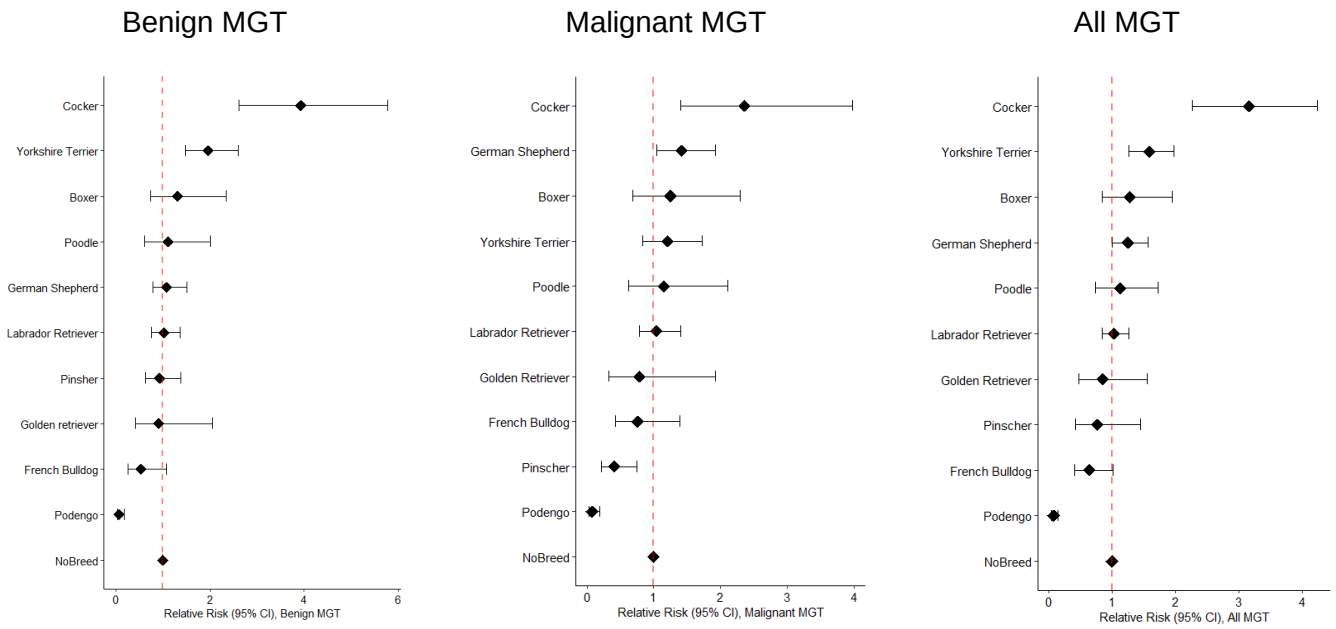

FIGURE 11 Forest plots representing the Risk Ratio by breed of benign MGT (left), malignant MGT (middle) and all MGT (right) (order by RR values).

Breed categories

The analysis of breeds aggregated according to the Fédération Cynologique Internationale (FCI) (Table 10) groups shows that both the group of Dachshunds have a lower mean age at diagnosis (7.7 years SD=2.2), while dogs belonging to the Companion and Toy Dogs group have a higher mean age (9.9 years, SD=2.1).

TABLE 10 Age distribution of MGT by FCI breed category.

FCI category	n (%)	Mean (SD)	Median (IQR)
Sheepdogs and Cattledogs	94 (8.1)	9.1 (2.4) [ac]	9.0 (4.0)
Pinscher and Schnauzer (Molossoids)	112 (9.7)	8.7 (2.5) [a]	10.0 (3.0)
Terriers	112 (9.7)	9.3 (2.2) [ab]	9.0 (3.0)
Dachshunds	6 (0.5)	7.7 (2.2) [ab]	7.5 (2.5)
Spitz and primitive types	19 (1.65)	8.5 (2.6) [ab]	8.0 (1.7)
Scent hounds and related breeds	15 (1.3)	8.73 (2.1) [ab]	8.0 (2.5)
Pointing	7 (0.6)	9.3 (2.1) [ab]	9.0 (2.0)
Retrievers	162 (14.0)	10.2 (2.4) [b]	10.0 (3.0)
Companion and Toy Dogs	42 (3.6)	9.9 (2.1) [ab]	10.0 (2.0)
No-breed	578 (50.0)	9.9 (2.9) [bc]	10.0 (4.0)
Undefined	8 (0.69)	8.71 (3.5) [ab]	8.0 (5.0)

Letters indicates the results of ANOVA followed by Tukey test.

Regarding the age distribution by FCI breed category, using the violin chart (Figure 12), it is possible to observe that Dachshunds show a higher density of MGT at 7 years of age in contrast to Companion and toy dogs with more cases rounding ten years.

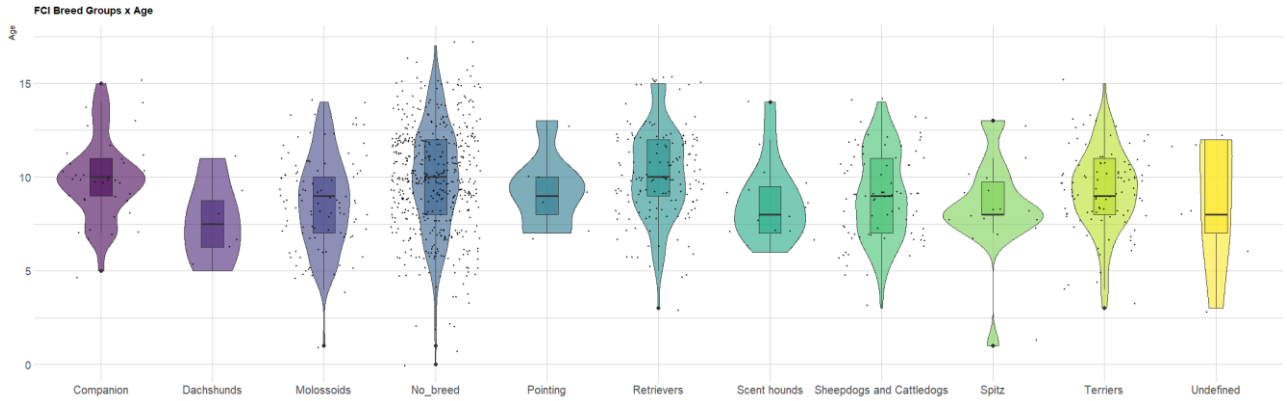

FIGURE 12 Violin chart of the age distribution in years of MGT by FCI breed category.

4.3.2.2. Tumors characteristics

Taking MGT topography into consideration, the analysis of this study was compromised since 96.8% of the cases were classified as Mammary Gland, NOS. This result could be related to the lacking site-specific information, performed by clinicians. Concerning the distribution of the MGT by morphology (Table A4), the main subtypes diagnosed are complex adenoma (n=220, 19.1%), followed by benign mixed tumor, NOS (n=218, 18.9%), complex carcinoma (n=205, 17.8%), tubular carcinoma (n=118, 10.2%) and tubular adenoma (n=114, 9.9%). The analysis of the distribution of the most frequent morphologies by the main breeds (with n>10) (Figure 13) shows that Boxers had more cases of solid carcinoma (22.7%) and Pinscher showed a higher percentage of complex adenomas (39.4%).

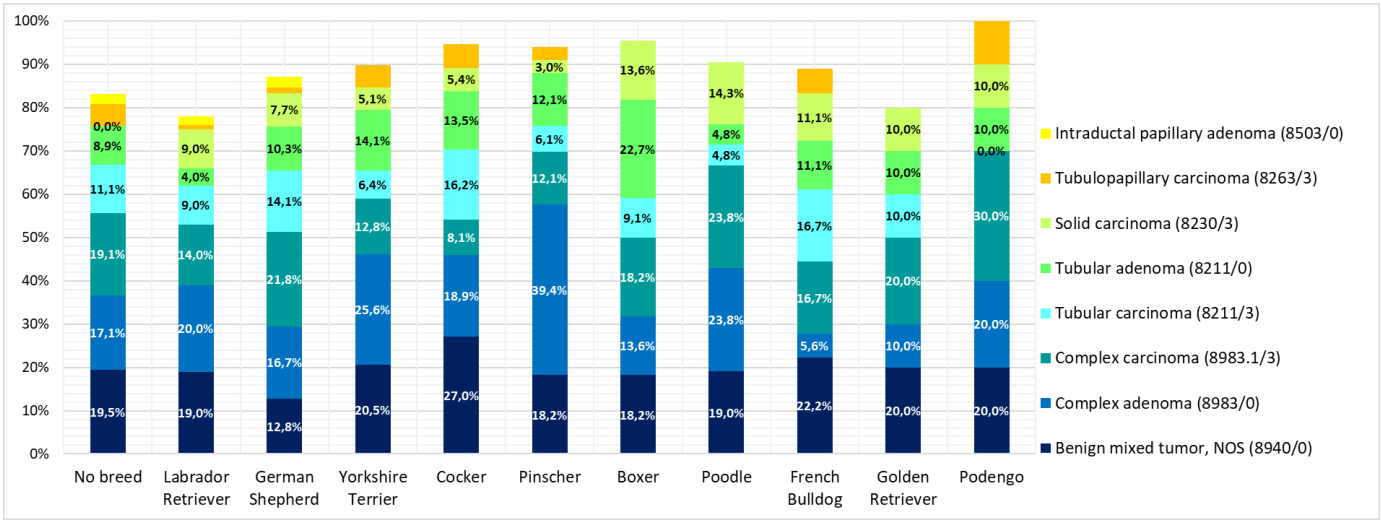

FIGURE 13 Distribution of the MGT morphologies per breeds (with n> 10).

To improve the analysis of the different morphology patterns between breeds, a CA was performed with the variables showed in Figure 13. In figure 14 it is possible to observe that Pinscher are more associated with complex adenoma and cocker with benign mixed tumor and tubular adenoma. From both Figures, it seems that French Buldog, German Shepherd Golden Retriever and Boxer share a closer profile. Indeed, the great majority of the breeds did not show a breed-specific pattern of morphologies. However, there are morphologies that are dissimilar from others (e.g., tubulopapilary carcinoma x solid carcinoma).

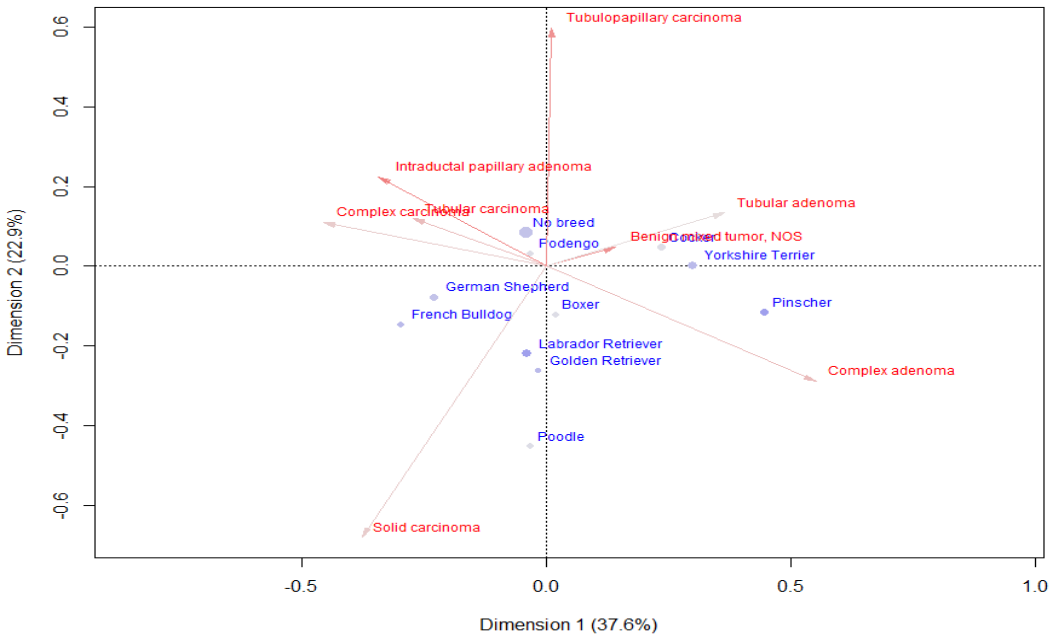

FIGURE 14 Correspondence analysis for mains breeds (n>10) by the main morphologies of MGT.

4.3.2.3. Distribution of MGT by municipalities

Figure 19 represent the distribution by municipalities of MGT and the corresponding female dogs´ population in Porto district. Vila Nova de Gaia, Matosinhos, Maia and Gondomar show a greater number of MGT cases registered. The labels in Figure 19 represent the MGT annual incidence risk per 10,000, that is higher in the municipalities of Porto, Marco de Canaveses, Matosinhos, Trofa, Maia, Povoa de Varzim and Vila Nova de Gaia.

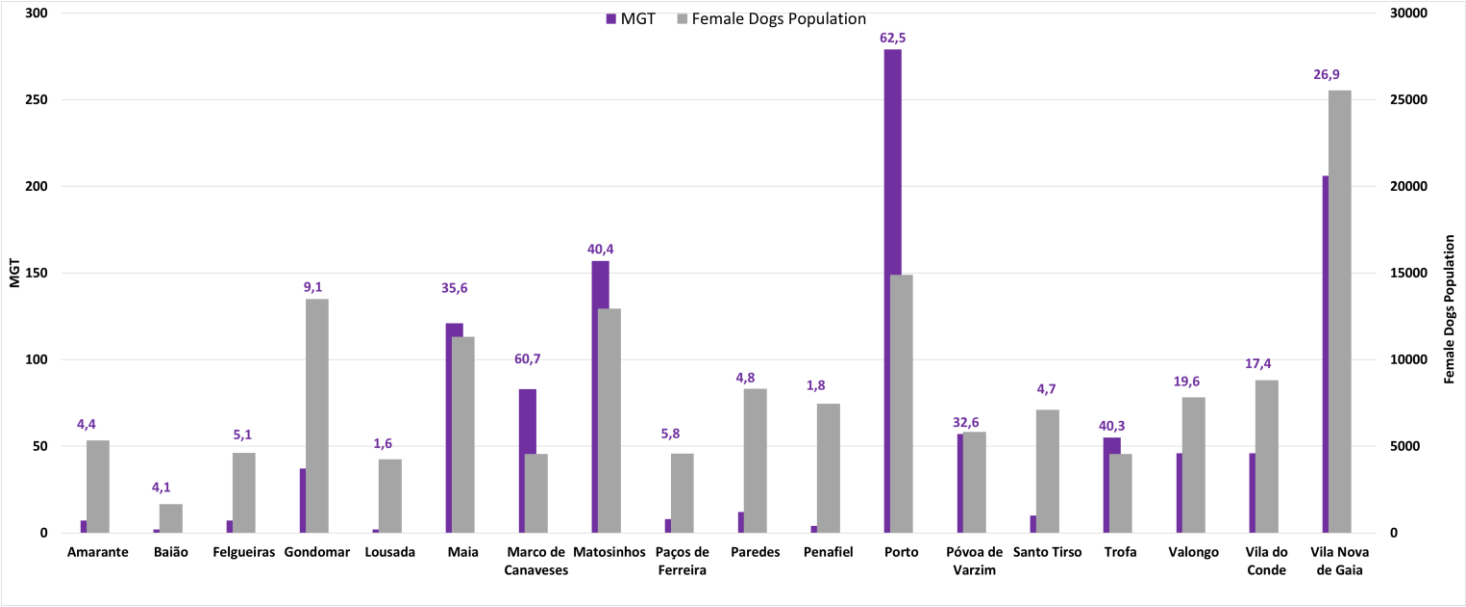

FIGURE 15 Distribution per municipalities of canine MGT (on left) and female dogs population (on right) in Porto district. The labels represent the MGT annual incidence rate per 10,000.

4.3.3. Characteristics of the canine malignant MGT

Since RON does not present human benign tumors and in order to carry out a comparative analysis, canine malignant MGT (mMGT) were analysed separately. Of the 1155 MGT, 535 corresponded to malignant tumors (46.32%), with a mean age of 9.89 years (SD=2.65). 98.8% (n=527) corresponded to female dogs while 1.5% (n=8) corresponded to male dogs. The female dogs mMGT mean age was 9.92 years (SD=2.6) and for male dogs was 8.38 years (SD=4.6).

Regarding morphologies, the most frequent were the complex carcinoma with 38.3% (n=205), followed by tubular carcinoma with 22.1% (n=118) and solid carcinoma with 14.4% of cases (n=77) (Figure 15). Four mophology types dominate the lanscape with more than 90% of the cases.

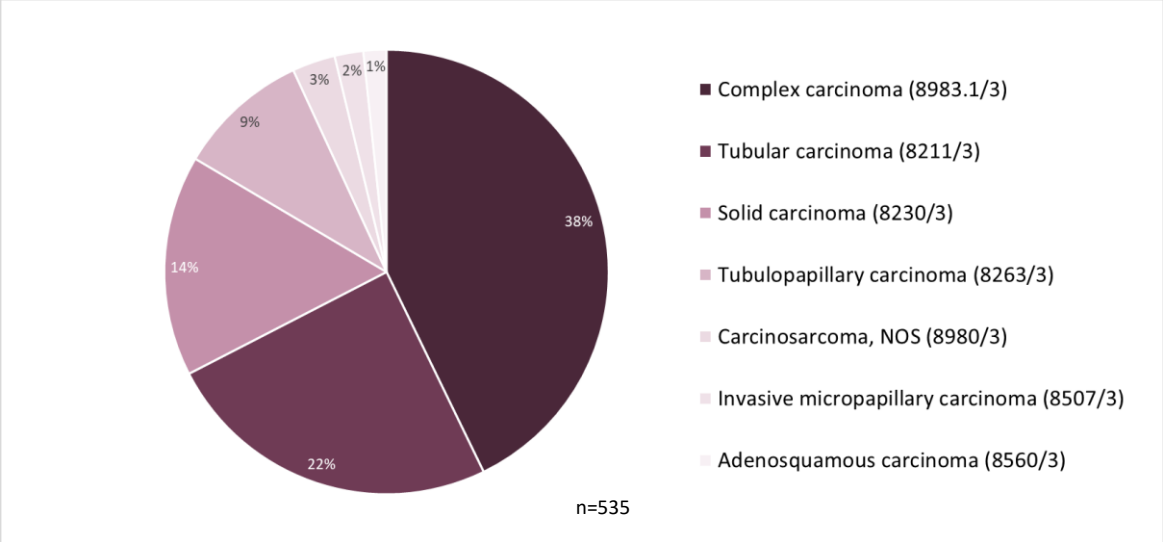

FIGURE 16 Distribution of the main canine mMGT morphologies, in Porto district.

The analysis of the distribution of the main malignant morphologies by main breeds (n>10) (figure 17) revealed that Cocker and Beagle had a higher proportion tubular carcinomas (40.0% and 42.9% respectively) while Poodle, Boxer and French Bulldog show a predominance of solid carcinomas. On other hand, Pinscher presents the highest proportion of invasive micropapillary carcinomas (9.1%) (Figure 17).

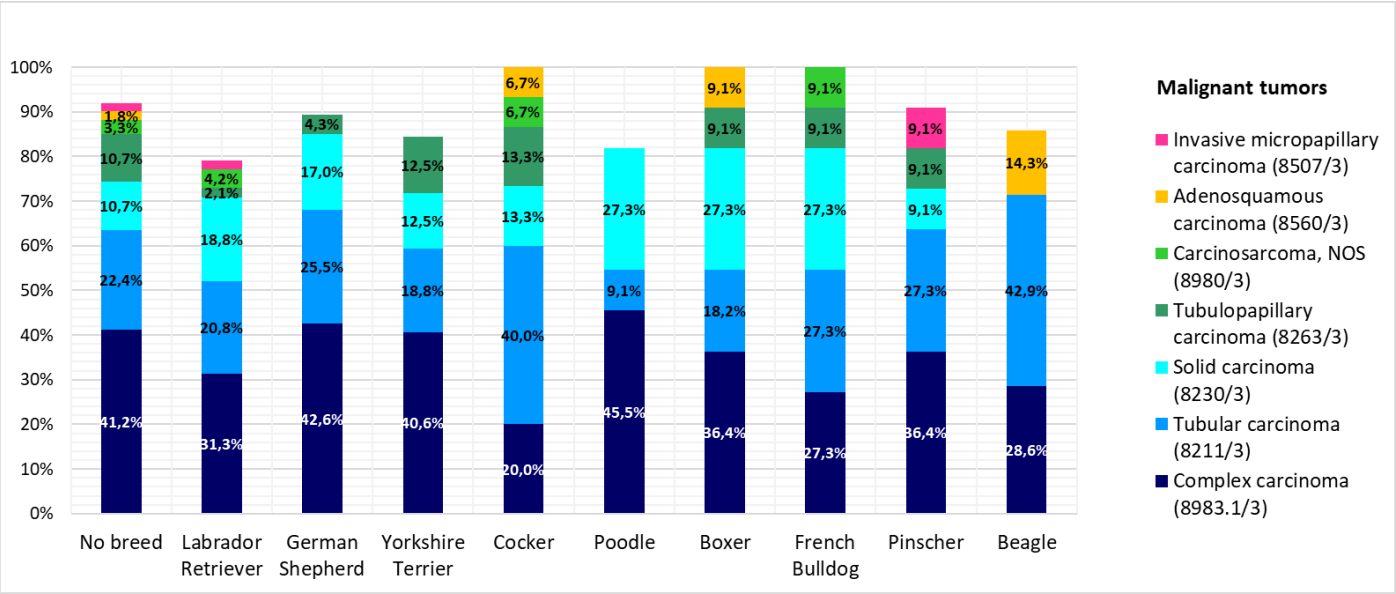

FIGURE 17 Distribution of the main mMGT by breeds (n> 10).

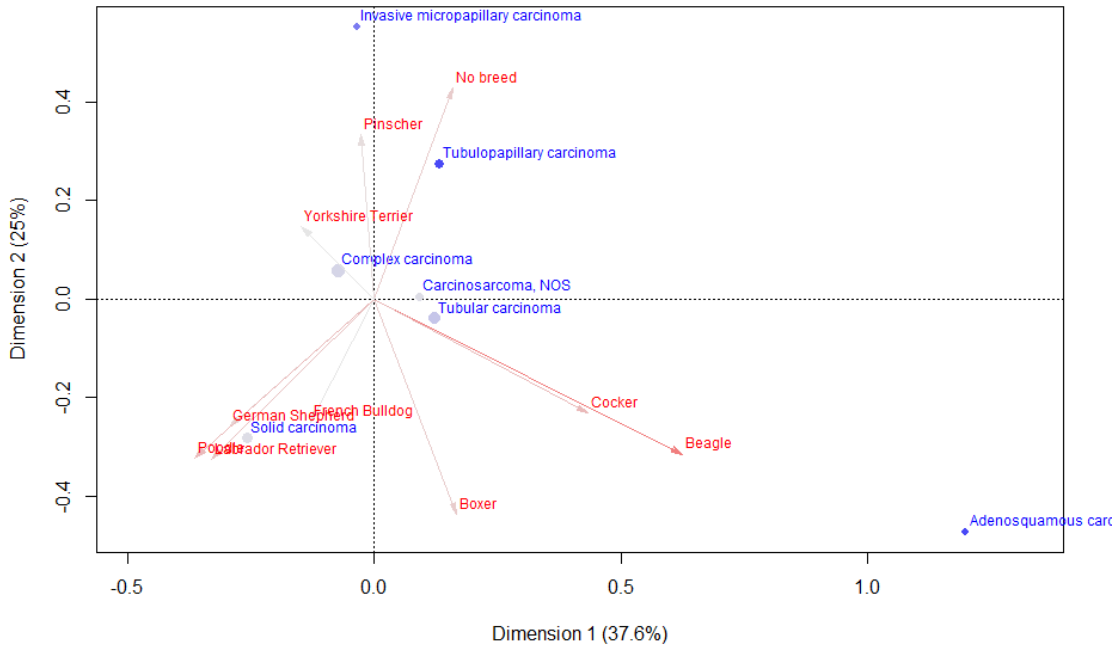

FIGURE 18 Correspondence analysis of Breeds with n greater than 10 x Main malignant MGT morphologies.

To recognize these different patterns of morphologies by breed, a CA was carried out. Figure 18 is more informative than Figure 14 since allows for more clear associations between breeds and morphology types. In figure 18, it is possible to identify similar patterns between German Shepherd, French Bulldog, Poodle and Labrador retriever with a high association to solid carcinoma. Cocker, Beagle and Boxer are not far from

Adenosaquamous carcinoma. Pinsher and no-breed aggregate with Tubulopapilary carcinoma and Invasive micropapillary carcinoma.

Concerning the distribution of canine mMGT by municipalities (Table 12), Porto, Vila Nova de Gaia, Matosinhos and Maia described a superior number of registered cases on the Vet-OncoNet platform and the malignancy proportion (MP) of them was very similar in line with mean total malignancy.

TABLE 11 Canine mMGT distribution and respective Malignancy Proportion (MP) by municipalities, in Porto district.

Municipalities	n	(%)	$_{m}$ MGT	(%MP)
Amarante	7	(0.6)	4	(57)
Baião	2	(0.2)	0	-
Felgueiras	8	(0.7)	3	(38)
Gondomar	41	(3.5)	21	(51)
Lousada	2	(0.2)	2	(100)
Maia	**121**	**(10.5)**	51	**(42)**
Marco de Canaveses	86	(7.4)	37	(43)
Matosinhos	**159**	(**13.8)**	79	**(50)**
Paços de Ferreira	8	(0.7)	5	(63)
Paredes	12	(1.0)	4	(33)
Penafiel	4	(0.3)	2	(50)
Porto	**282**	**(24.4)**	128	**(45)**
Póvoa de Varzim	58	(5.0)	32	(55)
Santo Tirso	11	(1.0)	7	(64)
Trofa	55	(4.8)	25	(45)
Valongo	46	(4.0)	25	(54)
Vila do Conde	47	(4.1)	24	(51)
Vila Nova de Gaia	**206**	(**17.8)**	86	**(42)**
Total	1155	(100)	535	(46)

4.3.4. Comparative analysis in Porto district

In order to fulfil one of the main objectives of this work, a comparative analysis of WBC and female dogs mMGT cases in the district of Porto was carried out. This analysis aims to assess whether there are similarities between the cases regarding age, sex, topography, morphology and geographic distribution.

4.3.4.1. Age

The Z-Score was calculated to allow a comparative analysis between the ages of WBC and female dogs mMGT. Figure 19 shows the WBC histogram per age and the corresponding Z-score, and it stands out the existence of two age peaks, one before and one after the mean age. In the case of female dogs mMGT (Figure 20), analysing their histogram and the corresponding Z-score, there is only one frequency peak at the mean age.

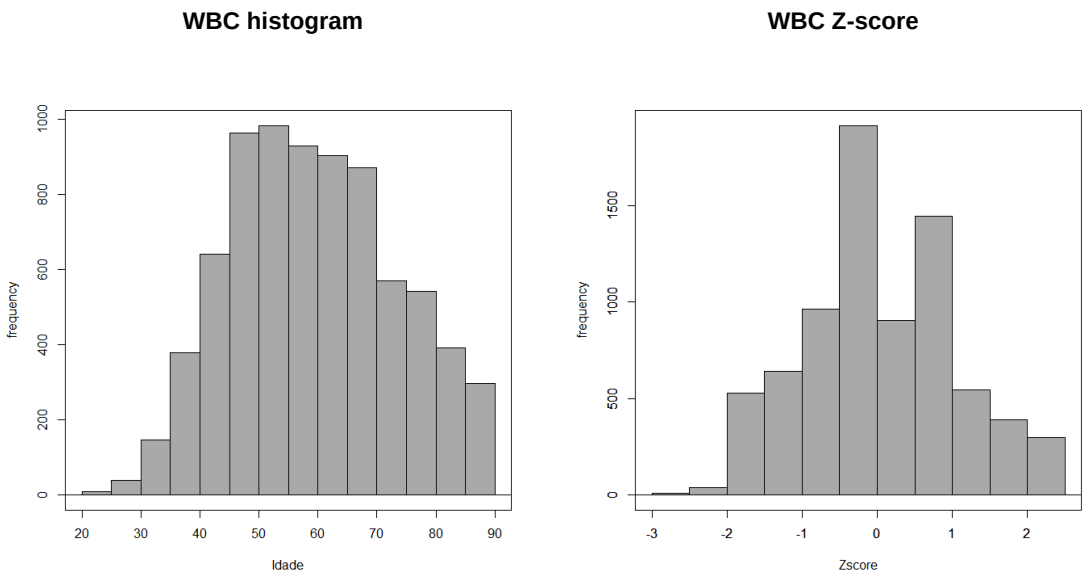

Figure 19 Histogram of WBC distribution per age (left) and the correspondent Z-score histogram (right).

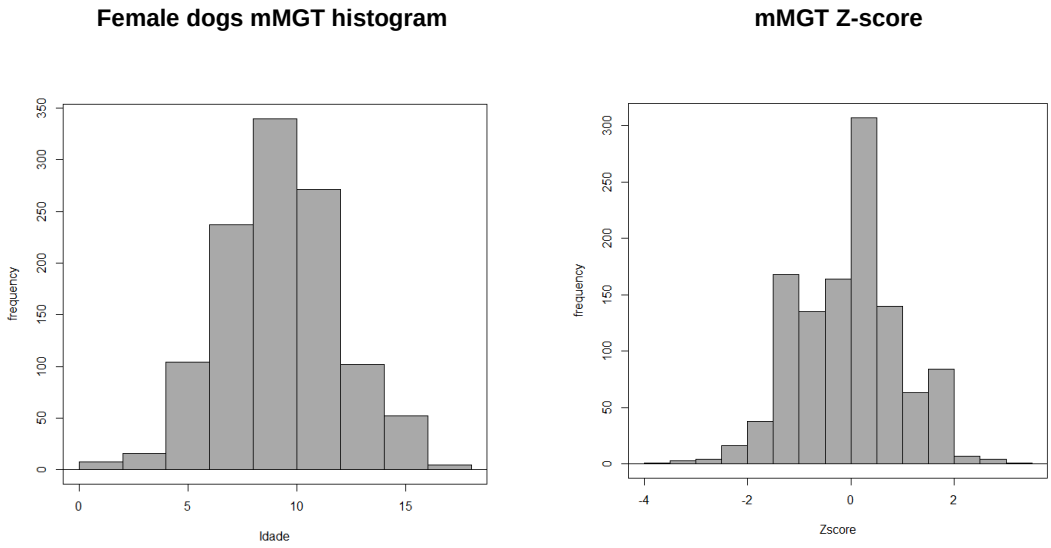

FIGURE 20 Histogram of female dogs mMGT distribution per age (left) and the correspondent Z-score histogram (right).

The results of Z-score (Table 12) analysis shows that both distributions are similar with no differences between the median of Z-scores (Wilcoxon rank sum test, p-value=0.667). However, the variances are statistically different (F test= 0.895, p-value=0.011).

TABLE 12 Descriptive analysis of women and female dogs Z-scores

	Mean (SD)		IQR	0%	25%	50%	75%	100%	N	Variance
Women Z-score	0.00030	(1.001)	1.43	-2.64	-0.85	-0.13	0.58	2.01	7674	1.001*
Female Dogs Z-score	0.00022	(0.947)	1.11	-3.60	-0.64	0.00	0.47	3.06	1271	0.897

*p<0.05, F test.

For a better visualization, a combine density plot of both Z-scores (Figure 21) were performed, highlighting a high overlapping of age distributions in both species. However, the result of the two samples K-S test showed that the distributions of women and female dogs Z-scores are statically different (K-S=4.3, p-value < 0.001).

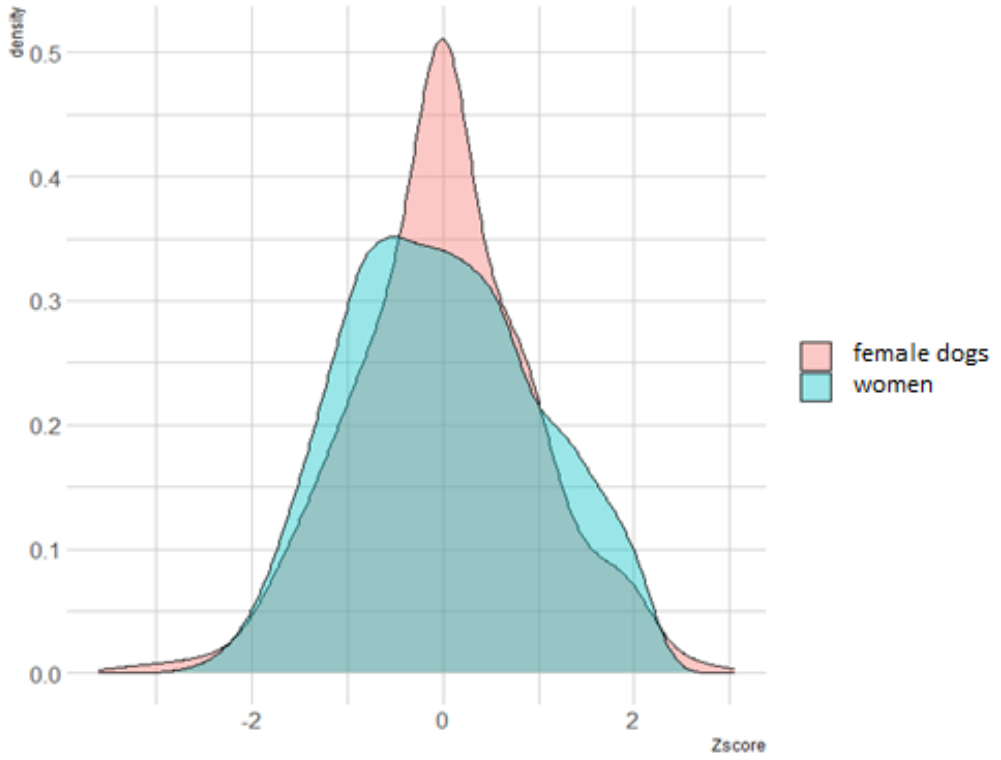

FIGURE 21 Density plot of women and female dog Zscores

4.3.4.2. Sex

The results achieved in this study indicate that both in human and in dogs, the proportion of sex distribution is very similar. In canine mMGT, 98.5%(n=527) are in female dogs resting only 1.5% in males (n=8). In human counterpart, this analysis also indicates that breast cancer is more common in women (n=7584, 99%) than in men (n=90, 1%). Interestingly to note that in men the cases are concentrated in the final part of the life, different from male dogs, that cases are distributed along the life.

4.3.4.3. Topography

Regarding canine mMGT topography, the analysis of this study was compromised since the majority of the cases were classified as mammary gland, NOS. This result could be related to the lacking site-specific information, performed by clinicians, causing a bias.

One of the most frequent WBC topographies documented in this study was the UOQ. The results did not allow a comparative analysis by topography.

4.3.4.4. Morphology

Starting from the most frequent morphology in women (highlighted in clear orange in Table 13) Infiltrating duct carcinoma, NOS (8500/3) with 74.06% (n=5617), in the female dogs this same morphology exists in only 0.19% (n=1) (Table 13). Both Lobular carcinoma, NOS (8520/3), Infiltrating duct mixed with other types of carcinomas (8523/3) and Infiltrating duct and lobular carcinoma (8522/3) are not described in Vet-ICD-O-canine-1 and therefore there is no comparability (Table 13).

Comparing some morphologies in particular (highlighted in clear blue in Table 13), Invasive micropapillary carcinoma of breast (8507/3) presented 0.55% (n=42) of cases in women, and in female dogs it corresponded to 1.90% of cases of mMGT (Invasive micropapillary carcinoma, 8507 /3, n=10). In women the morphology Intraductal papillary adenocarcinoma with invasion (8503/3) presented 0.46% (n=35) of the cases and in the female dogs it corresponded to 0.95% (n=5) (Table 13).

Starting from the most frequent morphology in the female dogs (highlighted in pinkish in Table 13), Complex carcinoma (8983.1, n=202, 38.33%) is not described in the ICD-O-3.2, not showing correspondence in women. Tubular carcinoma (8211/3) presented 21.82% (n=115) of the mMGT cases and in women it represented 0.37% (n=28) (Table 13).

Interesting, Solid carcinoma in female dogs with 14.61% (n=77) was not seen in women. Also, Inflammatory carcinoma was low in both species (0.57% for female dogs and 0.08% for women).

TABLE 13 Distribution of WBC and female dogs mMGT morphologies, according to ICD-O-3.2 and Vet-ICD-O-canine-1 (ordered by ICD-O-3.2 reference code).

Women Breast Cancer morphology	ICD-O-3.2	n	%	Female Dog mMGT morphology	Vet-ICDO	n	%
Neoplasm, malignant	8000/3	97	1.28	Neoplasm, malignant	8000/3	2	0.38
	8010/2			Carcinoma in situ, NOS	8010/2	3	0.57
Carcinoma, NOS	8010/3	153	2.02				
	8021/3			Carcinoma, anaplastic, NOS	8021/3	5	0.95
Pleomorphic carcinoma	8022/3	1	0.01				
Papillary carcinoma, NOS	8050/3	9	0.12				
Squamous cell carcinoma, NOS	8070/3	1	0.01	Squamous cell carcinoma, NOS	8070/3	7	1.33
Adenocarcinoma, NOS	8140/3	5	0.07				
Adenoid cystic carcinoma	8200/3	4	0.05				
Cribriform carcinoma, NOS	8201/3	6	0.08				
Tubular adenocarcinoma	8211/3	28	0.37	Tubular carcinoma	8211/3	115	21.82
				Solid carcinoma	8230/3	77	14.61
Neuroendocrine carcinoma, NOS	8246/3	6	0.08				
Papillary adenocarcinoma, NOS	8260/3	4	0.05				
	8263/3			Tubulopapillary carcinoma	8263/3	45	8.54
Clear cell adenocarcinoma, NOS	8310/3	1	0.01				
	8314/3			Lipid-rich carcinoma	8314/3	1	0.19
Apocrine adenocarcinoma	8401/3	2	0.03				
Mucinous adenocarcinoma	8480/3	104	1.37	Mucinous adenocarcinoma	8480/3	1	0.19
Signet ring cell carcinoma	8490/3	1	0.01				
Infiltrating duct carcinoma, NOS	8500/3	5617	74.06	Ductal carcinoma	8500/3	1	0.19
Comedocarcinoma, NOS	8501/3	3	0.04	Comedocarcinoma	8501/3	5	0.95
Glycogen-rich carcinoma	8502/3	3	0.04				
Secretory carcinoma	8502/3	3	0.04				
Intraductal papillary adenocarcinoma with invasion	8503/3	35	0.46	Intraductal papillary carcinoma	8503/3	5	0.95
Encapsulated papillary carcinoma with invasion	8504/3	19	0.25				
Invasive micropapillary carcinoma of breast	8507/3	42	0.55	Invasive micropapillary carcinoma	8507/3	10	1.90
Medullary carcinoma, NOS	8510/3	17	0.22				
Atypical medullary carcinoma	8513/3	3	0.04				
Duct carcinoma, desmoplastic type	8514/3	1	0.01				
Lobular carcinoma, NOS	8520/3	707	9.32				
Infiltrating ductular carcinoma	8521/3	53	0.70				
Infiltrating duct and lobular carcinoma	8522/3	204	2.69				
Infiltrating duct mixed with other types of carcinoma	8523/3	341	4.50				
Infiltrating lobular mixed with other types of carcinoma	8524/3	18	0.24				
Polymorphous adenocarcinoma	8525/3	1	0.01				
Inflammatory carcinoma	8530/3	6	0.08	Inflammatory carcinoma	8530/3	3	0.57
Paget disease, mammary	8540/3	22	0.29				
Paget disease and intraductal carcinoma of breast	8543/3	3	0.04				
Acinar cell carcinoma	8550/3	1	0.01				
Adenosquamous carcinoma	8560/3	2	0.03	Adenosquamous carcinoma	8560/3	8	1.52
	8562/3			Carcinoma and malignant myoepithelioma	8562/3	3	0.57

Adenocarcinoma with spindle cell metaplasia	8572/3	1	0.01				
Adenocarcinoma with neuroendocrine differentiation	8574/3	1	0.01				
Metaplastic carcinoma, NOS	8575/3	31	0.41				
Sarcoma, NOS	8800/3	1	0.01	Sarcoma, NOS	8800/3	1	0.19
Giant cell sarcoma	8802/3	1	0.01				
				Undifferentiated sarcoma	8805/3	3	0.57
				Fibrosarcoma, NOS	8810/3	2	0.38
Liposarcoma, NOS	8850/3	1	0.01				
Dedifferentiated liposarcoma	8858/3	1	0.01				
Leiomyosarcoma, NOS	8890/3	1	0.01				
	8940/3			Mixed carcinoma, NOS	8940/3	5	0.95
Carcinosarcoma, NOS	8980/3	2	0.03	Carcinosarcoma, NOS	8980/3	15	2.85
Myoepithelial carcinoma	8982/3	1	0.01	Malignant myoepithelioma	8982/3	4	0.76
				Complex carcinoma	8983.1	202	38.33
Phyllodes tumor, malignant	9020/3	4	0.05				
Hemangiosarcoma	9120/3	4	0.05				
				Osteosarcoma, NOS	9180/3	4	0.76
Malignant lymphoma, non-Hodgkin, NOS	9591/3	1	0.01				
Hodgkin lymphoma, NOS	9650/3	1	0.01				
Malignant lymphoma, small B lymphocytic, NOS	9670/3	1	0.01				
Diffuse large B-cell lymphoma, NOS	9680/3	4	0.05				
Burkitt lymphoma, NOS	9687/3	1	0.01				
Marginal zone B-cell lymphoma, NOS	9699/3	3	0.04				
Myeloid sarcoma	9930/3	1	0.01				
Total		**7584**	**100.00**			**527**	**100.00**

Most frequent WBC Most frequent mMGT Similar frequencies

4.3.4.5. Geographic distribution

The geographic distribution of WBC and female dogs mMGT in Porto district was determined taking into account the data of women population available in INE website (Table A5), and the data of female dogs' population from SIAC (Table A6). The municipalities with the highest population of women corresponded to Vila Nova de Gaia with 16.9% (n=159096), followed by Porto with 12.7% (n=119394) and Matosinhos with 9.9% (n=93454). Concerning the female dog's population, the municipality of Vila Nova de Gaia had 16.7% (n=25546), followed by Porto with 9.7% (n=14891) and Gondomar with 8.8% (n=13487).

Table A5 shows the distribution of WBC by municipality, indicating that in Vila Nova de Gaia were described 17.6% (n=1297) of cases, followed by Porto with 17.5% (n=1403) and Matosinhos with 12.6% (n=886). Regarding the distribution of female dogs mMGT, the municipality of Porto had 24.3% (n=128) of cases, followed by Vila Nova de Gaia 16.3% (n=86) and Matosinhos with 14.4% (n=76) (Table A6).

The above-mentioned data allowed the calculation of the annual crude incidence risk of WBC and mMGT by municipality, represented in Table 14. It was possible to observe that in Porto and Matosinhos the distribution of the cases was higher in both species, indicating women with an annual crude incidence risk of 19.6 and 15.8, respectively, and female dogs with 28.7 and 19.6, respectively. In Marco de Canaveses, the annual crude incidence risk per 10 000 female dogs was the highest (27.1) in the entire district of Porto (Table 14).

TABLE 14 Women and female dogs' crude incidence rate of mammary malignant tumors by municipality in Porto district.

Municipality	**Annual Crude Incidence Risk per 10 000**	
	Women	Female dogs
Amarante	9.2	1.9
Baião	10.5	0.0
Felgueiras	9.7	2.2
Gondomar	13.3	5.2
Lousada	8.1	1.6
Maia	12.6	14.1
Marco de Canaveses	10.5	**27.1**
Matosinhos	**15.8**	**19.6**
Paços de Ferreira	9.7	3.6
Paredes	9.9	1.6
Penafiel	10,1	0.9
Porto	**19.6**	**28.7**
Póvoa de Varzim	13.6	18.3
Santo Tirso	13.1	3.3
Trofa	12.4	17.6

Valongo	11.8	10.7
Vila do Conde	13.8	9.1
Vila Nova de Gaia	13.7	11.2
Total	13.4	11.5

With the crude incidence rate results from Table 14, maps of the geographic distribution of the WBC and female dogs mMGT were made. Figures 20 and 21 show that coastal municipalities with elevated urban densities such as Porto, Matosinhos, had a higher crude incidence rate, in contrast to interior municipalities.

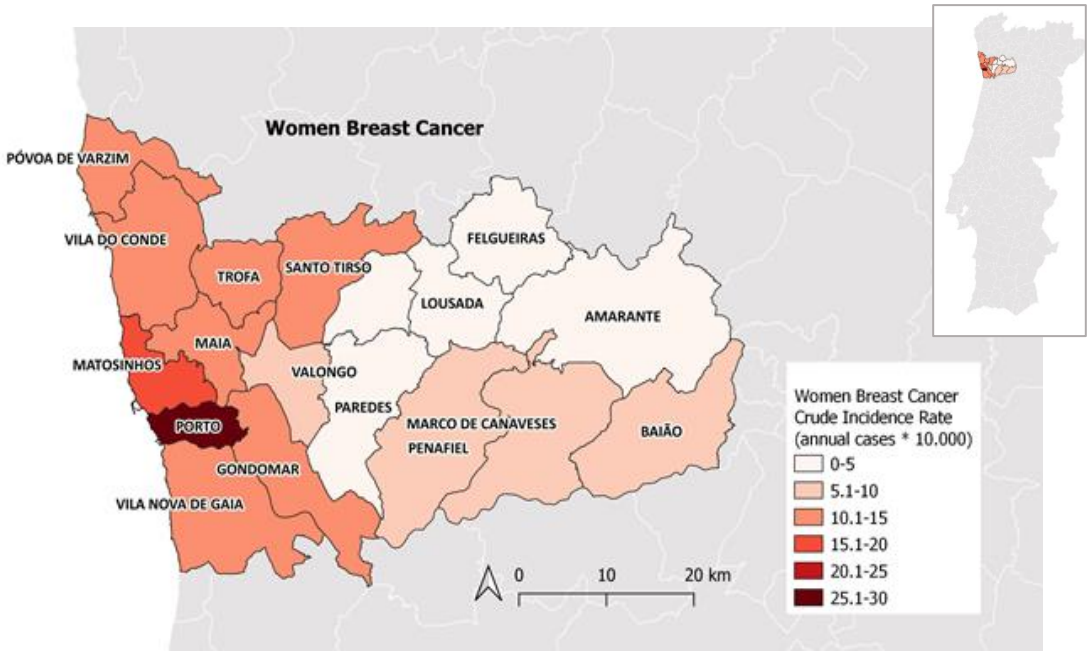

FIGURE 21 Map of the geographical distribution of WBC crude incidence rate per 10 000 women by municipality in the district of Porto.

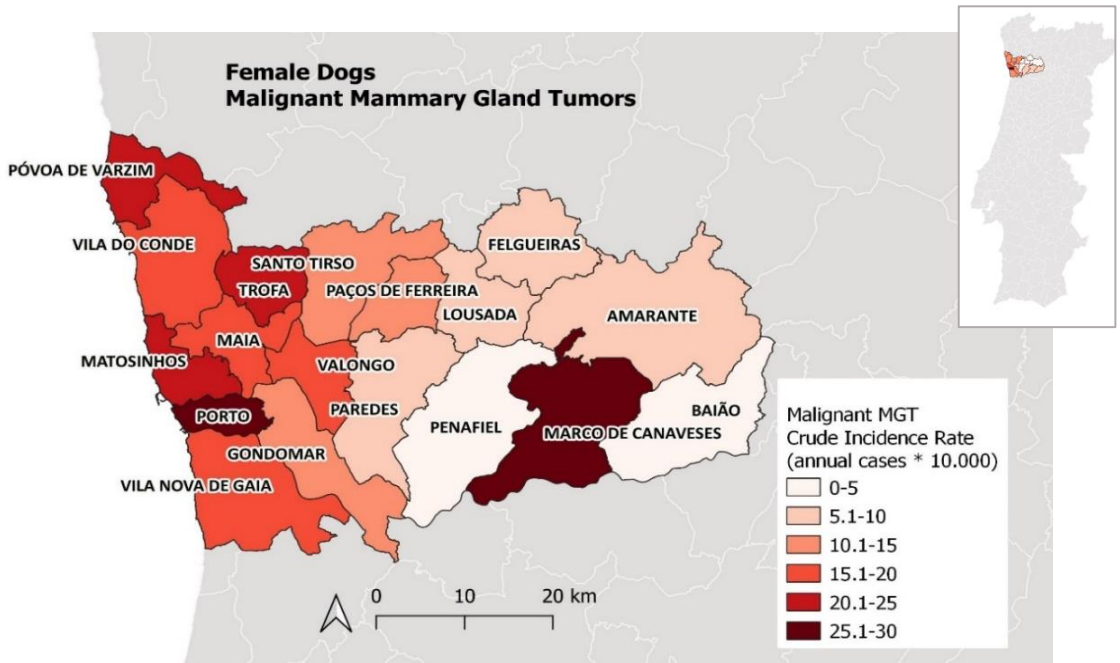

FIGURE 22 Map of the geographical distribution of mMGT crude incidence rate per 10 000 female dogs by municipality in the district of Porto.

A correlation analysis of the WBC and female dogs mMGT cIRs by municipalities of Porto district were performed (Figure 22) and the results shows a R of 0.69 and R^2 of 0.47 (*p-value*<0.01).

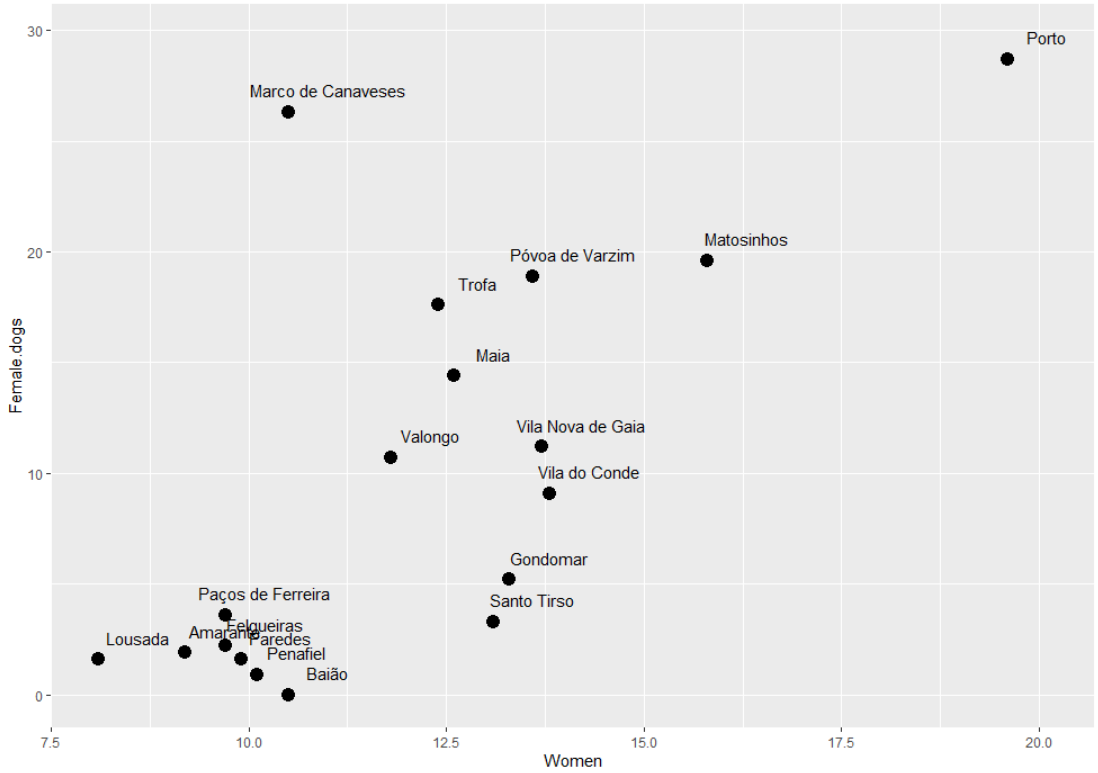

FIGURE 23 Scatterplot of WBC and female dogs mMGT crude annual incidence rates, by municipalities of Porto district.

As seen in figure 22, Marco de Canaveses seems to be an outlier. Estimating Cook's distance to verify outliers in correlations, it was found that this municipality had a high value (Cook's distance=1.29). The Cook's distance is considered high if it is greater than 0.5 and extreme if it is greater than 1. Therefore, a new correlation analysis was performed removing this point. The Pearson correlation test was repeated, excluding this municipality and R increased to 0.85 (p-value<0.01) (Figure 23).

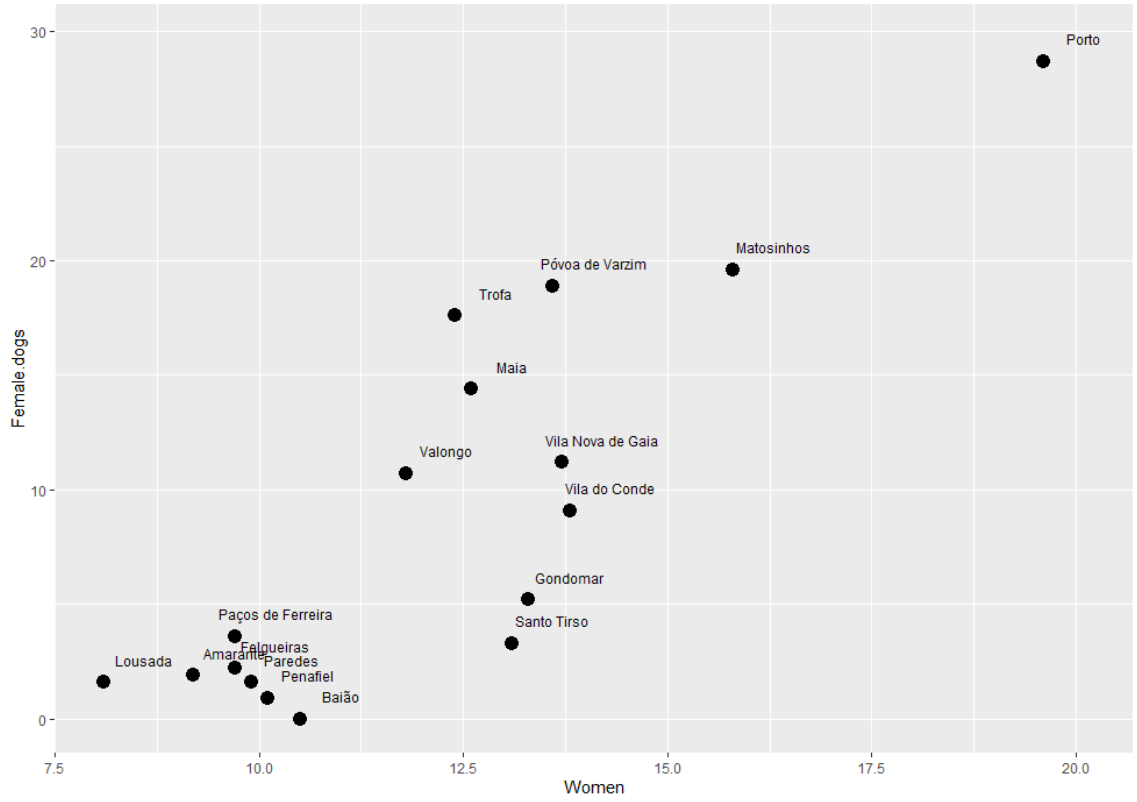

FIGURE 24 Scatterplot of WBC and female dogs mMGT crude incidence rates, by municipalities of Porto district (excluding Marco de Canaveses municipality).

4.4. Discussion

At first, this is a pioneering work considering HBC and canine MGT from a *One Health* perspective and the study of their geographical distribution in Porto District. Studying the epidemiologic characteristics of human and canine mammary cancers living at the same geographic area and thus subjected to analogous environmental effects, make available to describe and compare a similar set of remarkably characteristics in both species. Within the scope of this analysis, there are similarities in the distribution by sex, being predominant in women and female dogs and, regarding age, there is a very similar pattern. Regarding tumor morphology, with the contribution of Vet-ICD-O-canine-1, it was found that the most frequent morphologies differ between both species. In canine MGT, the study showed that there are certain breeds with higher relative risk (Cocker and Yorshire Terrier) and others with a protective effect (Pinscher and Podengo) for neoplasia development. In the end, the study highlighted the high correlation between the crude incidence risk of WBC and female dogs mMGT in Porto District´ municipalities, supporting the hypothetical value of the dog as a sentinel for human oncological epidemiology.

Age

Age is the most important known risk factor for BC and It has been described a peak in the incidence at the age of women menopause and then gradually decrease or remain constant (93, 94), which is corroborated by the results achieved in this analysis. In dogs, as in women, this risk increases significantly with age in geriatric female dogs with a peak of diagnosis at 11–13 years of age (65, 100) and a mean age at diagnosis of 9.9 years similar to other recent studies (101). In this study, the Z-Score calculation allowed a comparative analysis between the ages of WBC and female dogs mMGT. It was showed that the age distributions in both species overlapped, which is supported by previous studies (99).

Sex

The results achieved in this study indicate that both BC and MGT are more common in women/female than in men/males, which is corroborated by other studies (91, 92). The role of the endocrine environment, which is defined by the length of exposure to oestrogen and progesterone, has been implicated in the development of MGT (113, 114). Unfortunately, the information about the reproductive status (spayed) of female dogs was not able to be considered in this study since many registries lacks this information. This topic will be important in the future to promote, together with VetLabs and clinicians, the inclusion of the reproductive status of dogs and at what age they were neutered.

Topography

In women, one of the most frequent topographies documented in this analysis was the UOQ (upper-outer quadrant) similar to other studies (157). The acknowledged explanation for this incidence in the UOQ is that this region holds a greater proportion of the epithelial tissue, which is the target site for breast cancer (157). In dogs the analysis was compromised since the majority of the cases were classified as mammary gland, NOS. This result could be related to the lacking site-specific information, performed by clinicians. Some studies previously described that the caudal and inguinal abdominal mammary glands were the most frequently affected (158), and could be related to the larger amount of parenchyma tissue within these mammary glands and, consequently, greater hormonal stimulation (69).

Morphology

The distribution of the WBC by morphology revealed that infiltrating duct carcinoma, NOS, corresponded to the most frequent type of tumor, followed by lobular carcinoma, NOS, which is similar to the literature already published (159). In female dogs, the most frequent mMGT were complex carcinoma, followed by tubular carcinoma and solid carcinoma, confirming what has been reported in the literature (63). In some punctual morphologies there was a correspondence between WBC and female mMGT dogs, namely in invasive micropapillary carcinoma of breast (8507/3) and intraductal papillary adenocarcinoma with invasion (8503/3). In fact, one of the most aggressive types of BC is Invasive micropapillary carcinoma (IMPC) (160). Previous studies evaluating canine IMPC showed several similarities to the corresponding human disease (71, 161). As in women and female dogs, inflammatory carcinoma had a low distribution which is corroborated by previous studies (162, 163).

These observations suggested that the canine MGT might be an adequate model for pathological comparison with HBC (164). This analysis was only possible with the contribution of Vet-ICD-O-canine-1, the veterinary counterpart of ICD-O-3.2. An essential tool for studies in the field of comparative oncology.

A relevant aspect to mention is that more than half of MGT reported in this study in the female dogs were benign. As in previous publications, complex adenoma and benign mixed tumour characterize the main benign tumour forms (165). In fact, benign mammary tumors are also common throughout a women's lifetime, from early reproductive life to the postmenopausal part of life, making it a potential health concern to a large number of women (166-171). The aetiology and risk of this entities have not been widely studied, regardless of an increasing incidence of benign mammary tumors detected by population-

based mammographic screening (172). Nevertheless, the exact incidence rates are unknown. Moreover, previous studies on benign mammary tumors have often been small-scale and inconsistent in their pathological disease classification. Therefore, there are no up-to-date studies of the incidences, and risk factors have not been well established (166, 167, 173).

Of importance, a history of certain benign tumors is also a risk factor for breast cancer; benign proliferative disease with or without atypia increases the risk approximately 4- and 2-fold, respectively (172, 173). Since, similarly to the female dogs, benign breast diseases in women are an important risk factor for BC, it may be important in the future to evaluate possible associations, enhancing the role of canine model.

Breed

Breed is reported to be a risk factor for MGT in dogs (106, 107). However, the breeds reported to be at risk differ in different studies, and in different geographic locations (106). Poodles (toy and miniature), spaniels, pointers, German shepherd, Maltese terrier, Yorkshire terrier and dachshund have all been reported to be predisposed (107). This result could be related to the overpopulation of certain breeds such as Labrador Retrievers and German Shepherds. In this analysis, no-breed dogs were the most affected, followed by Labrador retrievers, Yorkshire terrier and German shepherd. However, and it is a great achievement of this study, to calculate the IR per breed and with this it was possible to remove the bias of the uncertainty of breeds´ population. Thus, in Porto, Cocker and Yorkshire terriers were the most affected breeds by MGT in contrast to Pinscher and Podengo that have a protective effect against the development of mMGT.

A study in Japan reported a lower incidence of malignancy in mammary tumors from small breed dogs (174) which is also suggested in our study in which purebred dogs like Pinschers had a protective effect for the development of mMGT. Nevertheless, Pinschers showed a higher percentage of complex adenomas in this study.

Grouping the breeds according to the FCI, dogs belonging to the Companion and Toy Dogs group have a higher median (10 years) at diagnosis. French bulldogs present a distribution at a younger age. Age differences breed based of cancer onset may inform future screening programs in specific breeds for an early detection of cancer. This variation in incidence of mammary tumor risk between breeds suggests a significant heritable genetic component to the disease in dogs (175).

Geography

Surprisingly, the results of this study demonstrate a high correlation between the crude incidence risks of WBC and female dogs mMGT in the district of Porto. This finding

strength even more the hypothetical value of the dog as a sentinel for human oncological epidemiology. This fact is in line with a recent study that demonstrated a close geographical association at the municipality level between human and canine non-Hodgkin's lymphoma(NHL) cases in Porto region (38).

A note should be added regarding the elevated crude incidence rate in female dogs mMGT in Marco de Canaveses. One hypothesis relies on the fact that there are a reduced number of veterinary centers in the neighbouring regions of this municipalities and ends up working as a funnel for cancer cases from other surrounding cities.

The correlation scatterplot that shows the correlation between both species, suggests something very interesting like the existence of clusters. Carrying out a cluster analysis could be a next step to take in the continuity of this study.

The existence of some differences between human and canine cases could be due to absence of available information in some regions. One limitation of this study relies on the unavailability of information of the precise owner´s postal code using instead the postal code of the veterinary practice. However and according to recent study (176) the distance to the veterinary hospital was the main contributor to the estimated the Catchment Area (CA), which is expected and has traditionally been the main parameter considered. Moreover, to diminish this bias, the analysis was performed at municipality level. On the other hand, dogs have a more confined daily mobility and reduced migration than people, leading to higher levels of exposure to potentially hazardous environmental risk factors. It seems fair to presume that dogs may contribute to the early identification of risk environments with less bias than humans, strengthening their sentinel role in human health investigation (177). Further epidemiological studies should be driven to investigate carcinogen factors and the genetic and epigenetic role in this study area.

4.5. Conclusion

Dogs develop MGT spontaneously and demonstrate a remarkably similarity in epidemiologic and clinical characteristics to HBC. Starting from tools like the human and companion animal oncology registries in Portugal and the neoplasm classification systems (ICD-O-3.2 and the current veterinary counterpart, Vet-ICD-O-canine-1), it was possible to carry out this comparative analysis. This work has shown similarities in the distribution by sex, being predominant in women and female dogs and, regarding age, there was a very similar pattern. Concerning tumor morphology, there are some differences between both species. In canine MGT, there are certain breeds with higher relative risk (Cocker and Yorshire Terrier) and others with a protective effect (Pinscher and Podengo) for neoplasia development. In this study, the results highlighted a high correlation between

the incidence risks of WBC and female dogs mMGT in the district of Porto. The two species, that ever more share common environments and have similar exposomes. These outcomes reinforce the hypothesis that dogs should be considered as possible sentinels for human oncological epidemiology.

5. Conclusions and future directions

This study reflects a pioneering work in the field of comparative oncology between two cancer registries, human and companion animal in *One Health* context. Vet-OncoNet is an *avant-garde* registry regarding companion animals in Portugal and therefore this work is an opportunity, together with the know-how of human medicine, to promote and enhance their purposes. More than a database, human and animal oncology registries must be a basis of accessible knowledge to the entire collaborative oncology network.

The outcomes from this comparative study provide strong evidence that dogs could be considered an epidemiological sentinel for breast cancer. This is in line with another recent study that demonstrated a close geographical association at the municipality level between human and canine non-Hodgkin's lymphoma (NHL) cases in Porto region (38).

Similarly, to the female dogs, benign breast diseases in women are an important risk factor for BC and it may be important in the future to evaluate possible associations, enhancing the role of canine model.

As future directions, the investigation of the existence of carcinogen factors and the genetic and epigenetic role in this region will be an important path to follow in comparative oncology studies. This Master Thesis is another contribution to answering the question: can a dog's tumors help diagnose cancer in humans? (in *Jornal Expresso*, 2023) (178).

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7. Annex

Table A1: Vet-ICD-O-canine-1, First Edition, 11 Mammary gland tumors (37).

Vet-ICD-O-canine-1, First Edition

ICD-O-3.2 code	Vet-ICD-O-1 code	Veterinary term	Level	Topography	Notes/sources
		MAMMARY GLAND TUMORS			
		EPITHELIAL NEOPLASMS		**C50._**	
		Benign			
		Simple benign tumors			
8211/0	8211/0	Tubular adenoma	Preferred		
		Simple adenoma, NOS	Synonym		
8982/0	8982/0	Myoepithelioma	Preferred		
		Myoepithelial tumor	Synonym		
		Non-simple benign tumors			
8983/0	8983/0	Complex adenoma	Preferred		Adenomyoepithelioma, NOS is the ICD-O-3.2 preferred term.
		Adenomyoepithelioma	Synonym		
8940/0	8940/0	Benign mixed tumor, NOS	Preferred		Pleomorphic adenoma is the ICD-O-3.2 preferred term.
		Pleomorphic adenoma	Synonym		
9010/0	9010/0	Fibroadenoma, NOS	Preferred		
		Ductal-associated benign tumors			
NONE	8500/0	Ductal adenoma	Preferred		Unlike in the WHO classification of human breast tumors, in dogs Ductal carcinoma of the mammary gland is considered as the malignant counterpart of Ductal adenoma. Therefore, and based on its ductal origin, the GIVCS working group decided to adopt the generic morphological code 8500 for this tumor followed by the appropriate 5th digit code for the biological behaviour. There is no entity corresponding to these tumors in the human breast, therefore "NONE" was indicated in the ICD-O-3.2 code column.
		Basaloid adenoma	Synonym		
8503/0	8503/0	Intraductal papillary adenoma	Preferred		Intraductal papilloma is the ICD-O-3.2 preferred term.
		Duct papilloma, NOS	Synonym		
		Intraductal papilloma	Synonym		
		Malignant epithelial neoplasms			The classification of canine mammary neoplasms not extending through the preexisting basal ~~ement~~ membrane is poorly standardized. Therefore, the latest classification of mammary tumors in dogs and cats discourages from the use of carcinoma in situ as a diagnostic entity. However, if the "in situ" stage is stated in a pathology report, the appropriate 5th digit code /2 should be used and applied to each histological type as below.
		Simple carcinomas			
8211/3	8211/3	Tubular carcinoma	Preferred		
		Tubular simple carcinoma	Synonym		
		Cribriform carcinoma (of ther mammary gland)	Synonym		The cribriform histotype of mammary carcinoma has been removed in the latest classification of mammary tumors in domestic animals and it has been included under Tubular carcinoma based on the assumption that it is actually a tubular carcinoma with small tubular lumina.
8263/3	8263/3	Tubulopapillary carcinoma	Preferred		Adenocarcinoma in tubulovillous adenoma is the ICD-O-3.2 preferred term.
8230/3	8230/3	Solid carcinoma	Preferred		
8507/3	8507/3	Invasive micropapillary carcinoma	Preferred		
8501/3	8501/3	Comedocarcinoma	Preferred		
8021/3	8021/3	Carcinoma, anaplastic, NOS	Preferred		
		Non-simple carcinomas			
NONE	8941.1/3	Carcinoma arising in a complex adenoma/benign mixed tumor	Preferred		This entity is not reported in the WHO classification of human breast tumors. Code 8941/3 is used for Carcinoma ex pleomorphic adenoma described in the group of salivary gland tumors (C07._, C08._). The GIVCS coding subgroup proposes the creation of a new code specific for this entity.
NONE	8983.1/3	Complex carcinoma	Preferred		In the WHO classification of human breast tumors, 8983/3 is used for coding Adenomyoepithelioma with carcinoma. Both the epithelial and myoepithelial component could be malignant, while in dogs only the epithelial component is malignant. Therefore, the GIVCS coding subgroup proposes a new veterinary code for this entity.
8562/3	8562/3	Carcinoma and malignant myoepithelioma	Preferred		Epithelial-myoepithelial carcinoma is the ICD-O-3.2 preferred term.
		Epithelial-myoepithelial carcinoma	Synonym		
8940/3	8940/3	Mixed carcinoma, NOS	Preferred		Mixed tumor, malignant, NOS is the ICD-O-3.2 preferred term.
		Mixed tumor, malignant, NOS	Synonym		
		Ductal-associated carcinomas			
8500/3	8500/3	Ductal carcinoma, NOS	Preferred		See comment for Ductal adenoma. Infiltrating duct carcinoma, NOS is the ICD-O-3.2 preferred term.
8503/3	8503/3	Intraductal papillary carcinoma	Preferred		Intraductal papillary adenocarcinoma with invasion is the ICD-O-3.2 preferred term.
		Intraductal papillary carcinoma with invasion	Synonym		
		Papillary cystic carcinoma	Related		
		Malignant epithelial neoplasms – special types			
8070/3	8070/3	Squamous cell carcinoma, NOS	Preferred		
		Conventional squamous cell carcinoma	Synonym		
8560/3	8560/3	Adenosquamous carcinoma	Preferred		
8480/3	8480/3	Mucinous carcinoma	Preferred		Mucinous adenocarcinoma is the ICD-O-3.2 preferred term.
8314/3	8314/3	Lipid-rich carcinoma	Preferred		
8032/3	8032/3	Spindle cell carcinoma, NOS	Preferred		
		Spindle cell squamous cell carcinoma	Related		
8982/3	8982/3	Malignant myoepithelioma	Preferred		Myoepithelial carcinoma is the ICD-O-3.2 preferred term.
		Myoepithelial carcinoma	Synonym		
8530/3	8530/3	Inflammatory mammary carcinoma	Preferred		The ICD-O-3.2 preferred term is Inflammatory carcinoma. This is a clinico-pathologic entity rather than a morphological diagnosis. Several histotypes can evolve into an Inflammatory mammary carcinoma. The GIVCS coding subgroup proposes the use of this code when clinical information is available in association to fitting histologic features.
		Malignant mesenchymal neoplasms of the mammary gland			
8810/3	8810/3	Fibrosarcoma, NOS	Preferred		
9120/3	9120/3	Hemangiosarcoma , NOS	Preferred		
9180/3	9180/3	Osteosarcoma, NOS	Preferred		
9220/3	9220/3	Chondrosarcoma, NOS	Preferred		
		Other sarcomas			
8980/3	8980/3	Carcinosarcoma, NOS	Preferred		
		NEOPLASM OF THE TEAT		**C50.0**	
		Benign ductal-associated neoplasms			
NONE	8500/0	Ductal adenoma	Preferred		
		Basaloid adenoma	Synonym		
8503/0	8503/0	Intraductal papillary adenoma	Preferred		Intraductal papilloma is the ICD-O-3.2 preferred term.
		Duct papilloma, NOS	Synonym		
		Intraductal papilloma	Synonym		
		Malignant ductal-associated neoplasms			
8500/3	8500/3	Ductal carcinoma	Preferred		Infiltrating duct carcinoma, NOS is the ICD-O-3.2 preferred term.
8503/3	8503/3	Intraductal papillary carcinoma	Preferred		Intraductal papillary adenocarcinoma with invasion is the ICD-O-3.2 preferred term.
		Intraductal papillary carcinoma with invasion	Synonym		
		Papillary cystic carcinoma	Related		
8540/3	8540/3	Carcinoma with epidermal infiltration (Paget-like disease)	Preferred		Paget disease, mammary is the ICD-O-3.2 preferred term.
		Paget disease, mammary	Synonym		

Table A2: List of the distribution of the HBC by age group and in Porto district, between 2010 and 2015.

Age group	Women	Men	Total
20-24	0.11%	1.11%	0.12%
25-29	0.53%	0.00%	0.52%
30-34	1.91%	2.22%	1.92%
35-39	4.98%	1.11%	4.94%
40-44	8.41%	4.44%	8.37%
45-49	12.67%	3.33%	12.56%
50-54	12.92%	4.44%	12.82%
55-59	12.16%	8.89%	12.12%
60-64	11.68%	20.00%	11.78%
65-69	11.35%	12.22%	11.36%
70-74	7.34%	15.56%	7.44%
75-79	7.04%	10.00%	7.08%
80-84	5.06%	7.78%	5.10%
85+	3.82%	8.89%	3.88%
Total	**100.00%**	**100.00%**	**100.00%**

Table A3: List of the distribution of the HBC by morphology in Porto district, between 2010 and 2015 (ICDO-3 code, N and %).

HBC Morphologies	ICDO-3 Code	n	%
Infiltrating duct carcinoma, NOS	8500/3	5679	74.00
Lobular carcinoma, NOS	8520/3	707	9.21
Infiltrating duct mixed with other types of carcinoma	8523/3	345	4.50
Infiltrating duct and lobular carcinoma	8522/3	204	2.66
Carcinoma, NOS	8010/3	165	2.15
Mucinous adenocarcinoma	8480/3	105	1.37
Neoplasm, malignant	8000/3	99	1.29
Infiltrating ductular carcinoma	8521/3	57	0.74
Invasive micropapillary carcinoma of breast	8507/3	42	0.55
Intraductal papillary adenocarcinoma with invasion	8503/3	36	0.47
Metaplastic carcinoma, NOS	8575/3	31	0.40
Tubular adenocarcinoma	8211/3	28	0.36
Paget disease, mammary	8540/3	23	0.30
Encapsulated papillary carcinoma with invasion	8504/3	20	0.26
Medullary carcinoma, NOS	8510/3	18	0.23
Infiltrating lobular mixed with other types of carcinoma	8524/3	18	0.23
Papillary carcinoma, NOS	8050/3	9	0.12
Neuroendocrine carcinoma, NOS	8246/3	6	0.08
Cribriform carcinoma, NOS	8201/3	6	0.08
Inflammatory carcinoma	8530/3	6	0.08
Adenocarcinoma, NOS	8140/3	5	0.07
Phyllodes tumor, malignant	9020/3	4	0.05

Papillary adenocarcinoma, NOS	8260/3	4	0.05
Adenoid cystic carcinoma	8200/3	4	0.05
Diffuse large B-cell lymphoma, NOS	9680/3	4	0.05
Hemangiosarcoma	9120/3	4	0.05
Secretory carcinoma	8502/3	3	0.04
Atypical medullary carcinoma	8513/3	3	0.04
Paget disease and intraductal carcinoma of breast	8543/3	3	0.04
Marginal zone B-cell lymphoma, NOS	9699/3	3	0.04
Comedocarcinoma, NOS	8501/3	3	0.04
Glycogen-rich carcinoma	8315/3	3	0.04
Adenosquamous carcinoma	8560/3	2	0.03
Apocrine adenocarcinoma	8401/3	2	0.03
Carcinosarcoma, NOS	8980/3	2	0.03
Duct carcinoma, desmoplastic type	8514/3	1	0.01
Acinar cell carcinoma	8550/3	1	0.01
Malignant lymphoma, non-Hodgkin, NOS	9591/3	1	0.01
Adenocarcinoma with neuroendocrine differentiation	8574/3	1	0.01
Hodgkin lymphoma, NOS	9650/3	1	0.01
Sarcoma, NOS	8800/3	1	0.01
Leiomyosarcoma, NOS	8890/3	1	0.01
Giant cell sarcoma	8802/3	1	0.01
Malignant lymphoma, small B lymphocytic, NOS	9670/3	1	0.01
Liposarcoma, NOS	8850/3	1	0.01
Polymorphous adenocarcinoma	8525/3	1	0.01
Pleomorphic carcinoma	8022/3	1	0.01
Squamous cell carcinoma, keratinizing, NOS	8071/3	1	0.01
Clear cell adenocarcinoma, NOS	8310/3	1	0.01
Burkitt lymphoma, NOS	9687/3	1	0.01
Signet ring cell carcinoma	8490/3	1	0.01
Dedifferentiated liposarcoma	8858/3	1	0.01
Squamous cell carcinoma, NOS	8070/3	1	0.01
Myeloid sarcoma	9930/3	1	0.01
Myoepithelial carcinoma	8982/3	1	0.01
Adenocarcinoma with spindle cell metaplasia	8572/3	1	0.01
Total		**7674**	**100.00**

Table A4: List of the distribution of the MGT by morphology in Porto district, (VET ICDO-3 code, N and %).

Canine MGT Morphology	Vet-ICDO code	N	%
Complex adenoma	8983/0	220	19.05
Benign mixed tumor, NOS	8940/0	218	18.87
Complex carcinoma	8983.1	205	17.75
Tubular carcinoma	8211/3	118	10.22
Tubular adenoma	8211/0	114	9.87
Solid carcinoma	8230/3	77	6.67
Tubulopapillary carcinoma	8263/3	46	3.98
Intraductal papillary adenoma	8503/0	16	1.39
Neoplasm, metastatic	8000/6	16	1.39
Carcinosarcoma, NOS	8980/3	15	1.30
Invasive micropapillary carcinoma	8507/3	10	0.87
Lipoma, NOS	8850/0	9	0.78
Adenosquamous carcinoma	8560/3	8	0.69
Squamous cell carcinoma, NOS	8070/3	7	0.61
Papillary adenoma	8260/0	6	0.52
Carcinoma, anaplastic, NOS	8021/3	5	0.43
Mixed carcinoma, NOS	8940/3	5	0.43
Fibroadenoma, NOS	9010/0	5	0.43
Ductal adenoma	8500/0	5	0.43
Tubulopapillary adenoma	8263/0	5	0.43
Comedocarcinoma	8501/3	5	0.43
Intraductal papillary carcinoma	8503/3	5	0.43
Osteosarcoma, NOS	9180/3	4	0.35
Malignant myoepithelioma	8982/3	4	0.35
Carcinoma in situ, NOS	8010/2	4	0.35
Undifferentiated sarcoma	8805/3	3	0.26
Cystic adenoma	8440/0	3	0.26
Carcinoma and malignant myoepithelioma	8562/3	3	0.26
Inflammatory carcinoma	8530/3	3	0.26
Myoepithelioma, NOS	8982/0	2	0.17
Neoplasm, malignant	8000/3	2	0.17
Fibrosarcoma, NOS	8810/3	2	0.17
Osteochondroma	9210/0	1	0.09
Mucinous adenocarcinoma	8480/3	1	0.09
Ductal carcinoma	8500/3	1	0.09
Sarcoma, NOS	8800/3	1	0.09
Lipid-rich carcinoma	8314/3	1	0.09
Total		**1155**	**100.00**

Table A5: List of the distribution of the women population and WBC cases by municipalities in Porto district, between 2010 and 2015 (N and %).

Municipality	Women Population (%)		WBC Cases (%)	
Amarante	27904	(3.0)	154	(2.0)
Baião	9688	(1.0)	61	(0.8)
Felgueiras	29436	(3.1)	172	(2.2)
Gondomar	87484	(9.3)	699	(9.1)
Lousada	24217	(2.6)	118	(1.6)
Maia	73919	(7.8)	561	(7.3)
Marco de Canaveses	26567	(2.8)	167	(2.2)
Matosinhos	93454	(9.9)	886	(12.6)
Paços de Ferreira	28476	(3.0)	165	(2.1)
Paredes	44421	(4.7)	264	(3.6)
Penafiel	36176	(3.8)	220	(2.9)
Porto	119394	(12.7)	1403	(17.5)
Póvoa de Varzim	33313	(3.5)	271	(3.8)
Santo Tirso	35741	(3.8)	280	(3.5)
Trofa	20272	(2.1)	151	(2.0)
Valongo	51881	(5.5)	368	(4.9)
Vila do Conde	793	(4.4)	347	(4.5)
Vila Nova de Gaia	159096	(16.9)	1297	(17.6)
Total	943232	(100.0)	7584	(100.0)

Table A6: List of the distribution of the female dogs population and female mMGT cases by municipalities in Porto district (N and %).

Municipality	Female Dogs Population (%)		Female mMGT (%)	
Amarante	5324	(3.5)	3	(0,6)
Baião	1645	(1.1)	0	-
Felgueiras	4618	(3.0)	3	(0.6)
Gondomar	13487	(8.8)	21	(4.0)
Lousada	4248	(2.8)	2	(0.4)
Maia	11318	(7.4)	48	(9.1)
Marco de Canaveses	4557	(3.0)	37	(7.0)
Matosinhos	12948	(8.5)	76	(14.4)
Paços de Ferreira	4581	(3.0)	5	(0.9)
Paredes	8322	(5.4)	4	(0.8)
Penafiel	7452	(4.9)	2	(0.4)
Porto	14891	(9.7)	128	(24.3)
Póvoa de Varzim	5828	(3.8)	32	(6.1)
Santo Tirso	7094	(4.6)	7	(1.3)
Trofa	4547	(3.0)	24	(4.6)
Valongo	7824	(5.1)	25	(4.7)
Vila do Conde	8803	(5.8)	24	(4.6)
Vila Nova de Gaia	25546	(16.7)	86	(16.3)
Total	153033	(100.0)	527	(100.0)