Doctoral Thesis

One Medicine - One Oncology. Swiss Feline Cancer Registry

Author[s]: Graf, Ramona

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ONE MEDICINE – ONE ONCOLOGY

Swiss Feline Cancer Registry

A thesis submitted to attain the degree of

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(Dr. sc. ETH Zurich)

presented by

RAMONA GRAF

M.sc. in Biomedical Sciences, University of Berne

born on 10.12.1978

citizen of Guggisberg, BE

accepted on the recommendation of

Prof. Gerd Folkers (examiner)

Prof. Andreas Pospischil (co-examiner)

PD Dr. Vivianne Otto (co-examiner)

Prof. Cornelia Halin Winter (co-examiner)

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Summary

Cancer registries are a key feature of any epidemiological study or prevention and control strategy. Moreover, companion animal tumour registries are intended to assist in different aspects of research on tumour development, pathogenesis, genetics and treatment. Traditionally, comparative cancer research is based on murine models, which lack many features that define human cancer, including growth over longer time periods, genomic instability, function of the immune system and a significant heterogeneity of tumour cells and tumour microenvironments. To fill this gap, spontaneous tumours in dogs and cats reflect more features of human cancer. Furthermore, sharing the living environment with humans, they are exposed to similar risk factors, therefore acting as sentinels for recognition of environmental factors implicated in oncogenesis.

Comparison of data from canine and feline tumour registries has recently gained increasing interest in the context of the ‘One Medicine-One Pathology’ concept, part of the ‘One Health Initiative’. The One Health concept is a worldwide strategy for expanding collaborations and communications of multiple disciplines in all aspects of health care for humans, animals and the environment. It is believed that an achieved synergism will improve public health, scientific knowledge as well as biomedical research. To learn more about tumours in companion animals, such as cancer development and risks, knowledge on the occurrence of tumours in pets needs to be expanded because statistics on the incidence of cancer in pet animals are very rare. As part of our research project ‘One Medicine-One Oncology–Incidence and Geographical Distribution of Tumours in Dogs and Cats in Switzerland 1955–2008’, this thesis is based on extensive data collection and interpretation of cat data, compiled between 1965 and 2008 by three veterinary diagnostic laboratories based in Switzerland.

Tumours were classified according to the tumour type, malignancy and physical location following the guidelines of the International Classification of Oncology for Humans (ICD-O-3), which subsequently allows comparisons with human cancer registries. In addition to a general overview of the available dataset (first published paper), statistics on the most common tumour types and tumour locations and the influence of breeds, ages and sexes were analysed (second published paper).

With 51,322 cat data, including 18,375 tumours, this feline cancer registry is, to our knowledge, the largest available. This huge amount of data from over 50,000 individual cats allowed us to analyse correlations that have not been possible so far due to limited data collection. We were able to look at more different cat breeds and discovered not only that Siamese cats had a significant likelihood of developing a tumour in the mammary gland, but that for Oriental shorthair, Somali and Abyssinian...
cats this possibility was even higher. The influence of external factors on tumour development is
nicely demonstrated with the introduction of the feline leukaemia virus (FeLV) vaccine, which not
only reduced the occurrence of lymphomas but is most probably also responsible for the increased
appearance of fibrosarcomas ever since. The European shorthair cat was the most likely to develop
a fibrosarcoma, as well as squamous cell carcinomas, which both most frequently occur in the
skin/subcutis.
This dissertation contains a feline cancer registry that forms a basis of knowledge about tumours in
cats that can be used for further research in epidemiology, as well as tumour aetiology, development
and treatment in a comparative way.
Zusammenfassung

Preface

This thesis has been conducted at the Collegium Helveticum, a trans-disciplinary institute (ETHZ & UZH) with the endeavour to include aspects of science, arts, and the humanities into research and to discuss topics in this broad context. The research project was initiated by Prof Andreas Pospischil and Prof. Kay Axhausen within the framework of the fellowship period “Reproducibility, Prediction, and Relevance” and sought to investigate tumours in cats and dogs and their spatial distribution in Switzerland. No other topic would have suited me better. I had the great pleasure and privilege to work in the interesting and diverse environment of the Collegium Helveticum and gain insights in many different disciplines and topics.

I would like to thank my study supervisor and co-examiner Andreas Pospischil for his continuous support and help during this study; it could not have been better. I appreciate very much his friendly and agreeable manner and his extensive knowledge in many fields.

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Further, I would like to thank my study team and co-authors for their inputs and various support.

Sincerest thanks goes to the in-house at the Collegium Helveticum who made work much more pleasant. Thanks for the conversations and laughter.

Many thanks go to my family, especially to my mother Ursula Graf, who always believed in me and supported me along the way.

Last but not least, thanks to all my friends who bear with me.
1. General Introduction

Cats are the most popular pet animals around the world, with an estimate of 600 million individuals (pets, strays, homeless and feral cats), living on every continent except Antarctica. The family Felidae nowadays includes around 38 species, which are widely distributed across the world, inhabiting diverse ecological niches through divergent morphological and behavioural adaptations (Sunquist & Sunquist, 2014). The available archaeological evidence indicates that the process of wildcat domestication began when humans became farmers and formed agricultural villages, about 8,000 - 10,000 years ago. The earliest evidence of cat–human association shows their co-occurrence in Cyprus around 9500 years ago and in central China around 5000 years ago (Vigne et al., 2004; Hu et al., 2014; Neer et al., 2014). Archaeological remains and anthropological clues suggest that, unlike other species domesticated as guards and hunters (dogs), for agriculture (cow, pig, sheep), or transport (horse, donkey), the cat began its association with humans as a commensal, feeding on rodent pests infesting grain stores of the first farmers (Budiansky, 1992; Clutton-Brock, 1999). There is little reason to believe that an early agricultural community would have actively chosen wildcats as a house pets. Cats do not perform directed tasks, live a solitary existence, and defend their territory, which makes them more attached to places than to people. The best explanation therefore is that wildcats exploiting human environments were simply tolerated by people and, over time, gradually diverged from their “wild” relatives (Driscoll et al., 2007, 2009). Thus, whereas adaptation to human dominion in farm animals and dogs was largely driven by artificial selection, the original domestic cat was a product of natural selection. Aesthetic qualities such as hair colour and pattern differentiate wildcats from domesticated populations and breeds; however, over 90% of domestic cats living today are random-bred house or feral cats that choose their own mates and sometimes still reproduce with wildcats (Driscoll et al., 2007). Most of the cat breeds distinguished today originated within the past 150 years, largely due to selection for aesthetic rather than functional traits (Kurushima et al., 2013; Montague et al., 2014). Through the long history of domestication, in which cats have been idolized by some and stigmatized by others, they have maintained a high degree of autonomy and are not dependent on humans to survive. People in the western world still have an ambivalent relationship with cats: loved and cared for like a family member by some, used as mousers on farms by others. There are as well many stray cats that inhabit, for example, industrial regions or allotments and avoid contact with humans. However, cats that have a loving home enjoy extensive veterinary medical surveillance, which, together with that of dogs, is second only to human medicine (O’Brien, 2004). The increasing importance of human-pet
relationships and owners’ greater willingness to invest financially in this relationship has led to similar treatments for cats as for human diseases and has further boosted studies in the field of companion animal medicine (Bresalier et al., 2015). The similarity of human and animal diseases had led to the study of diseases across different species borders, expanding interdisciplinary collaborations and communications in all aspects of health care for humans, animals and the ecosystem (One Health) (FAO - WHO - OIE - Worldbank - UNICEF, 2008; Meisser et al., 2011). The foundations of such a One Health approach lie in the late 19th century, when Rudolf Virchow (1821-1902) noted the link between animal and human diseases and coined the term zoonosis (Saunders, 2000; Evans & Leighton, 2014; Bresalier et al., 2015). The main focus of the One Health concept nowadays still lies on cooperation in the field of infectious diseases and zoonoses by comparing infectious agents in animals and humans and in preventing epidemics by monitoring disease occurrence and patterns (epidemiology) (FAO - WHO - OIE - Worldbank - UNICEF, 2008; Jones et al., 2008). In this field, feline infectious agents have already offered powerful natural models for human infectious diseases like HIV-AIDS (feline immunodeficiency virus (FIV)) and SARS [feline coronavirus (FCoV)], as well as oncoviruses [feline leukaemia virus - (FeLV/)] (Carpenter & Brien, 1995; O’Brien et al., 1997, 2002; Willett et al., 1997; Wilkerson et al., 2002; O’Brien, 2004; Pontius et al., 2007; Brown et al., 2008; Bienzle, 2014). However, a modern One Health concept not only includes infectious diseases but also expands to many fields of interdisciplinary collaboration including hereditary diseases or cancer. Over 250 feline hereditary pathologies are described in the veterinary literature and approximately half of them have established homology with human genetic defects (O’Brien et al., 2002; Menotti-Raymond & O’Brien, 2008). Feline models played an important role in elucidating molecular pathogenesis and could now be of critical importance in evaluating and optimizing the range of therapeutic strategies prior to clinical trials in humans. Moreover, they offer the possibility of evaluating long-term treatment effects (Haskins et al., 1979; Menotti-Raymond & O’Brien, 2008). In the past 20 years, pets with spontaneously occurring tumours started to be considered a valuable resource in studying neoplasm, and it is believed that comparative oncology will play a paramount role in translational medicine (Matyas, 1982; Paoloni & Khanna, 2007; Gordon et al., 2009; Withrow et al., 2013; Schiffman & Breen, 2015). As for today, translational oncology still strongly relies on research on mice, although they lack many features that define human cancer. But even though efficacy of oncology drugs in preclinical mouse models are often unpredictable, mouse models are still indispensable in research and in the preclinical drug development process. (Van Dyke & Jacks, 2002; Hansen & Khanna, 2004; Frese & Tuveson, 2007; Simon, 2008; Cheon & Orsulic, 2011). Including companion animals with naturally occurring tumours into clinical trials, may give scientists additional information about the efficacy of drugs
early in the trial process. Dogs with naturally occurring tumours have already contributed successfully to clinical trials, however clinical trials with companion animals are still rare. In order to push and facilitate the inclusion of pets in clinical trials, twenty academic comparative oncology centres in the USA have set up a network, the Comparative Oncology Trials Consortium (COTC). They provide the infrastructure and resources needed to integrate clinical trials for pets with naturally occurring cancers into the development pathways for new drugs, which could be beneficial for both human and animal medical care.

In order to learn more about naturally occurring tumours in companion animals, such as cancer development and risks, knowledge on the occurrence of tumours in pets needs to be expanded. Statistics on the incidence of cancer in pet animals are not widely available. One of the largest cancer registries for companion animals, the California Animal Neoplasm registry, was published almost 50 years ago and covered a three-year period (Dorn et al., 1968a, 1968b). A few animal registries followed, however over rather short periods of time and a limited number of animals. (Brodey et al., 1969; Priester & Mantel, 1971; Patnaik et al., 1975; MacVean et al., 1978; Moe et al., 2001, 2008; Merlo et al., 2008; Vascellari et al., 2009; Brønden et al., 2010; Nordtvedt et al., 2011) Therefore, today only fragmentary information is available on companion animal tumours.

Lasting contributions to anatomy and pathology of humans and animals date back to the last three centuries BC when Alexandrian Greeks described many pathological features, such as wound healing and inflammation, tumors and hemorrhoids. The beginning of modern medicine and pathology, however, began during the 18th century when it became generally accepted that diseases were organ based. Giovanni Baptiste Morgagni (1682–1771) who described 640 autopsies and structurally correlated the symptoms of his patients with the pathological findings at autopsy fostered the growing belief that diseases had an anatomical substrate. (Malkin, 1993; Tweel & Taylor, 2010)

From the mid-nineteenth century onwards it was the improvement of the microscope that influenced the future of pathology. Although the first microscope had been constructed in 1591, increased availability, improved optics and reduced cost made the use of the microscope popular. The microscope totally changed concepts of disease from whole organs, to focus upon cells.
Johannes Müller (1801–1858) was the source from which both histology and cellular pathology arose. He was one of the first to use the microscope for tissue analysis. His contributions, together with Rudolf Virchow (1821–1902) who recognized the continuity of cellular life, marked a new era in histology in the second half of the nineteenth century. (Bracegirdle, 1978; Malkin, 1993; Cook, 2000; Titford, 2006; Tweel & Taylor, 2010; Musumeci, 2014)

The progress of histopathology spawned numerous attendant advances in technique necessary for modern practice. Thus in the beginning slices of fresh tissue were cut by hand and examined unstained. Several methods like boiling, alcohol, acetic acid and chromium trioxide were tried out to harden biological specimens that would enable thin slices to be cut. The fixative effects of formalin, now still the most popular fixative, were discovered by Isaac Blum (1833–1903) in 1893. The first hand held microtome was introduced by Hill in 1770 but the use of the microtome for
animal tissues did not occur until 1848. The problems involved in cutting thin sections of tissue were not completely solved until tissues could be infiltrated with paraffin wax first used in the 1870s. (Bracegirdle, 1978; Malkin, 1993; Cook, 2000; Titford, 2006; Tweel & Taylor, 2010; Musumeci, 2014)

The present-day rotary microtome is modeled after the Minot (1886)

In the beginning, naturally occurring stains such as madder and indigo, but mainly carmine were used. Hematoxylin, still the most used stain, was first successfully used in 1863, followed by several other staining methods in the 1880s. Automatic slide-stainers first appeared in histology laboratories during the 1960s and provided reproducible results. In the late 1990s, automatic special stainers came on the market. (Titford, 2006; Musumeci, 2014; Alturkistani et al., 2016)
The rise of ‘precision medicine’ began in the 1980s with the development of immunohistochemistry (ICH). This method permitted pathologists to investigate the expression of various proteins on histological slides. These expression levels would soon turn out to be important for subclassifications of tumors that were relevant when therapies became available which targeted special proteins detectable by immunohistochemistry. (Titford, 2006; Musumeci, 2014)
The realization that some cancers involve one or more gene abnormalities, investigations at the genetic level have moved into the focus of interest in pathology. The sequencing or detection of structural alterations of single genes (e.g. the amplification of the HER2 gene) has resulted in the development of diagnostic histological subtypes of tumors that may affect patient management. Recently, the rise of next generation sequencing has changed research into tumor pathology. Using this method, a large number of genes can be investigated by just one single investigation to deliver an enormous amount of information. Unfortunately, genetic examinations of animal tumors have hardly been performed although their genetic alterations could add useful information on cancer etiology. (Birner et al., 2016)

Veterinary records in several of the university animal hospitals in Switzerland date back to the 1950s. During that time, biopsies were not yet submitted and therefore only tissue from autopsies were examined. No automatic slide stainers were available making histology very laborious. The first diagnoses were written by hand replaced by punchcards that were introduced in 1964. Since 1987, diagnoses are stored in an electronic patient record system.

KEYDEX punch card Vetsuisse faculty's Institute for Veterinary Pathology, Zürich
Autopsy record 1965- Vetsuisse faculty's Institute for Veterinary Pathology, Zürich

Having records that date back to the 1950s, gave us the opportunity to gather, process and analyse large amounts of data in order to construct animal cancer registries that provide valuable information *inter alia* for veterinary practitioners, researchers and epidemiologists. (Graf *et al.*, 2015, 2016, Grüntzig *et al.*, 2015, 2016; Pospischil *et al.*, 2016)
Katrin Grüntzig (2015)

The dataset of cat tumours spans over 40 years and contains data from 51,322 individual cats, from whom, tissues or cells, an organ or parts of an organ, had been removed and sent to a pathology laboratory for examination. Samples are normally sent to such laboratories when there is a suspicion of a tumour and in 18,375 of our examined samples, this suspicion was confirmed. From most of the 51,322 cats, we had information about the age of the cat, the breed, the sex and neuter status, the year of examination, the method of examination and the place of residence. Together with the results from the examinations (tumour morphology and topography), we had sufficient information for statistical evaluations. This dissertation is based on the feline cancer registry, which was published in two separate papers in the Journal of Comparative Pathology. The first publication, Swiss feline cancer registry: a retrospective study on the occurrence of tumours in cats in Switzerland from 1965 to 2008 (Graf et al., 2015), presents a general overview of the available dataset, describing the number of data, the most common tumour types and tumour locations and how tumours were distributed over the available breeds, ages and sexes. This epidemiological bird’s eye view formed the basis for our subsequent analyses that were presented in the second paper, Swiss feline cancer registry 1965-2008: the influence of sex, breed and age on tumour types and tumour locations (Graf et al., 2016). The most common tumour types and tumour locations were analysed according to time trends and a logistic regression model was used to examine differences between breeds, ages and sexes on certain tumour types/locations. These analyses do not confirm
any hypotheses; they plainly demonstrate correlations in a given dataset. They are the bases, upon which hypotheses can be generated that need to be tested and confirmed through further investigations. It provides indications for cancer researchers on aspects that could be influential in the development of cancer, and would consequently be helpful in the understanding of this complex disease. All the examination reports were read and coded according to topographical and morphological keys of the International Classification of Oncology for Humans (ICD-O-3). This laboratory task should lay the foundation for a systematic continuation of the tumour registration for companion animals. Moreover, it allows the direct comparison with the human cancer registry; for example, on the occurrence of tumours, the age and sex of the patients as well as annual trends and spatial distributions of tumours. Some further research projects based on this dataset of companion animal tumours are already in progress.
2. Swiss Feline Cancer Registry: A Retrospective Study of the Occurrence of Tumours in Cats in Switzerland from 1965 to 2008

2.1 Summary

Cancer is one of the leading causes of death in companion animals. Information on the epidemiology of cancer is instrumental for veterinary practitioners in patient management; however, spontaneously arising tumours in companion animals also resemble those in man and can provide useful data in combating cancer. Veterinary cancer registries for cats are few in number and have often remained short-lived. This paper presents a retrospective study of tumours in cats in Switzerland from 1965 to 2008. Tumour diagnoses were coded according to topographical and morphological keys of the International Classification of Oncology for Humans (ICD-O-3). Correlations between breed, sex and age were then examined using a multiple logistic regression model. A total of 18,375 tumours were diagnosed in 51,322 cats. Of these, 14,759 (80.3%) tumours were malignant. Several breeds had significantly lower odds ratios for developing a tumour compared with European shorthair cats. The odds of a cat developing a tumour increased with age, up to the age of 16 years, and female cats had higher risk of developing a tumour compared with male cats. Skin (4,970; 27.05%) was the most frequent location for tumours, followed by connective tissue (3,498; 19.04%), unknown location (2,532; 13.78%) and female sexual organs (1,564; 8.51%). The most common tumour types were epithelial tumours (7,913; 43.06%), mesenchymal tumours (5,142; 27.98%) and lymphoid tumours (3,911; 21.28%).

2.2 Introduction

Cancer is a widespread disease and is a major cause of death in man and companion animals (Dorn, 1967). Cancer registries provide data for epidemiological studies that allow for incidence calculation, risk factor identification and development of prevention and control strategies, as well as treatment and spatial evaluation. Such studies have the potential to influence the therapy of individual cancer patients (Parkin, 2006; Vascellari et al., 2009; Nødtvedt et al., 2011a). Human cancer registries were already established in the 1940s (Parkin, 2006); however, veterinary cancer registries have existed only sporadically and for short periods of time (Dobson et al., 2002; Parkin,
One of the earliest cancer registries for companion animals was the California Animal Neoplasm registry, which started in 1963 with the goal of identifying all tumours in animals in the region over a 3-year period (Dorn et al., 1968a, b). Several registries in other countries followed (Moe et al., 2001, 2008; Merlo et al., 2008; Vascellari et al., 2009; Brønden et al., 2010; Nødtvedt et al., 2011b). Due to termination of many animal registries, as well as lack of communication and collaboration between the different registries, their potential as information sources has not been fully exploited and this renders them largely underused (Brønden et al., 2007).

Registry continuation, together with collaboration among registries, increases the size of the database, allowing the evaluation of temporary trends, fluctuations in cancer occurrence and appraisal of potential environmental and individual risk factors. Risk factors for specific cancers such as age, breed, gender and neuter status can be assessed and are a valuable source of information for veterinary practitioners (Dorn, 1967; Vascellari et al., 2009; Brønden et al., 2010). For most neoplastic diseases in animals, there are no standard treatments, which allows some latitude in prospective clinical trials. New therapeutic agents could be tested on pets with potential benefits for both man and animals (Vail and MacEwen, 2000; Paoloni and Khanna, 2008).

Current animal models for studying cancer consist of rodents with chemically- or virally-induced tumours. These models have many limitations and fail to reflect many aspects of naturally occurring human cancer (Hewitt, 1978; Hansen and Khanna, 2004). Companion animals with spontaneously developing tumours are more analogous to human cancer cases (Dorn, 1967; Priester, 1977; MacEwen, 1990; Vail and Thamm, 2004; Rowell et al., 2011). One reason is that these animals share the same environment with their owners and therefore are exposed to similar risk factors. Furthermore, there are striking histopathological, anatomical, genetic and biomolecular similarities between feline, canine and human tumours (Calabrese, 1986; Porrello et al., 2004, 2006; Withrow et al., 2013). A computerized database for companion animal tumours with a coding system corresponding to human cancer registry coding is therefore desirable (Monsein, 1991; Folk and Allen, 2004).

Feline tumours have not been investigated extensively in the past and studies on the feline population have mostly been performed with very sparse data (Withrow et al., 2013). To our knowledge, there is no feline cancer registry that has existed for a significant period of time and has allowed decent data collection.

The aim of the present retrospective study was to prepare and analyse cat patient records from all over Switzerland, which had been stored for the past 40 years. By this means, a feline cancer
registry was created that can be continued over subsequent years and used to answer epidemiological questions and investigate similarities between feline and human cancers.

### 2.3 Material and Methods

#### 2.3.1 Data Source

For this retrospective study, feline patient records were gathered from three veterinary diagnostic laboratories in Switzerland: the Vetsuisse faculty's Institute for Veterinary Pathology, Zürich (IVPZ), the Institute für Tierpathologie, Bern (ITP) and a private veterinary diagnostic laboratory (Zyto-Histo Diagnostik in Rorbas Freienstein, Switzerland).

The records retrieved from IVPZ-SLK (1965–1988) were patient records ($n = 10,799$) from feline post-mortem and biopsy samples analysed by histopathology. Diagnoses were recorded on punch cards using diagnostic key words (Keydex®, Fa. Royal McBee; Stünzi and Lott-Stolz, 1967). An external company (Scydoc®, Zug, Switzerland) performed the digitalization of the punch cards and results were crosschecked and completed using the original typed reports.

The records retrieved from the IVPZ-APPX (1987–2008) were patient records ($n = 26,844$) from feline biopsy, cytology and post-mortem examinations (analysed by histopathology), and were available from the electronic patient record system at IVPZ (www.APPX.com).

The records retrieved from the ITP-Berne (1983–2008) were digitized patient records ($n = 12,028$) from feline biopsy and post-mortem examinations, analysed by histopathology.

The records retrieved from Zyto-Histo Diagnostik (2007–2008) were digitized patient records ($n = 1,651$) based on samples of biopsy histopathology.

#### 2.3.2 Data Preparation and Modification

Data from the different sources were merged and standardized on the basis of breed, age, gender and neuter status, place of origin (canton), year and method of examination.

Tumour diagnoses were coded according to topographical and morphological keys of the International Classification of Oncology for Humans (ICD-O-3). Cysts were not counted as tumours.

Both benign and malignant tumours were included.

The 18 most frequent feline breeds with at least 90 individuals were registered; the remaining breeds were classified as ‘other breeds’. In a number of patient records the breed was not recorded in the original database and for these cases breed was classified as ‘unknown’. In other patient
records the breed was only recorded for purebred cats and not for European shorthair cats. The latter were grouped as 'unknown'; although it can be assumed that most of them were in fact European shorthair cats. In the early records, European shorthair cats were called 'house cats'. These were amalgamated under the term 'European shorthair cats'. The sex of the animals was recorded as one of: male, male neutered, female, female neutered and unknown.

The origins of the samples were unevenly distributed over Switzerland, with most of the samples deriving from the canton of Zurich. The canton as a variable was therefore integrated as a confounding factor. The year of submission was also integrated as a confounding factor because over time histological examinations have become more common and the number of submissions had increased accordingly. Another variable included was the method of examination due to different purposes of analysis. While biopsy and cytology samples were used for directed tumour cell searches, post-mortem examinations often uncovered the presence of a tumour. To unify anatomical locations where the same was meant, two specifications were changed: leucosis with the location 'bone marrow' was changed to the location 'unknown' and fibrosarcomas with the location 'skin' were changed to the location 'soft tissue' (i.e. subcutis).

### 2.3.3 Statistical Evaluation

The feline cancer registry is patient-based since there are only estimates of the cat population in Switzerland. Data editing and all statistical analyses were performed using Stata Software (StataCorp., 2011; Stata Statistical Software: Release 12; College Station, Texas, USA). Analyses were carried out using Chi-Square/Fisher's exact test. Significant variables were further integrated and analysed in a multiple logistic regression model (using binary logistic models and stepwise backward procedure). The following variables were included in the final model as fixed terms: canton of origin, age, sex/neuter status, breed, year and method of examination. \( P \leq 0.05 \) was considered significant and odds ratios (ORs) with 95% confidence intervals (CI) were calculated.

### 2.4 Results

#### 2.4.1 Dataset

The dataset consisted of a total of 51,322 cats that underwent pathological examination. The number of patients with confirmed tumours was 17,856 (34.79%). Of these, 485 cats (2.7%) had
multiple primary tumours, adding up to a total of 18,375 diagnosed tumour lesions. Of these, 14,759 (80.32%) were malignant. The number of post-mortem examinations (Fig. 1) remained roughly the same from 1965–2008, but the number of biopsy submissions (Fig. 2) and cytological examinations (Fig. 3) steadily increased after 1995. The average proportion of cats with tumours diagnosed by post-mortem examination was 16.56% (3,202/19,340); for biopsy samples this was 50.9% (11,828/23,236) and for cytology specimens 32.3% (2,825/8,746).

**Fig. 1.** Number of post-mortem sample submissions in the years 1965-2008 and the number of tumours detected in these samples.

**Fig. 2.** Number of biopsy sample submissions in the years 1965-2008 and the number of tumours detected in these samples.
2.4.2 Breed Distribution

The numbers of cats belonging to a given breed varied. Most cats were European shorthairs. In the statistical evaluation, this breed was used as the standard against which all other breeds were compared. Table 1 lists the distribution of cat breeds as well as their tumour frequency and the proportion of malignant tumours. European shorthair cats 24,023/51,322 (46.81%) accounted for almost half of the patients. Many patient records (17,861/51,322; 34.8%) lacked a breed annotation. Tumour frequency varied from 15.93% (54/339) in Birman cats to 40.94% (9,834/24,023) in European shorthair cats. The frequency of malignant tumours also differed between breeds and ranged from 62.16% (23/36, Burmese) to 94.44% (16/17, Devon rex).

Fig. 3. Number of cytology sample submissions in the years 1965-2008 and the number of tumours detected in these samples.
Using multiple regression analysis including all confounding factors, the odds for a single cat breed of developing a tumour were compared with those of the European shorthair cat (OR = 1) (Fig. 4). No other breed had significantly higher odds of developing a tumour than the European shorthair cat; however, several breeds had significantly lower ORs (Fig. 4). For malignant tumours only, the picture did not change substantially. There were only two breeds that showed significant changes compared with the overall tumour count. Chartreux cats had significantly lower odds of developing malignant tumours compared with the European shorthair cat ($P < 0.05$, OR = 0.74 [CI = 0.57; 0.97]), while the OR of Devon rex cats did not differ significantly from that of European shorthair cats ($P = 0.15$, OR = 0.64 [CI = 0.35; 1.17]).
Fig. 4. Odds ratios (ORs) and 95% confidence intervals (CIs) for tumour diagnoses for the most common cat breeds compared with the European shorthair cat (OR = 1). Unknown breed ($P = 0.4, OR = 0.98 [CI = 0.92; 1.03]$, Persian ($P < 0.01, OR = 0.59 [CI = 0.54; 0.65]$), Siamese ($P < 0.01, OR = 0.84 [CI = 0.75; 0.94]$), Maine Coon ($P < 0.01, OR = 0.73 [CI = 0.59; 0.9]$), Abyssinian ($P < 0.01, OR = 0.58 [CI = 0.44; 0.77]$), Other breeds ($P < 0.01, OR = 0.66 [CI = 0.49; 0.89]$), British shorthair ($P < 0.01, OR = 0.66 [CI = 0.49; 0.9]$), Birman ($P < 0.01, OR = 0.38 [CI = 0.28; 0.53]$), Chartreux ($P = 0.32, OR = 0.88 [CI = 0.68; 1.13]$), Norwegian forest ($P < 0.05, OR = 0.73 [CI = 0.54; 0.99]$), Domestic longhair ($P < 0.01, OR = 0.58 [CI = 0.43; 0.78]$), Burmesian ($P < 0.01, OR = 0.52 [CI = 0.34; 0.78]$), Turkish Angora ($P = 0.72, OR = 0.94 [CI = 0.65; 1.35]$), Mixed breed ($P = 0.77, OR = 0.93 [CI = 0.59; 1.48]$), Oriental shorthair ($P = 0.39, OR = 1.24 [CI = 0.76; 2.02]$), Ragdoll ($P = 0.1, OR = 0.64 [CI = 0.38; 1.08]$), Somali ($P = 0.69, OR = 1.11 [CI = 0.68; 1.81]$), Devon Rex ($P < 0.05, OR = 0.46 [CI = 0.25; 0.83]$).
2.4.3 Sex Distribution

Of the 51,322 cats recorded, the majority were neutered males (n = 15,652) followed by neutered females (n = 12,388), entire females (n = 10'828) and entire males (n = 9,396). In some specimens (n = 3,058) the sex of the cat was not specified.

Tumours occurred most frequently in neutered female cats (43.63%, 5,405/12,388), followed by neutered males (36.62%, 5,731/15,652), entire females (32.43%, 3,512/10,828) and entire males (25.78%, 2,422/9,396). If, however, all confounding factors (age, sex/neuter status, breed, year and method of examination and canton of origin) were taken into account, the picture looked very different: the odds of a neutered male cat developing a tumour were significantly lower compared with those of entire males (P<0.01, OR = 0.88 [CI = 0.82; 0.94]). Similarly, the odds of a neutered female cat developing a tumour were significantly lower than those of an entire female (P<0.01, OR = 0.85 [CI = 0.80; 0.91]).

For tumours generally, the odds of a female cat developing a tumour compared with those of a male cat were significantly higher (P<0.01, OR = 1.18 [CI = 1.14; 1.24]). However, when only malignant tumours were considered, the neutered male versus entire male (P<0.01, OR = 0.88 [CI = 0.82; 0.94]) and the female versus male (P<0.01, OR = 1.20 [CI = 1.15; 1.26]) ORs were similar to those where all tumours were considered. The ORs of neutered female cats versus entire female cats did not differ significantly (P = 0.07, OR = 0.94 [CI = 0.88; 1.00]).

The sex distribution of the cats varied depending on the method of diagnosis (i.e. post mortem, biopsy or cytology). For post-mortem samples the likelihood of entire cats having a tumour was higher compared with that of neutered cats; in biopsy specimens the reverse was the case. In cytology specimens, no clear trend was discerned. In all examination methods female cats had higher odds of developing a tumour than did male cats. (Fig. 5)
Fig. 5. Odds ratios (ORs) and 95% confidence intervals (CIs) for tumour diagnoses comparing neutered with entire and female with male cats, analyzed separately by examination method. Entire cats were set as standard (OR = 1) in the neutered/entire comparison and male cats in the female/male comparison.

Post-mortem samples: male neutered ($P = 0.33$, OR = 1.07 [CI = 0.94; 1.22]), female neutered ($P < 0.01$, OR = 1.26 [CI = 1.10; 1.45]), female ($P < 0.05$, OR = 1.10 [CI = 1.00–1.20]).

Biopsy samples: male neutered ($P < 0.01$, OR = 0.80 [CI = 0.72; 0.88]), female neutered ($P < 0.01$, OR = 0.73 [CI = 0.66; 0.79]), female ($P < 0.01$, OR = 1.25 [CI = 1.18; 1.33]).

Cytology samples: male neutered ($P = 0.14$, OR = 1.14 [CI = 0.96; 1.35]), female neutered ($P = 0.62$, OR = 0.96 [CI = 0.82; 1.13]), female ($P < 0.05$, OR = 1.13 [CI = 1.03; 1.25]).
2.4.4 Age Distribution

The highest number of samples per age group expressed in years were from cats <1 year of age. Very few samples were from cats >20 years of age and these were assembled in one group: ‘age >20’.

The odds of a cat developing a tumour increased with age, peaked at 16 years of age, and then decreased slightly (cats age <1 = set as standard, OR = 1). Malignant tumours arose more frequently in older cats (Figs. 6, 7).

**Fig. 6.** Age distributions of cats (n = 51,322) from 1965 to 2008

**Fig. 7.** Odds of a cat developing a tumour, depending on its age. The odds ratios are given relative to cats aged less than one year
2.4.5 Multiple Tumours

Relatively few cats ($n = 485$) had more than one primary tumour. Of all patients with a tumour diagnosis ($n = 17,856$), they represented only 2.7%. There were no differences between cats of different sexes. The only breed that differed significantly from European shorthair cats was the Siamese, which had a much lower multiple tumour rate ($P < 0.02$, OR = 0.36 [0.16-0.83]). Most diagnoses of several primary tumours derived from post-mortem examinations.

2.4.6 Classification of the Most Common Tumour Types According to ICD-O-3

A summary of the most common tumour types in cats ($n = 18,375$) revealed that epithelial tumours (ICD-O-3: 8010–8587; 9050–9058, $n = 7,913$; 43.06%) were the most common, followed by mesenchymal tumours (ICD-O-3: 8680–8711; 8800–9040; 9120–9150; 9580, $n = 5,142$; 27.98%), lymphoid tumours (ICD-O-3: 9590–9700; 9731–9732; 9740–9742; 9750–9755; 9800–9931; 9960, $n = 3,911$; 21.28%), unclassified tumours (ICD-O-3: 8000, $n = 476$; 2.59%), melanoma (ICD-O-3: 8720–8730, $n = 349$; 1.9%), skeletal tumours (ICD-O-3: 9180–9262, $n = 336$; 1.83%) and neural neoplasia (ICD-O-3: 9380–9460; 9503–9522; 9530; 9540–9570, $n = 197$; 1.07%) (Fig. 8). The frequency of these tumour types for each examination method is shown in Table 2.

2.4.7 Malignancy of the Most Common Tumour Types

The highest percentage of malignant neoplasms was found among skeletal tumours (94.64%, 318/336) followed by melanomas (326/349, 93.64%), lymphoid tumours (3,493/3,911, 89.34%), mesenchymal tumours (4,358/5,142, 84.75%), epithelial tumours (5,846/7,913, 73.88%) and unclassified tumours (343/476, 72.06%). A low malignancy rate was seen for neural neoplasia with 28.93% (57/197). Number per tumour type and proportion of malignant tumours are shown in Fig. 8.

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Post-mortem tumour count ($n = 3,916$)</th>
<th>Post-mortem %</th>
<th>Biopsy samples tumour count ($n = 12,068$)</th>
<th>Biopsy samples %</th>
<th>Cytology tumour count ($n = 2,851$)</th>
<th>Cytology %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial</td>
<td>1,281</td>
<td>37.39</td>
<td>5,715</td>
<td>47.24</td>
<td>912</td>
<td>31.99</td>
</tr>
<tr>
<td>Mesenchymal</td>
<td>280</td>
<td>8.17</td>
<td>4,116</td>
<td>34.02</td>
<td>746</td>
<td>26.17</td>
</tr>
<tr>
<td>Lymphoid</td>
<td>1,529</td>
<td>44.63</td>
<td>1,902</td>
<td>11.29</td>
<td>980</td>
<td>34.37</td>
</tr>
<tr>
<td>Unclassified</td>
<td>132</td>
<td>3.85</td>
<td>188</td>
<td>1.55</td>
<td>136</td>
<td>3.47</td>
</tr>
<tr>
<td>Melanoma</td>
<td>12</td>
<td>0.35</td>
<td>303</td>
<td>2.5</td>
<td>31</td>
<td>1.19</td>
</tr>
<tr>
<td>Skeletal</td>
<td>56</td>
<td>1.63</td>
<td>259</td>
<td>2.14</td>
<td>21</td>
<td>0.74</td>
</tr>
<tr>
<td>Neural</td>
<td>123</td>
<td>3.59</td>
<td>72</td>
<td>0.6</td>
<td>2</td>
<td>0.07</td>
</tr>
</tbody>
</table>
2.4.8 Most Common Anatomical Tumour Locations

The skin (4,970/18,375, 27.05%) was the most frequent location for tumours, followed by connective tissue (3,498, 19.04%), unknown location (2,532, 13.78%), female sexual organs (1,564, 8.51%), gastrointestinal tract (1,373, 7.47%), respiratory system (1,223, 6.66%), oral cavity/pharynx (980, 5.33%), lymph nodes (351, 1.91%), musculoskeletal system (345, 1.88%), endocrine glands (339, 1.84%), haemopoietic system (329, 1.79%), abdominal cavity (257, 1.4%) and urinary tract (232, 1.26%). The frequency of these anatomical tumour locations for each examination method is shown in Table 3.

2.4.9 Malignancy Rates in the Most Common Anatomical Tumour Locations

The highest percentage of malignant tumours was found among tumours in lymph nodes with 97.72% (343/351), followed by tumours of unknown location (2,419/2,532, 95.54%) and tumours in the abdominal cavity (243/257, 94.55%), the musculoskeletal system (321/345, 93.04%), the urinary system (213/232, 91.81%), the haemopoietic system (299/329, 90.88%), the oral cavity/pharynx (862/980, 87.96%), the gastrointestinal tract (1,196/1,373, 87.11%), the respiratory system (1,050/1,223, 85.85%), the connective tissue (2,981/3,498, 85.22%), the female sexual organs (1,280/1,564, 81.84%) and the skin (3,232/4,970, 65.03%). A lower malignancy rate

Fig. 8. Number of the most common tumour types (>1%) and proportion of malignant tumours.
was present in the endocrine glands with 25.37% (86/339). Number of tumours per anatomical location and the proportion of malignant tumours are represented in Fig. 9.

### Table 3

**Most common anatomical tumour locations (>1%) for post-mortem, biopsy and cytology samples**

<table>
<thead>
<tr>
<th>Location</th>
<th>Post-mortem</th>
<th>Post-mortem %</th>
<th>Biopsy samples</th>
<th>Biopsy samples %</th>
<th>Cytology samples</th>
<th>Cytology %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>tumour count (n = 5,426)</td>
<td></td>
<td>tumour count (n = 12,089)</td>
<td></td>
<td>tumour count (n = 2,851)</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>105</td>
<td>3.06</td>
<td>4,225</td>
<td>34.92</td>
<td>640</td>
<td>22.43</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>109</td>
<td>3.18</td>
<td>2,982</td>
<td>21.65</td>
<td>107</td>
<td>14.23</td>
</tr>
<tr>
<td>Unknown location</td>
<td>1,344</td>
<td>45.07</td>
<td>863</td>
<td>7.13</td>
<td>125</td>
<td>4.38</td>
</tr>
<tr>
<td>Female sexual organs</td>
<td>61</td>
<td>1.78</td>
<td>1,451</td>
<td>11.99</td>
<td>52</td>
<td>1.82</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>469</td>
<td>13.69</td>
<td>570</td>
<td>4.71</td>
<td>354</td>
<td>11.72</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>511</td>
<td>15.92</td>
<td>326</td>
<td>2.69</td>
<td>586</td>
<td>13.34</td>
</tr>
<tr>
<td>Oral cavity/pharynx</td>
<td>57</td>
<td>1.66</td>
<td>822</td>
<td>6.79</td>
<td>101</td>
<td>3.54</td>
</tr>
<tr>
<td>Lymph node</td>
<td>11</td>
<td>0.32</td>
<td>101</td>
<td>0.83</td>
<td>239</td>
<td>8.38</td>
</tr>
<tr>
<td>Musculoskeletal system</td>
<td>58</td>
<td>1.69</td>
<td>221</td>
<td>1.83</td>
<td>66</td>
<td>2.31</td>
</tr>
<tr>
<td>Endocrine glands</td>
<td>169</td>
<td>4.93</td>
<td>139</td>
<td>1.15</td>
<td>31</td>
<td>1.09</td>
</tr>
<tr>
<td>Haemopoietic system</td>
<td>111</td>
<td>3.24</td>
<td>72</td>
<td>0.6</td>
<td>146</td>
<td>5.12</td>
</tr>
<tr>
<td>Abdominal cavity</td>
<td>18</td>
<td>0.53</td>
<td>27</td>
<td>0.22</td>
<td>212</td>
<td>7.44</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>71</td>
<td>2.07</td>
<td>89</td>
<td>0.74</td>
<td>72</td>
<td>2.53</td>
</tr>
</tbody>
</table>

![Fig. 9](image)

**Fig. 9.** Number of the most common anatomical locations (>1%) and proportion of malignant tumours.

### 2.4.10 Tumour Types in Anatomical Locations

Finally, a combined analysis of the occurrence of the different histological tumour types in the most common anatomical locations (>1%) was performed (Fig. 10).
**Fig. 10.** The most common tumour locations (>1%) and the corresponding histological tumour types in these locations. Diagnoses with a frequency of <1% were combined into ‘other tumours’. Circle and segment dimensions correspond to the proportions in the overall location/tumour type count.
2.5 Discussion

Veterinary cancer registries increase knowledge of the occurrence and distribution of tumours in companion animals over time. They may also enhance awareness of risk factors and allow improvement in prevention and treatment strategies. In addition, spontaneously arising companion animal tumours could serve as sentinels for human cancers. Unfortunately, there are few animal cancer registries and many of them only cover short periods of time, mainly due to economic considerations. The advantage of the data presented here is that they were collected over more than 40 years, which has allowed us to construct a retrospective feline cancer registry over a longer period of time. To our knowledge, there is no other feline cancer registry that covers such a long time span (1965 to 2008) and contains such a large amount of data (51,322 cats and 18,375 tumours).

The main difficulty for population-based veterinary cancer registries is to identify the size of the population at risk. This also applies to the present project. Since cats do not have to be registered in Switzerland, there are only estimates as to the size of the feline population. Therefore, incidence rates cannot be calculated and we have to settle for proportional calculations from the available patient datasets. Every animal cancer registry has struggled with this problem. In some studies the hospital-based patient dataset was used for calculations; in others, the population at risk was estimated using household or telephone surveys in a well-defined geographical area (Stableforth, 1952; Dorn et al., 1968a, b; Patnaik et al., 1975; MacVean et al., 1978; Priester and Mantel, 1980; Brønden et al., 2007; Egenvall et al., 2009; Vascellari et al., 2009; Nødtvedt et al., 2011a).

In addition, different inclusion criteria and methodologies as well as different tumour classifications were used. A comparison of the results from the few available registries is therefore difficult. We faced similar problems when generating our dataset from four sets of patient records. A number of pathologists had worked on the cases, and not all of them applied the same criteria when it came to specifying the location of the tumour. This was particularly true for the location of leucosis (i.e. lymphoma) in cats. While some pathologists invariably ascribed leucosis in cats to an ‘unknown’ location, others described the location as ‘bone marrow’, and this was independent of the sample source. To homogenize the definition of the location and to avoid confusion, we recoded all ‘bone marrow’ locations as ‘unknown’. We did not, however, recode those cases of leucosis in which another, specific location of the tumour tissue was indicated. Among veterinary pathology cancer registries there seems to be some uncertainty concerning tumours that may be multicentric, such as lymphoma. In one registry this diagnosis is integrated into ‘haemopoietic tissue’ (MacVean et al., 1978); in two others into ‘lymphoid tissue’ (Cotchin, 1952; Vascellari et al., 2009). One registry used
the combination ‘haemopoietic/lymphoid’ (Priester and Mantel, 1980) and the registries of Dorn et al. (1968a, b) just used the term ‘lymphosarcoma’ without additional statements as to location. A similar problem was encountered with the diagnosis ‘fibrosarcoma’ in the subcutaneous tissue. Some pathologists reported ‘skin’ as the location since a skin biopsy sample was taken; others reported ‘soft tissue’. Here as well, we unified the location and recoded the ‘skin’ locations to ‘soft tissue’.

The criterion for including a patient record in our dataset was that a post-mortem investigation followed by histopathology, biopsy or cytology examination had been performed. The number of submissions increased markedly when biopsy analyses grew in popularity. Once the different methodologies were established, the proportion of tumours diagnosed remained stable. The proportion of tumours in biopsy and cytology specimens was higher than in post-mortem examinations, because such samples were taken due to the clinical suspicion of a tumour. Based on all of the specimens analysed, 34.97% of all cats were found to have a tumour and most tumours were malignant (80.32%). A relatively low tumour rate with a high malignancy rate has also been described in other studies (Dorn et al., 1968a; MacVean et al., 1978; Vascellari et al., 2009).

Our dataset showed that no other breed had significantly higher odds of developing a tumour than the European shorthair cat. However, there were several breeds that had significantly lower ORs. Not many studies have focused on the frequency of tumours in different feline breeds and this is mainly due to a limited number of patients and breeds in the datasets. Patnaik et al. (1975) investigated non-haemopoietic neoplasms in feline necropsy examinations and found a higher tumour incidence in domestic shorthair, Persian and Himalayan cats compared with Siamese cats. Priester and Mantel (1980) found that domestic shorthair cats had a slightly higher risk than Persian and Siamese cats, and in a study in Northern Italy, purebreds were found to have a higher risk of developing malignant tumours than crossbreeds (Vascellari et al., 2009). Every study shows a different result, making a comparison with our results very difficult.

Our data show that the odds of a cat developing a tumour increased with age, peaked at 16 years of age and then slightly decreased. Similar data have been published with age peaks at 14 (Patnaik et al., 1975) and 12 (Vascellari et al., 2009) years, respectively. Other registries described an increasing tumour risk with increasing age of the cat (Cotchin, 1952; Priester and Mantel, 1980).

In our data we found a clear difference in tumour frequencies between neutered and entire cats with higher odds of developing a tumour in entire cats, both for males and females. To our knowledge there is no other publication that compares tumour occurrence in entire and neutered cats. However, there are publications on the differences between male and female cats. Our analyses reveal higher odds of female cats developing a tumour compared with male cats. This is in
accordance with the studies of Patnaik et al. (1975) and Vascellari et al. (2009), which showed that female cats have a higher risk of developing a tumour than do males. Priester and Mantel (1980) found no gender difference when looking at all tumours, but a higher risk for male cats (not significant) with regard to malignant tumours.

Concerning tumour type and anatomical location, we are in agreement with the available registries that the most common tumour types are epithelial, mesenchymal or haemopoietic/lymphoid and the most common locations are skin and connective tissue, mammary gland and lymphoid/haemopoietic tissue (Dorn et al., 1968a, b; Patnaik et al., 1975; MacVean et al., 1978; Priester and Mantel, 1980; Vascellari et al., 2009). In earlier studies lymphomas were diagnosed more often, probably because the disease was more common, owing to the fact that there was no vaccination for feline leukaemia virus available at that time. There is a bias in these proportions, because tumours of the skin, connective tissue and female sexual organs (i.e. mammary gland) are more easily detected by physical examination than other tumours, where more advanced technological investigations are necessary.

The statistical evaluation of sex and breed in our dataset shows the importance of the inclusion of confounding factors. The bivariate analysis differs from the results of the multiple logistic regressions. In a retrospective study, however, one has to work with the information that exists and the number of available factors is normally limited. To find out which factors may contribute to the development of tumours (e.g. age at castration, nutrition or other diseases), it is advisable for future data registration to register as much information as possible.

In order to shed more light on the role of breed, age, sex and other factors in tumour formation, more and better quality information is necessary. Furthermore, to compare frequency rates of cancer among different countries or regions, uniform inclusion criteria as well as a specific international classification should be applied.

It would be desirable to compare incidence rates of cancer in companion animals with those of their human counterparts. Such comparisons would be valuable, but for this it is necessary to know the number of animals at risk. In Switzerland, such numbers are available for dogs, because it has been mandatory to have an animal identification number (microchip) since 2006. This should also be required for cats.
2.6 Acknowledgments

We gratefully acknowledge the help of the IVPZ staff, D. Erni, N. S. Schenker and G. Lott, during collection and processing of primary data and all colleagues of the Collegium Helveticum, who contributed in various ways. We are grateful to the veterinary practitioners who submitted cases over a long period of time, which made this and further studies possible. Finally, we greatly appreciate H. Murray's revision of the English version. This study was financed through the financial support of the University of Zurich to A. Pospischil for acting as a fellow at the Collegium Helveticum during his fellowship period of 2009 to 2016. This chapter has been published as:

3. Swiss Feline Cancer Registry 1965-2008: the Influence of Sex, Breed and Age on Tumour Types and Tumour Locations

3.1 Summary

Cancer registries are valuable sources for epidemiological research investigating risk factors underlying different types of cancer incidence. The present study is based on the Swiss Feline Cancer Registry that comprises 51,322 feline patient records, compiled between 1965 and 2008. In these records, 18,375 tumours were reported. The study analyses the influence of sex, neutering status, breed, time and age on the development of the most common tumour types and on their locations, using a multiple logistic regression model. The largest differences between breeds were found in the development of fibrosarcomas and squamous cell carcinomas, as well as in the development of tumours in the skin/subcutis and mammary gland. Differences, although often small, in sex and neutering status were observed in most analyses. Tumours were more frequent in middle-aged and older cats. The sample size allowed detailed analyses of the influence of sex, neutering status, breed and age. Results of the study are mainly consistent with previous analyses; however, some results cannot be compared with the existing literature. Further investigations are necessary, since feline tumours have not been investigated in depth to date. More accurate comparisons would require the definition of international standards for animal cancer registries.

3.2 Introduction

Cancer registries are important tools for establishing cancer control and prevention strategies. They are used in epidemiological research to examine risk factors underlying the incidence of different types of cancer. Tumour initiation and progression are influenced by several factors whose precise interactions are still unknown.

Demographic variables such as sex, age (Parkin, 2006) and breed (Dorn et al., 1968b; Thrusfield, 2007) are typically used to analyse the development of specific cancers.

Companion animals with spontaneously developing tumours are, moreover, valuable resources for investigating the complexity of human cancer pathogenesis, progression and therapy. Pets and
people share the same environment and are therefore exposed to similar risk factors. Furthermore, their tumours undergo analogous genetic and molecular alterations and they display similar levels of tumour heterogeneity that result in similar mechanisms of cancer development, resistance to therapy, recurrence and metastasis (Thrusfield, 1988; MacEwen, 1990; Paoloni and Khanna, 2008; Dorn et al., 1968a). Finally, in-depth examination of animal tumours could lead to the identification of new genes associated with cancer, relevant environmental risk factors and the development of new prognostic, diagnostic and therapeutic applications (Vail and MacEwen, 2000).

The present study is based on analysis of the Swiss Feline Cancer Registry, which consists of 51,322 feline patient records compiled between 1965 and 2008 (Graf et al., 2015). In this extended examination of data from the registry, we analyse the influence of sex, neutering status, breed and age on the development of the most common feline tumour types (i.e. adenoma/adenocarcinoma, fibrosarcoma, lymphoma and squamous cell carcinoma) and tumour locations (i.e. skin and subcutis, mammary gland, gastrointestinal tract, cardiorespiratory system and oral cavity/pharynx), their distribution and relative frequency over the period of study.

3.3 Material and Methods

Data from the Swiss Feline Cancer Registry (Graf et al., 2015) were used for extended analysis. Three veterinary diagnostic laboratories in Switzerland provided the case records. Feline breeds with at least 90 individual records were investigated further; the remaining breeds were classified as ‘other breeds’. The sex of the animals was grouped as following: male, neutered male, female, neutered female and unknown.

To unify the classification of some of the anatomical locations, we changed two specifications: leucosis with the location ‘bone marrow’ was changed to the location ‘unknown’ and fibrosarcomas with the location ‘skin’ were changed to the location ‘soft tissue’ (subcutis).

Since there is no obligatory registration of cats in Switzerland there are only approximate estimates of the size of the feline population. Therefore, proportional calculations from the available patient datasets are given.

Data, wherever applicable, were analysed in two groups. In the first group all tumours (i.e. benign and malignant together) were analysed and in the second group only malignant tumours were included.

Using ICD-0-3 for human patients (WHO, 2013), tumour names were sometimes slightly different from those used in veterinary pathology (i.e. malignant lymphoma, mast cell sarcoma and
fibromatous neoplasia). ‘Basal cell tumour’ is also an old term, which is now usually replaced with the terms ‘trichoblastoma’ or ‘sweat gland ductular adenoma’.

Data editing and statistical analyses were performed using Stata Software (StataCorp, 2011; Stata Statistical Software: Release 12; StataCorp, College Station, Texas, USA). Statistical analyses were carried out using Chi-square/Fisher's exact test. Significant variables were further integrated and analysed in a multiple logistic regression model (using binary logistic models and stepwise backward procedure). The following variables were included in the final model as fixed terms: canton of origin, age, sex/neutering status, breed, year and method of examination. \( P \leq 0.05 \) was considered to be significant and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. The power was set at >0.8.

### 3.4 Results

The Swiss Feline Cancer Registry consists of the records of 51,322 cats that underwent pathological examination. The number of patients with confirmed tumours was 17,856 (34.79%). Some cats were diagnosed with multiple primary tumours, adding up to a total of 18,375 diagnosed tumours. Of these diagnoses, 14,759 (80.32 %) tumours were malignant. Most cats were of the European shorthair breed. In the statistical evaluation, this breed was used as the standard for comparisons with the remaining breeds.

Breed, sex and age distribution of the entire dataset are presented in Graf et al. (2015). The following results introduce the most common tumour types and anatomical locations in cats, the influence of age, breed and sex as well as occurrence over the years.

#### 3.4.1 Adenoma/Adenocarcinoma

Adenoma/adenocarcinoma was the most common tumour diagnosed between 1965 and 2008. Among the 18,375 diagnosed tumours, 3,515 (19.1%) were either an adenoma or an adenocarcinoma. Of the total number, 2,613 (74.3%) were malignant (adenocarcinomas). In the 1960s, approximately half of the diagnosed tumours were adenomas/adenocarcinomas. Their relative frequency decreased over the period covered by this study. (Fig. 1)
The most common anatomical locations of adenoma/adenocarcinoma and adenocarcinoma were the mammary gland, gastrointestinal tract and cardiorespiratory tract (Fig. 2).

Using multiple logistic regression analysis, the odds of cat breeds developing an adenoma/adenocarcinoma were compared with those of the European shorthair cat (OR = 1). Two analyses were carried out, one using the group adenoma/adenocarcinoma (benign and malignant) and one using only adenocarcinomas (malignant) (Fig. 3). In both analyses, only a few breeds had higher odd ratios in comparison with European shorthair cats. Siamese cats (OR= 2.44 [2.07, 2.89])
and Oriental shorthair (OR = 2.86 [1.45, 5.61]) had the highest odds ratios when frequency of adenocarcinoma was calculated (see supplementary data).

Fig. 3. Odds ratios (ORs) and 95% confidence intervals (CIs) for the most common breeds that develop adenoma/adenocarcinoma (benign and malignant, n = 3,515) or adenocarcinoma (malignant, n = 2,613) compared with the European shorthair cat (OR = 1).

Analyses of the influence of age revealed that the odds of cats developing an adenoma/adenocarcinoma or adenocarcinoma increased with age. The odds of a neutered male cat developing an adenoma/adenocarcinoma or adenocarcinoma were significantly higher compared with entire male cats. There was no significant difference between neutered and entire female cats. The odds of a female cat developing an adenoma/adenocarcinoma or adenocarcinoma compared with those of a male cat were significantly higher (Table 1).
3.4.2 Fibroma/Fibrosarcoma

Of 18,375 diagnosed tumours, 3,386 (18.4%) were either a fibroma or a fibrosarcoma. Of these, 3,209 (94.8%) were malignant. Fibroma/fibrosarcoma was a rare diagnosis in the 1960s, but its relative frequency has increased since. This is especially true starting from the 1990s, where fibroma/fibrosarcoma occurrences increased substantially (Fig. 4).

Because fibromas were rare and have no important effect on the analyses, further investigations focused on fibrosarcomas only. The most common anatomical locations for fibrosarcoma were the connective tissues, including subcutis (skin) with 88.5%, followed by unknown location (5.7%) and oral cavity/pharynx (3.1%).

No breed had significantly higher odds of developing a fibrosarcoma compared with the European shorthair cat (OR = 1). However, several breeds had odds ratios that were significantly lower (Fig. 5) (see supplementary data).
Analyses of the influence of age revealed that fibrosarcomas occurred more frequently in middle-aged and older cats. Neutered and entire male cats had the same odds of developing a fibrosarcoma. Neutered female cats had significantly higher odds than entire female cats. The odds of a female cat developing a fibrosarcoma compared with those of a male cat were significantly higher (Table 1).

### 3.4.3 Lymphoma

Of 18,375 diagnosed tumours, 2,868 (15.6%) were classified as lymphoma. This tumour type was relatively frequent from 1972 to 1994, where up to 38% of tumour diagnoses were of this type. In the mid-1990s the frequency of lymphoma dropped substantially and the relative frequencies have remained between 10% and 15% since (Fig. 6).
The most common anatomical locations for lymphoma were unknown location, gastrointestinal tract and lymph node (Fig. 7).

Oriental shorthair and Somali cats had significantly higher odd ratios for developing lymphomas compared with those of European shorthair cats. Persian, Maine Coon, British and Norwegian forest cats had significantly lower odds ratios (Fig. 8) (see supplementary data).
Fig. 8. Odds ratios (ORs) and 95% confidence intervals (CIs) for the most common breeds that develop lymphoma \( (n = 2,868) \) compared with the European shorthair cat (OR = 1).

Analyses of the influence of age revealed that the mean age of a cat developing lymphoma was 8.5 years. Lymphomas appeared in all age categories, but were the most frequent tumour type in young cats (<5 years) compared with other tumour types. The odds of a neutered cat developing lymphoma were significantly higher than for entire cats, for both males and females. The odds of a female cat developing lymphoma compared with those of a male cat were significantly lower (Table 1).

3.4.4 Squamous Cell Carcinoma

Of 18,375 diagnosed tumours, 1,811 (9.9%) were squamous cell carcinomas. The frequency of squamous cell carcinomas constantly decreased between the 1960s and the early 1990s, and then increased again (Fig. 9).
The most common anatomical locations for squamous cell carcinomas were the skin (49.3%), followed by the oral cavity/pharynx (29%) and unknown location (9.7%). No other breed had significantly higher odds of developing a squamous cell carcinoma than the European shorthair cat (OR = 1). However, several breeds had significantly lower odds ratios (Fig. 10) (see supplementary data).

*Fig. 9.* Relative diagnosis frequency of squamous cell carcinoma ($n = 1,811$) expressed as a percentage of overall tumour diagnoses ($n = 18,375$) during the years 1965–2008.

*Fig. 10.* Odds ratios (ORs) and 95% confidence intervals (CIs) for the most common breeds that develop squamous cell carcinoma ($n = 1,811$) compared with the European shorthair cat (OR = 1).
Analyses of the influence of age revealed that the odds of developing a squamous cell carcinoma increased with age with a mean age at diagnosis of 12.2 years. The odds of a neutered cat developing a squamous cell carcinoma were significantly higher compared with entire cats, for both males and females. There was no significant difference between the odds for female and male cats (Table 1).

### 3.4.5 Skin and Subcutis

Skin and subcutis were the most common anatomical locations for tumours between 1965 and 2008. Of 18,875 diagnosed tumours, 7,629 (41.5%) were located in the skin and subcutis. Of these, 5,804 (76.1%) were malignant. Benign skin and subcutaneous tumours had a frequency of around 10% between 1965 and 2008. Malignant tumours increased in the 1990s from around 20% to almost 40% of the overall tumour findings (Fig. 11).

![Fig. 11. Relative diagnosis frequency of skin and subcutaneous tumours expressed as a percentage of the overall tumour diagnoses between 1965 and 2008. Malignant tumours of the skin/subcutis (n = 5,804) and benign tumours of the skin/subcutis (n = 1,825).](image)

The most common tumour types affecting the skin and subcutis were fibrosarcoma, basal cell tumours and squamous cell carcinoma (Fig. 12).
The European shorthair cat (OR = 1) had the highest odds of developing a tumour in the skin/subcutis; several breeds had significantly lower odds ratios (Fig. 13). In the evaluation of the skin without the subcutis ($n = 4,970$), similar results were seen (see supplementary data).

**Fig. 12.** Occurrence of the most common tumour types in the skin and subcutis. All tumours ($n = 7,629$; left) and malignant tumours ($n = 5,804$; right).

**Fig. 13.** Odds ratios (ORs) and 95% confidence intervals (CIs) for the most common breeds that develop benign or malignant tumours ($n = 7,629$) or malignant tumours ($n = 5,804$) of the skin/subcutis compared with the European shorthair cat (OR = 1).
Analyses of the influence of age revealed that the odds of a cat developing a tumour or a malignant tumour of the skin or subcutis increased with age, with a mean age at diagnosis of 10.5 years. Increasing odds with age were also found for the location skin (without subcutis), with a mean of 10.8 years. Differences in sex/neutering status for developing a tumour of the skin skin/subcutis or skin were small (Table 2).

<table>
<thead>
<tr>
<th>Tumour location</th>
<th>Male neutered versus male entire (OR = 1)</th>
<th>Female neutered versus female entire (OR = 1)</th>
<th>Female versus male (OR = 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( OR (95% CI) )</td>
<td>( OR (95% CI) )</td>
<td>( OR (95% CI) )</td>
</tr>
<tr>
<td>Skin and subcutis(^*)</td>
<td>1.06 (0.98, 1.15)</td>
<td>1.18 (1.11, 1.28)</td>
<td>1.04 (0.98, 1.09)</td>
</tr>
<tr>
<td>Skin and subcutis(^†)</td>
<td>1.08 (0.99, 1.18)</td>
<td>1.26 (1.13, 1.37)</td>
<td>1.07 (1.01, 1.14)</td>
</tr>
<tr>
<td>Skin(^*)</td>
<td>1.02 (1.01, 1.03)</td>
<td>1.12 (1.08, 1.17)</td>
<td>1.00 (0.94, 1.07)</td>
</tr>
<tr>
<td>Skin(^†)</td>
<td>1.13 (1.10, 1.17)</td>
<td>1.21 (1.17, 1.25)</td>
<td>1.04 (0.97, 1.12)</td>
</tr>
<tr>
<td>Mammary gland(^*)</td>
<td>0.75 (0.68, 0.83)</td>
<td>0.62 (0.56, 0.69)</td>
<td>21.17 (16.68, 25.86)</td>
</tr>
<tr>
<td>Mammary gland(^†)</td>
<td>0.86 (0.81, 1.5)</td>
<td>0.60 (0.54, 0.67)</td>
<td>21.85 (16.73, 25.54)</td>
</tr>
<tr>
<td>Gastrointestinal tract(^*)</td>
<td>1.81 (1.70, 1.93)</td>
<td>1.55 (1.46, 1.64)</td>
<td>1.92 (1.82, 1.94)</td>
</tr>
<tr>
<td>Intestine(^†)</td>
<td>1.61 (1.47, 1.79)</td>
<td>1.34 (1.26, 1.43)</td>
<td>1.87 (1.74, 1.92)</td>
</tr>
<tr>
<td>Gastrointestinal system(^†)</td>
<td>1.55 (1.50, 1.61)</td>
<td>1.20 (1.15, 1.26)</td>
<td>1.13 (1.09, 1.18)</td>
</tr>
<tr>
<td>Lung/bronchus(^*)</td>
<td>2.35 (1.78, 3.11)</td>
<td>2.22 (1.75, 2.82)</td>
<td>1.24 (1.11, 1.49)</td>
</tr>
<tr>
<td>Oral cavity/pharynx(^†)</td>
<td>1.31 (1.03, 1.62)</td>
<td>1.35 (1.08, 1.69)</td>
<td>0.84 (0.75, 0.96)</td>
</tr>
</tbody>
</table>

\(^*\) All tumours.
\(^†\) Malignant tumours.

### 3.4.6 Mammary Gland

Of 18,375 diagnosed tumours, 1,501 (8.2%) were in the anatomical location of the mammary gland. Of these, 1,249 (83%) were malignant. The frequency of mammary gland tumours compared with overall tumour findings did not change substantially from 1965 to 2008 (Fig. 14).

![Fig. 14. Relative diagnosis frequency of mammary tumours expressed as a percentage of overall tumour diagnoses between 1965 and 2008. Malignant mammary tumours (n = 1,249) and benign mammary tumours (n = 252).](image)
The most common mammary tumour types were adenoma/adenocarcinoma (83.08%), fibromatous neoplasia (3.8%) and epithelial neoplasia not otherwise specified (NOS) (3.6%). Adenocarcinoma (91.4%) and epithelial neoplasia NOS (2.4%) were found most often when comparing malignant tumours only.

No breed had significantly lower odds of developing a mammary tumour/malignant tumour than the European shorthair cat (OR =1). However, several breeds had significantly higher odds ratios (Fig. 15) (see supplementary data).

**Fig. 15.** Odds ratios (ORs) and 95% confidence intervals (CIs) for the most common breeds that develop a tumour (benign and malignant, \( n = 1,501 \)) in the mammary glands or a malignant tumour (\( n = 1,249 \)) in the mammary glands compared with the European shorthair cat (OR = 1).

Analyses of the influence of age revealed that the highest odds ratios of developing a tumour/malignant tumour in the mammary gland were in cats aged 8 to 16 years. Neutered and entire male cats had no significant differences in the odds of developing a tumour/malignant tumour in the mammary gland. Neutered female cats had significantly lower odds than entire female cats in both analyses. The odds of a female cat developing a tumour/malignant tumour in the mammary gland compared with a male cat were much higher (Table 2).
3.4.7 Gastrointestinal Tract

Of 18,375 diagnosed tumours, 1,373 (7.5%) were in the gastrointestinal tract. Of these, 1,196 (87.1%) were malignant. Due to the fact that benign tumours in the gastrointestinal tract were rare and had no important effect on the analyses, further investigations focused on malignant tumours only. The frequency of malignant tumours in the gastrointestinal tract compared with the overall tumour locations decreased from 1965 to 2008 (Fig. 16).

![Graph](image1)

**Fig. 16.** Relative diagnosis frequency of malignant tumours in the gastrointestinal tract \((n = 1,196)\) expressed as a percentage of overall tumour diagnoses between 1965 and 2008.

Exploring in more detail the segments of the gastrointestinal tract: 50.2% of the malignant tumours were in the intestine, 27.8% in the liver and gallbladder, 13.6% in the pancreas, 6.3% in the stomach, 1.5% in the anal region and 0.75% in the oesophagus.

The most common malignant tumours in the gastrointestinal tract overall were adenocarcinomas and lymphoma (Fig. 17). In the intestine, the most common malignant tumours were lymphoma (40.7%), adenocarcinoma (40%) and sarcoma (7.3%).

![Pie chart](image2)

**Fig. 17.** Occurrence of the most common malignant tumour types \((n = 1,196)\) in the gastrointestinal tract.
Persian (OR = 0.64 [0.48, 0.84]) and Maine Coon (OR = 0.45 [0.22, 0.91]) cats had significantly lower odds of developing a malignant tumour in the gastrointestinal tract compared with the European shorthair cat (OR = 1). Siamese (OR = 1.45 [1.12, 1.87]) cats were the only breed with significantly higher odds (Fig. 18) (see supplementary data).

**Fig. 18.** Odds ratios (ORs) and 95% confidence intervals (CIs) for the most common breeds that develop a malignant tumour of the gastrointestinal tract (n = 1,196) compared with the European shorthair cat (OR = 1).

For evaluation of the intestine only: Siamese (OR = 1.92 [1.40, 2.64]), Chartreux (OR = 2.65 [1.39, 5.02] and Somali (OR = 3.41 [1.25, 9.36] cats had significantly higher odds, and Persian (OR = 0.5 [0.32, 0.76] and Maine Coon (no tumour) cats had significantly lower odds of developing a malignant tumour in the intestine compared with European shorthair cats (see supplementary data).

Analyses of the influence of age revealed that the odds of developing a malignant tumour in the gastrointestinal tract increased with age, with a mean age at diagnosis of 11.2 years. Cats aged 10 to 14 years (mean 10.8 years) had the highest odds of developing a malignant tumour in the intestine. The odds of a neutered cat developing a malignant tumour in the gastrointestinal tract
were significantly higher compared with entire cats, for both males and females. There was no significant difference between the odds for female and male cats (Table 2). Analyses of intestinal tumours also revealed higher odds for neutered cats, but no significant differences in the male/female comparison (Table 2).

### 3.4.8 Cardiorespiratory System

Of 18,375 diagnosed tumours, 1,223 (6.7%) were in the cardiorespiratory system. Of these, 1,050 (85.9%) were malignant. Due to the fact that benign tumours in the cardiorespiratory system were rare and had no important effect on the analyses, further investigations focused on malignant tumours only. The frequency of malignant tumours in the cardiorespiratory system compared with overall tumour findings did not change substantially from 1965 to 2008 (Fig. 19).

![Fig. 19. Relative diagnosis frequency of malignant tumours in the cardiorespiratory system (n = 1,050) expressed as a percentage of overall tumour diagnoses between 1965 and 2008.](image)

Most malignant tumours of the cardiorespiratory system derived from the lung/bronchus (70.2%) and from the nasal cavity/middle ear (21.0%). The most common malignant tumours in the cardiorespiratory tract were adenocarcinomas, lymphomas and epithelial neoplasia NOS (Fig. 20).
Evaluation of the lung/bronchus only showed that the most common malignant tumours were adenocarcinomas (48.3%), epithelial neoplasia NOS (22.1%) and lymphoma (13.6%).

No other breed had significantly higher odds of developing a malignant tumour in the cardiorespiratory system compared with the European shorthair cat (OR = 1). Abyssinian (OR = 0.24 [0.06, 0.95]) and Birman (OR = 0.13 [0.02, 0.92]) cats had significantly lower odds ratios (Fig. 21) (see supplementary data). No significant breed differences were found in the location lung/bronchus.

**Fig. 20.** Occurrence of the most common malignant tumour types \( n = 1,050 \) in the cardiorespiratory system.
Fig. 21. Odds ratios (ORs) and 95% confidence intervals (CIs) for the most common breeds that develop a malignant tumour in the cardiorespiratory system ($n = 1,050$) compared with the European shorthair cat (OR = 1).

Analyses of the influence of age revealed that the odds of developing a malignant tumour in the cardiorespiratory system increased with age. The same applied for the location lung/bronchus. The mean age of developing a tumour in the location lung/bronchus was 11.2 years.

The odds of a neutered cat developing a malignant tumour in the cardiorespiratory system were significantly higher compared with entire cats, for both males and females. The odds of a female cat developing a malignant tumour in the cardiorespiratory system compared with a male cat were significantly higher. The same was true for the location lung/bronchus (Table 2).

### 3.4.9 Oral Cavity and Pharynx

Of 18,375 diagnosed tumours, 980 (5.3%) were in the oral cavity/pharynx. Of these, 862 (88.0%) were malignant. Due to the fact that benign tumours in the oral cavity/pharynx were rare and had no important effect on the analyses, further investigations focused on malignant tumours only. In the 1970s and 1980s, the frequency of malignant tumours in the oral cavity/pharynx compared
with overall tumour findings ranged between 0 and 4%. In the 1990s their frequency increased and the relative frequencies have remained between 3 and 7% ever since (Fig.22).

Fig. 22. Relative diagnosis frequency of malignant tumours in the oral cavity/pharynx (n = 862) expressed as a percentage of overall tumour diagnoses between 1965 and 2008.

The most common malignant tumours in the oral cavity/pharynx were squamous cell carcinoma and fibrosarcoma. (Fig. 23).

Fig. 23. Occurrence of the most common malignant tumour types in the oral cavity/pharynx (n = 862).

No other breed had significantly higher odds of developing a malignant tumour in the oral cavity/pharynx compared with the European shorthair cat (OR =1). Unknown breed (OR = 0.82 [0.69, 0.99]), Siamese (OR = 0.45 [0.26, 0.75]) and Abyssinian (OR = 0.14 [0.02, 0.98]) cats had significantly lower odds ratios (Fig. 24) (see supplementary data).
Fig. 24. Odds ratios (ORs) and 95% confidence intervals (CIs) for the most common breeds that develop a malignant tumour in the oral cavity/pharynx (n = 862) compared with the European shorthair cat (OR = 1).

Analyses of the influence of age revealed that the odds of developing a malignant tumour in the oral cavity/pharynx increased with age, with a mean age at diagnosis of 12.2 years. The odds of a neutered cat developing a malignant tumour in the oral cavity/pharynx were significantly higher compared with an entire cat, for both males and females. The odds of female cats developing a malignant tumour in the oral cavity/pharynx compared with male cats were significantly lower (Table 2).

3.5 Discussion

This study provides a more in-depth evaluation of data contained within the Swiss Feline Cancer Registry. The most common tumour types and their locations were analysed with respect to possible influential variables, tumour distribution and frequency over the period of study. Only results where comparisons with other studies are possible will be discussed. However, it should be kept in mind that other registries have often used different methodologies, inclusion criteria, tumour classifications and statistical evaluations, and comparisons should be interpreted with caution. On the other hand, the data collected in this study derive from a large number of samples, which could explain why in some instances previously unrecognized risk factors were uncovered. (Edit: for many breeds that have so far not been analysed due to the lack of samples, an increased
risk for certain tumours have been detected. Furthermore, analysed on neuter status are hardly found in other publications. There’s no other publication that analysed time trends of tumours over the years because most cancer registries lasted only a short time (3-5 years)). Another reason for discrepancies with previous studies could derive from true differences in the genetic structure of the Swiss cat population as compared with the populations of other studies. Probably the most interesting results with respect to the possible aetiology of tumours relate to the frequencies of fibrosarcoma and lymphoma in this study. Between 1965 and 1990, the frequency of fibrosarcomas increased from 0% to around 10% of the overall tumour diagnoses. In the 1990s, fibrosarcoma frequency increased to approximately 20% and has remained stable ever since. A number of studies have revealed an association between the use of injectable products, including vaccines against rabies and feline leukaemia virus (FeLV) and the development of sarcomas located at injection sites (feline injection site sarcomas) (Hendrick and Goldschmidt, 1991; Hendrick et al., 1992, 1994; Kass et al., 1993; Macy and Hendrick, 1996). The inactivated animal rabies vaccine was developed between the 1950s and 1960s (Cabasso et al., 1965; Dietzgen and Kuzmin, 2012). The first FeLV vaccine became available in Switzerland in 1986 (Lutz, 1986). The substantial increase in sarcomas, which started in the 1990s, might therefore be related to the introduction of the FeLV vaccine in Switzerland.

The data show that fibrosarcomas occurred more frequently in middle-aged and older cats. There was a small difference between sex and neutering status. Significant differences were found between breeds. Some breeds had odds of developing a fibrosarcoma that were more than five times lower than those of the European shorthair cat. Existing studies found that fibrosarcomas mostly occur in older cats with no breed or sex predilection (Miller et al., 1991; Goldschmidt and Shofer, 1992). The present study is the first to reveal significant differences in the development of fibrosarcomas in cats of different sex and breed. This could be due to the high number of animals in the study; however, further studies are necessary to confirm these differences.

From the 1970s to the beginning of the 1990s, lymphoma was fairly frequent (up to 38%) compared with other tumour types. In the 1990s, its frequency decreased to around 10%. Many lymphomas were caused by FeLV (Jarrett et al., 1964; Hardy, 1980). The decrease in the frequency of lymphomas in the 1990s could therefore be explained by the introduction of the FeLV vaccine into Switzerland (Lutz, 1986).

The results show that the mean age for developing lymphoma was 8.5 years. Contrary to other tumours, lymphomas were also frequent in young cats. Neutered cats had higher odds of developing lymphoma compared with entire cats, and male cats had higher odds than females. Oriental
shorthair and Somali were the only breeds with a significantly higher odds ratio than that of European shorthair cats.

Studies carried out in North America (Meincke et al., 1972; Hardy, 1981), Australia (Sabine et al., 1974) and Japan (Haga et al., 1988) found that lymphoma occurs at mean ages of 4 to 6 years. More recent studies carried out in Australia (Court et al., 1997; Gabor et al., 1998) and North America (Vail et al., 1998; Louwerens et al., 2005) determined mean ages between 8 and 11 years. High incidences of lymphoma among young cats have also been described in other studies (Dorn et al., 1968b; Sabine et al., 1974; Gabor et al., 1998). A predisposition of males has been described in some studies (Dorn et al., 1968b; Court et al., 1997; Gabor et al., 1998; Vail et al., 1998), while no association was found in others (Meincke et al., 1972; Haga et al., 1988). No predisposition of neutered cats has been described.

Siamese/Oriental breeds were found to be overrepresented in some studies (Court et al., 1997; Gabor et al., 1998; Louwerens et al., 2005), while no breed prevalence was found in others (Haga et al., 1988). However, because of limited numbers of animals, Siamese cats were pooled in a group with the Oriental breeds in these studies.

Comparing the present data with other existing studies on the most common tumour types in cats, data on cutaneous tumours are in general agreement (Bostock, 1986; Stiglmair-Herb, 1987; Jörger, 1988; Miller et al., 1991). We show a higher frequency of fibrosarcomas compared with the other study carried out in Switzerland in 1988. This is due to the increase in fibrosarcomas in the 1990s. In Germany, the frequency of fibrosarcomas was already high (43%) in 1987 (Stiglmair-Herb, 1987).

A lower frequency of lymphomas in the gastrointestinal tract was seen in the present study compared with others (Cotchin, 1952; Patnaik et al., 1975; Rissetto et al., 2011). The reason for the relatively small number of lymphomas in the gastrointestinal tract could be because information on the location of most lymphomas was missing. Another reason could be that these tumours might have been classified as something other than lymphoma when the tumour involved viscera other than the intestine.

Adenocarcinomas as the most frequent tumour type in the lung/bronchus and squamous cell carcinoma as the most frequent tumour type in the oral cavity/pharynx have also been described by other investigators (Patnaik et al., 1975; Dorn and Priester, 1976; Stebbins et al., 1989; Hahn and McEntee, 1997; Meuten, 2002; D’Costa et al., 2012).

The high number of cats and the long study period in the present investigation allowed us to show the relative frequency of feline tumours over time. To our knowledge, there is no other study that
has published comparable numbers. Changes in frequency could reveal environmental influences. However, the time-dependent differences in the prevalence of certain tumours, particularly those with an irregular course, may reveal biases in changed detection methods or success in countermeasures/preventive measures, such as vaccination. Further studies and analysis would elucidate such courses in detail.

The frequency of tumour development increases with age for all tumour types and tumour locations. Mean ages calculated in the present study all correspond well with the mean ages calculated in other studies (Cotchin, 1952, 1961; Dorn et al., 1968b; Hayden, 1971; Weijer et al., 1972; Stuenzi et al., 1974; Patnaik et al., 1975; Hayes et al., 1981; Moulton et al., 1981; Stiglmair-Herb, 1987; Jörger, 1988; Stebbins et al., 1989; Ito et al., 1996; Hahn and McEntee, 1997; Rissetto et al., 2011).

The present study revealed higher odds of developing a tumour in neutered cats than in entire cats for many tumour types and tumour locations; however, differences were sometimes very small. Higher odds in entire cats compared with neutered cats were only found for females and mammary gland tumours.

Few studies have analysed the differences between neutered and entire cats except for investigations of mammary neoplasia. The increased risk for neoplasia in this organ system in entire cats has been described in several studies. The benefit of neutering appears to be dependent on the age at which the procedure is performed (Dorn et al., 1968b; Hayes et al., 1981; Misdongp et al., 1991; Overley et al., 2005). Cotchin (1952) and Rissetto et al. (2011) described a higher risk for neutered animals of developing a tumour in the intestine. We found that females had higher odds compared with males of developing adenomas/adenocarcinomas per se, and adenocarcinomas and in the skin/subcutis (malignant tumours), mammary gland, cardiorespiratory system and lung/bronchus. Males had higher odds compared with females for the oral cavity/pharynx. Other studies found no sex differences for squamous cell carcinoma in the skin/subcutis (Cotchin, 1961; Stiglmair-Herb, 1987; Jörger, 1988). Sex predilection is controversial regarding feline gastrointestinal, lung/bronchus and oral cavity/pharyngeal tumours. Some studies note a male overrepresentation in gastrointestinal tumours and others report equal representation between the sexes (Cotchin, 1952; Patnaik et al., 1975; Turk et al., 1981; Rissetto et al., 2011). Higher frequencies in females were found by Patnaik et al. (1975) in the lung/bronchus and oral cavity/pharynx. Equal rates were described by D’Costa et al. (2012) and Dorn et al. (1968b).

In contrast to the higher number of patient records in the present study, other studies grouped feline breeds according to a limited numbers of case records. Only approximate comparisons are therefore possible. In the present study, several breeds had much lower odds ratios for developing
squamous cell carcinoma compared with European shorthair cats. Miller et al. (1991) found that Siamese cats had fewer squamous cell carcinomas than expected, although this difference was not statistically significant. An increased risk in European shorthair and a decreased risk in Siamese, Himalayan and Persian cats was reported by Goldschmidt and Hendrick (2002).

In the present study, several breeds had significantly higher odds ratios for developing a tumour in the mammary gland compared with the European shorthair cat. The highest odds ratios were shown for Oriental shorthair, Somali, Abyssinian and Siamese cats. An overrepresentation among Siamese cats was described by two other studies (Hayes et al., 1981; Ito et al., 1996). Siamese cats had significantly higher odds of developing a malignant tumour of the gastrointestinal tract and Siamese, Chartreux and Somali cats had significantly higher odds of developing a tumour in the intestines compared with the European shorthair cat. An overrepresentation among Siamese cats was described in several studies (Patnaik et al., 1975; Turk et al., 1981; Cribb, 1988; Rissetto et al., 2011).

No breed predisposition was found for tumours of the lung/bronchus. No breed predispositions were reported in other studies, except for one that described Persian cats as being overrepresented (D’Costa et al., 2012).

In conclusion, this study has focused on the most frequent tumour types and tumour locations diagnosed in cats between 1965 and 2008, and the possible influence of sex, age and breed. The sampling period of more than 40 years allowed us to construct a comprehensive retrospective feline cancer registry. Compared with existing studies of feline tumours, most results are similar, but some contradict other studies and for some results there was no comparison. Since in many studies different methodologies, inclusion criteria, tumour classifications and statistical analyses were used, it would be desirable to define for future studies, international standards for animal cancer registries.

3.6 Acknowledgments

We gratefully acknowledge the help of the IVPZ staff, D. Erni, N. S. Schenker and G. Lott, during collection and processing of primary data and all colleagues of the Collegium Helveticum, who contributed in various ways. We are grateful to the veterinary practitioners who submitted cases over a long period of time, which made this and further studies possible. Finally, we greatly appreciate H. Murray’s revision of the English version. This study was financed through the financial support of the University of Zurich to A. Pospischil for acting as a fellow at the Collegium Helveticum during his fellowship period of 2009 to 2016. This chapter has been published as:
### 3.7 Supplementary Data

Odds ratios (OR) and 95% confidence intervals (CI) for adenomas/adenocarcinomas (benign and malignant) and adenocarcinomas (malignant) for the most common cat breeds compared to those for the European Shorthair cat (OR=1)

<table>
<thead>
<tr>
<th>Breed</th>
<th>Adenoma /Adenocarcinoma (benign + malignant)</th>
<th>Adenocarcinoma (malignant)</th>
<th>P-Value</th>
<th>OR and 95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Shorthair</td>
<td>1 (Standard)</td>
<td>1 (Standard)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown Breed</td>
<td>1.10 (1.01; 1.21)</td>
<td>1.21 (1.09; 1.34)</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persian</td>
<td>1.15 (1.00; 1.32)</td>
<td>1.25 (1.07; 1.47)</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siamese</td>
<td>1.92 (1.64; 2.24)</td>
<td>2.44 (2.07; 2.89)</td>
<td>0.00</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Maine Coon</td>
<td>0.98 (0.71; 1.37)</td>
<td>0.68 (0.42; 1.10)</td>
<td>0.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abyssinian</td>
<td>1.25 (0.84; 1.85)</td>
<td>1.51 (0.98; 2.33)</td>
<td>0.28</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Other Breeds</td>
<td>1.05 (0.68; 1.65)</td>
<td>1.44 (0.90; 2.32)</td>
<td>0.84</td>
<td></td>
<td>0.13</td>
</tr>
<tr>
<td>British Shorthair</td>
<td>0.73 (0.43; 1.23)</td>
<td>0.67 (0.34; 1.30)</td>
<td>0.24</td>
<td></td>
<td>0.23</td>
</tr>
<tr>
<td>Birman</td>
<td>1.16 (0.76; 1.80)</td>
<td>1.38 (0.85; 2.34)</td>
<td>0.49</td>
<td></td>
<td>0.20</td>
</tr>
<tr>
<td>Chartreux</td>
<td>1.89 (1.31; 2.74)</td>
<td>1.78 (1.14; 2.78)</td>
<td>0.00</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Norwegian Forest</td>
<td>0.69 (0.39; 1.20)</td>
<td>0.72 (0.37; 1.42)</td>
<td>0.19</td>
<td></td>
<td>0.35</td>
</tr>
<tr>
<td>Domestic Longhair</td>
<td>0.52 (0.28; 0.99)</td>
<td>0.69 (0.35; 1.36)</td>
<td>0.05</td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>Burmesian</td>
<td>0.52 (0.21; 1.27)</td>
<td>0.61 (0.22; 1.66)</td>
<td>0.15</td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>Turkish Angora</td>
<td>1.13 (0.62; 2.06)</td>
<td>1.20 (0.60; 2.38)</td>
<td>0.68</td>
<td></td>
<td>0.60</td>
</tr>
<tr>
<td>Mixed Breed</td>
<td>0.60 (0.24; 1.48)</td>
<td>0.65 (0.24; 1.78)</td>
<td>0.27</td>
<td></td>
<td>0.41</td>
</tr>
<tr>
<td>Oriental Shorthair</td>
<td>1.87 (0.96; 3.65)</td>
<td>2.86 (1.45; 5.61)</td>
<td>0.07</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ragdoll</td>
<td>1.20 (0.55; 2.63)</td>
<td>1.57 (0.68; 3.65)</td>
<td>0.65</td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>Somali</td>
<td>1.70 (0.89; 3.24)</td>
<td>2.04 (1.01; 4.13)</td>
<td>0.11</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Devon Rex</td>
<td>0.28 (0.07; 1.15)</td>
<td>0.42 (0.10; 1.72)</td>
<td>0.08</td>
<td></td>
<td>0.23</td>
</tr>
</tbody>
</table>
Odds ratios (OR) and 95% confidence intervals (CI) for fibrosarcomas for the most common cat breeds compared to those for the European Shorthair cat (OR=1)

<table>
<thead>
<tr>
<th>Breed</th>
<th>Fibrosarcoma</th>
<th>Odds Ratio (OR) and 95% Confidence Interval (CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Shorthair</td>
<td></td>
<td>1 (Standard)</td>
<td></td>
</tr>
<tr>
<td>Unknown Breed</td>
<td>0.99 (0.90; 1.08)</td>
<td></td>
<td>0.80</td>
</tr>
<tr>
<td>Persian</td>
<td>0.30 (0.24; 0.37)</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Siamese</td>
<td>0.36 (0.27; 0.48)</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Maine Coon</td>
<td>0.48 (0.33; 0.70)</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Abyssinian</td>
<td>0.14 (0.05; 0.36)</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Other Breeds</td>
<td>0.20 (0.09; 0.45)</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>British Shorthair</td>
<td>0.18 (0.08; 0.40)</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Birman</td>
<td>0.17 (0.07; 0.41)</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Chartreux</td>
<td>0.44 (0.24; 0.79)</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Norwegian Forest</td>
<td>0.31 (0.16; 0.61)</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Domestic Longhair</td>
<td>0.67 (0.39; 1.13)</td>
<td></td>
<td>0.13</td>
</tr>
<tr>
<td>Burmesian</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turkish Angora</td>
<td>1.00 (0.54; 1.88)</td>
<td></td>
<td>0.99</td>
</tr>
<tr>
<td>Mixed Breed</td>
<td>1.60 (0.76; 3.37)</td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td>Oriental Shorthair</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ragdoll</td>
<td>0.11 (0.02; 0.81)</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Somali</td>
<td>0.20 (0.05; 0.81)</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Devon Rex</td>
<td>0.68 (0.29; 1.57)</td>
<td></td>
<td>0.36</td>
</tr>
</tbody>
</table>
Odds ratios (OR) and 95% confidence intervals (CI) for malignant lymphoma for the most common cat breeds compared to those for the European Shorthair cat (OR=1)

<table>
<thead>
<tr>
<th>Breed</th>
<th>Malignant Lymphoma</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (OR) and 95% Confidence Interval (CI)</td>
<td></td>
</tr>
<tr>
<td>European Shorthair</td>
<td>1 (Standard)</td>
<td></td>
</tr>
<tr>
<td>Unknown Breed</td>
<td>1.21 (1.10; 1.34)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Persian</td>
<td>0.57 (0.47; 0.70)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Siamese</td>
<td>1.20 (0.99; 1.45)</td>
<td>0.06</td>
</tr>
<tr>
<td>Maine Coon</td>
<td>0.49 (0.31; 0.76)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Abyssinian</td>
<td>0.81 (0.49; 1.32)</td>
<td>0.40</td>
</tr>
<tr>
<td>Other Breeds</td>
<td>0.44 (0.23; 0.87)</td>
<td>0.02</td>
</tr>
<tr>
<td>British Shorthair</td>
<td>0.45 (0.23; 0.87)</td>
<td>0.02</td>
</tr>
<tr>
<td>Birman</td>
<td>0.58 (0.32; 1.06)</td>
<td>0.08</td>
</tr>
<tr>
<td>Chartreux</td>
<td>0.96 (0.60; 1.54)</td>
<td>0.87</td>
</tr>
<tr>
<td>Norwegian Forest</td>
<td>0.43 (0.21; 0.88)</td>
<td>0.02</td>
</tr>
<tr>
<td>Domestic Longhair</td>
<td>0.74 (0.41; 1.33)</td>
<td>0.32</td>
</tr>
<tr>
<td>Burmesian</td>
<td>0.97 (0.52; 1.79)</td>
<td>0.92</td>
</tr>
<tr>
<td>Turkish Angora</td>
<td>0.78 (0.38; 1.59)</td>
<td>0.49</td>
</tr>
<tr>
<td>Mixed Breed</td>
<td>1.03 (0.50; 2.11)</td>
<td>0.95</td>
</tr>
<tr>
<td>Oriental Shorthair</td>
<td>1.89 (1.05; 3.39)</td>
<td>0.03</td>
</tr>
<tr>
<td>Ragdoll</td>
<td>0.30 (0.07; 1.23)</td>
<td>0.10</td>
</tr>
<tr>
<td>Somali</td>
<td>2.59 (1.40; 4.78)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Devon Rex</td>
<td>0.44 (0.11; 1.78)</td>
<td>0.25</td>
</tr>
</tbody>
</table>
Odds ratios (OR) and 95% confidence intervals (CI) for squamous cell carcinoma for the most common cat breeds compared to those for the European Shorthair cat (OR=1)

<table>
<thead>
<tr>
<th>Breed</th>
<th>Squamous Cell Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (OR) and 95% Confidence Interval (CI)</td>
</tr>
<tr>
<td>European Shorthair</td>
<td>1 (Standard)</td>
</tr>
<tr>
<td>Unknown Breed</td>
<td>0.83 (0.74; 0.94)</td>
</tr>
<tr>
<td>Persian</td>
<td>0.51 (0.40; 0.64)</td>
</tr>
<tr>
<td>Siamese</td>
<td>0.22 (0.14; 0.36)</td>
</tr>
<tr>
<td>Maine Coon</td>
<td>0.17 (0.08; 0.39)</td>
</tr>
<tr>
<td>Abyssinian</td>
<td>0.24 (0.09; 0.65)</td>
</tr>
<tr>
<td>Other Breeds</td>
<td>0.64 (0.34; 1.21)</td>
</tr>
<tr>
<td>British Shorthair</td>
<td>0.30 (0.12; 0.72)</td>
</tr>
<tr>
<td>Birman</td>
<td>0.19 (0.06; 0.59)</td>
</tr>
<tr>
<td>Chartreux</td>
<td>0.33 (0.14; 0.80)</td>
</tr>
<tr>
<td>Norwegian Forest</td>
<td>0.20 (0.06; 0.62)</td>
</tr>
<tr>
<td>Domestic Longhair</td>
<td>0.47 (0.21; 1.05)</td>
</tr>
<tr>
<td>Burmesian</td>
<td>None</td>
</tr>
<tr>
<td>Turkish Angora</td>
<td>0.57 (0.21; 1.55)</td>
</tr>
<tr>
<td>Mixed Breed</td>
<td>None</td>
</tr>
<tr>
<td>Oriental Shorthair</td>
<td>None</td>
</tr>
<tr>
<td>Ragdoll</td>
<td>None</td>
</tr>
<tr>
<td>Somali</td>
<td>0.19 (0.03; 1.37)</td>
</tr>
<tr>
<td>Devon Rex</td>
<td>0.41 (0.10; 1.68)</td>
</tr>
</tbody>
</table>
Odds ratios (OR) and 95% confidence intervals (CI) for tumours of the skin and subcutis (all tumours and malignant tumours) for the most common cat breeds compared to those for the European Shorthair cat (OR=1)

<table>
<thead>
<tr>
<th>Breed</th>
<th>OR and 95% CI</th>
<th>P-Value</th>
<th>OR and 95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Shorthair</td>
<td>1 (Standard)</td>
<td></td>
<td>1 (Standard)</td>
<td></td>
</tr>
<tr>
<td>Unknown Breed</td>
<td>0.81 (0.76; 0.86)</td>
<td>0.00</td>
<td>0.79 (0.74; 0.85)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Persian</td>
<td>0.47 (0.42; 0.53)</td>
<td>0.00</td>
<td>0.34 (0.29; 0.40)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Siamese</td>
<td>0.48 (0.40; 0.56)</td>
<td>0.00</td>
<td>0.41 (0.33; 0.50)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Maine Coon</td>
<td>0.29 (0.21; 0.39)</td>
<td>0.00</td>
<td>0.27 (0.19; 0.39)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Abyssinian</td>
<td>0.19 (0.11; 0.32)</td>
<td>0.00</td>
<td>0.17 (0.09; 0.31)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Other Breeds</td>
<td>0.30 (0.20; 0.47)</td>
<td>0.00</td>
<td>0.32 (0.20; 0.51)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>British Shorthair</td>
<td>0.23 (0.15; 0.37)</td>
<td>0.00</td>
<td>0.14 (0.07; 0.28)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Birman</td>
<td>0.17 (0.10; 0.29)</td>
<td>0.00</td>
<td>0.14 (0.07; 0.28)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Chartreux</td>
<td>0.42 (0.28; 0.62)</td>
<td>0.00</td>
<td>0.40 (0.25; 0.62)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Norwegian Forest</td>
<td>0.33 (0.21; 0.50)</td>
<td>0.00</td>
<td>0.22 (0.12; 0.39)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Domestic Longhair</td>
<td>0.54 (0.37; 0.79)</td>
<td>0.00</td>
<td>0.62 (0.42; 0.94)</td>
<td>0.02</td>
</tr>
<tr>
<td>Burmesian</td>
<td>0.27 (0.13; 0.56)</td>
<td>0.00</td>
<td>0.04 (0.01; 0.30)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Turkish Angora</td>
<td>0.91 (0.59; 1.42)</td>
<td>0.69</td>
<td>0.74 (0.44; 1.24)</td>
<td>0.25</td>
</tr>
<tr>
<td>Mixed Breed</td>
<td>0.35 (0.16; 0.77)</td>
<td>0.01</td>
<td>0.27 (0.10; 0.73)</td>
<td>0.01</td>
</tr>
<tr>
<td>Oriental Shorthair</td>
<td>0.10 (0.02; 0.40)</td>
<td>0.00</td>
<td>0.13 (0.03; 0.53)</td>
<td>0.01</td>
</tr>
<tr>
<td>Ragdoll</td>
<td>0.32 (0.15; 0.71)</td>
<td>0.01</td>
<td>0.18 (0.06; 0.56)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Somali</td>
<td>0.19 (0.08; 0.47)</td>
<td>0.00</td>
<td>0.26 (0.11; 0.65)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Devon Rex</td>
<td>0.39 (0.19; 0.79)</td>
<td>0.01</td>
<td>0.54 (0.27; 1.08)</td>
<td>0.08</td>
</tr>
</tbody>
</table>
Odds ratios (OR) and 95% confidence intervals (CI) for tumours of the skin (without subcutis) (all tumours and malignant tumours) for the most common cat breeds compared to those for the European Shorthair cat (OR=1)

<table>
<thead>
<tr>
<th>Breed</th>
<th>All tumours of the skin</th>
<th>Malignant tumours of the skin</th>
<th>P-Value</th>
<th>Odds Ratio (OR) and 95% Confidence Interval (CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Shorthair</td>
<td>1 (Standard)</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Unknown Breed</td>
<td>0.78 (0.72; 0.84)</td>
<td>0.00</td>
<td></td>
<td>0.72 (0.66; 0.79)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Persian</td>
<td>0.62 (0.54; 0.71)</td>
<td>0.00</td>
<td></td>
<td>0.41 (0.34; 0.50)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Siamese</td>
<td>0.56 (0.47; 0.68)</td>
<td>0.00</td>
<td></td>
<td>0.44 (0.34; 0.56)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Maine Coon</td>
<td>0.29 (0.19; 0.43)</td>
<td>0.00</td>
<td></td>
<td>0.23 (0.13; 0.39)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Abyssinian</td>
<td>0.26 (0.14; 0.46)</td>
<td>0.00</td>
<td></td>
<td>0.22 (0.11; 0.47)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Other Breeds</td>
<td>0.41 (0.25; 0.66)</td>
<td>0.00</td>
<td></td>
<td>0.45 (0.25; 0.78)</td>
<td>0.01</td>
</tr>
<tr>
<td>British Shorthair</td>
<td>0.28 (0.16; 0.49)</td>
<td>0.00</td>
<td></td>
<td>0.13 (0.05; 0.35)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Birman</td>
<td>0.18 (0.09; 0.36)</td>
<td>0.00</td>
<td></td>
<td>0.10 (0.03; 0.31)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Chartreux</td>
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<td>0.00</td>
<td></td>
<td>0.47 (0.27; 0.82)</td>
<td>0.01</td>
</tr>
<tr>
<td>Norwegian Forest</td>
<td>0.44 (0.27; 0.72)</td>
<td>0.00</td>
<td></td>
<td>0.25 (0.12; 0.54)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Domestic Longhair</td>
<td>0.51 (0.31; 0.83)</td>
<td>0.01</td>
<td></td>
<td>0.59 (0.34; 1.02)</td>
<td>0.06</td>
</tr>
<tr>
<td>Burmesian</td>
<td>0.45 (0.22; 0.93)</td>
<td>0.03</td>
<td></td>
<td>0.08 (0.01; 0.55)</td>
<td>0.01</td>
</tr>
<tr>
<td>Turkish Angora</td>
<td>0.91 (0.54; 1.52)</td>
<td>0.71</td>
<td></td>
<td>0.67 (0.34; 1.32)</td>
<td>0.25</td>
</tr>
<tr>
<td>Mixed Breed</td>
<td>0.37 (0.15; 0.92)</td>
<td>0.03</td>
<td></td>
<td>0.21 (0.05; 0.84)</td>
<td>0.03</td>
</tr>
<tr>
<td>Oriental Shorthair</td>
<td>0.17 (0.04; 0.68)</td>
<td>0.01</td>
<td></td>
<td>0.24 (0.06; 1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Ragdoll</td>
<td>0.57 (0.26; 1.25)</td>
<td>0.16</td>
<td></td>
<td>0.35 (0.11; 1.13)</td>
<td>0.08</td>
</tr>
<tr>
<td>Somali</td>
<td>0.20 (0.06; 0.63)</td>
<td>0.01</td>
<td></td>
<td>0.31 (0.10; 0.99)</td>
<td>0.05</td>
</tr>
<tr>
<td>Devon Rex</td>
<td>0.21 (0.07; 0.67)</td>
<td>0.01</td>
<td></td>
<td>0.33 (0.11; 1.06)</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Odds ratios (OR) and 95% confidence intervals (CI) for tumours of the mamma (all tumours and malignant tumours) for the most common cat breeds compared to those for the European Shorthair cat (OR=1)

<table>
<thead>
<tr>
<th>Breed</th>
<th>All tumours of the mamma</th>
<th>P-Value</th>
<th>Malignant tumours of the mamma</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Shorthair</td>
<td>1 (Standard)</td>
<td></td>
<td>1 (Standard)</td>
<td></td>
</tr>
<tr>
<td>Unknown Breed</td>
<td>1.50 (1.31; 1.72)</td>
<td>0.00</td>
<td>1.54 (1.32; 1.78)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Persian</td>
<td>2.00 (1.64; 2.43)</td>
<td>0.00</td>
<td>1.74 (1.39; 2.18)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Siamese</td>
<td>3.68 (2.97; 4.56)</td>
<td>0.00</td>
<td>4.01 (3.21; 5.03)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Maine Coon</td>
<td>1.33 (0.79; 2.23)</td>
<td>0.28</td>
<td>1.00 (0.53; 1.91)</td>
<td>0.99</td>
</tr>
<tr>
<td>Abyssinian</td>
<td>4.46 (2.91; 6.82)</td>
<td>0.00</td>
<td>5.01 (3.23; 7.77)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Other Breeds</td>
<td>2.10 (1.17; 3.76)</td>
<td>0.01</td>
<td>2.36 (1.29; 4.33)</td>
<td>0.01</td>
</tr>
<tr>
<td>British Shorthair</td>
<td>0.61 (0.22; 1.66)</td>
<td>0.33</td>
<td>0.56 (0.18; 1.77)</td>
<td>0.32</td>
</tr>
<tr>
<td>Birman</td>
<td>2.76 (1.60; 4.78)</td>
<td>0.00</td>
<td>3.43 (1.98; 5.95)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Chartreux</td>
<td>1.98 (1.07; 3.63)</td>
<td>0.03</td>
<td>1.77 (0.88; 3.53)</td>
<td>0.11</td>
</tr>
<tr>
<td>Norwegian Forest</td>
<td>2.35 (1.31; 4.23)</td>
<td>0.00</td>
<td>2.16 (1.11; 4.17)</td>
<td>0.02</td>
</tr>
<tr>
<td>Domestic Longhair</td>
<td>0.78 (0.31; 1.91)</td>
<td>0.58</td>
<td>0.56 (0.18; 1.78)</td>
<td>0.33</td>
</tr>
<tr>
<td>Burmesian</td>
<td>0.72 (0.17; 3.00)</td>
<td>0.66</td>
<td>0.89 (0.21; 3.69)</td>
<td>0.87</td>
</tr>
<tr>
<td>Turkish Angora</td>
<td>2.46 (1.16; 5.23)</td>
<td>0.02</td>
<td>2.18 (0.93; 5.12)</td>
<td>0.07</td>
</tr>
<tr>
<td>Mixed Breed</td>
<td>0.57 (0.08; 4.18)</td>
<td>0.58</td>
<td>0.70 (0.10; 5.14)</td>
<td>0.73</td>
</tr>
<tr>
<td>Oriental Shorthair</td>
<td>6.14 (2.75; 13.69)</td>
<td>0.00</td>
<td>7.59 (3.4; 16.98)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ragdoll</td>
<td>1.56 (0.47; 5.20)</td>
<td>0.47</td>
<td>1.94 (0.58; 6.47)</td>
<td>0.28</td>
</tr>
<tr>
<td>Somali</td>
<td>4.64 (2.28; 9.46)</td>
<td>0.00</td>
<td>5.72 (2.80; 11.70)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Devon Rex</td>
<td>1.15 (0.35; 3.73)</td>
<td>0.82</td>
<td>1.42 (0.43; 4.61)</td>
<td>0.56</td>
</tr>
</tbody>
</table>
Odds ratios (OR) and 95% confidence intervals (CI) for malignant tumours of the gastrointestinal tract for the most common cat breeds compared to those for the European Shorthair cat (OR=1)

<table>
<thead>
<tr>
<th>Breed</th>
<th>Malignant tumours of the gastrointestinal tract</th>
<th>Odds Ratio (OR) and 95% Confidence Interval (CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Shorthair</td>
<td>1 (Standard)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown Breed</td>
<td>0.91 (0.78; 1.06)</td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>Persian</td>
<td>0.64 (0.48; 0.84)</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Siamese</td>
<td>1.45 (1.12; 1.87)</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Maine Coon</td>
<td>0.45 (0.22; 0.91)</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Abyssinian</td>
<td>0.63 (0.28; 1.42)</td>
<td></td>
<td>0.26</td>
</tr>
<tr>
<td>Other Breeds</td>
<td>0.57 (0.24; 1.39)</td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td>British Shorthair</td>
<td>0.46 (0.17; 1.23)</td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>Birman</td>
<td>0.47 (0.17; 1.25)</td>
<td></td>
<td>0.13</td>
</tr>
<tr>
<td>Chartreux</td>
<td>1.17 (0.62; 2.21)</td>
<td></td>
<td>0.62</td>
</tr>
<tr>
<td>Norwegian Forest</td>
<td>0.50 (0.19; 1.35)</td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>Domestic Longhair</td>
<td>0.83 (0.37; 1.88)</td>
<td></td>
<td>0.66</td>
</tr>
<tr>
<td>Burmesian</td>
<td>1.04 (0.43; 2.54)</td>
<td></td>
<td>0.93</td>
</tr>
<tr>
<td>Turkish Angora</td>
<td>0.88 (0.33; 2.39)</td>
<td></td>
<td>0.81</td>
</tr>
<tr>
<td>Mixed Breed</td>
<td>0.27 (0.04; 1.93)</td>
<td></td>
<td>0.19</td>
</tr>
<tr>
<td>Oriental Shorthair</td>
<td>0.98 (0.31; 3.11)</td>
<td></td>
<td>0.98</td>
</tr>
<tr>
<td>Ragdoll</td>
<td>0.73 (0.18; 2.98)</td>
<td></td>
<td>0.67</td>
</tr>
<tr>
<td>Somali</td>
<td>2.13 (0.86; 5.27)</td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>Devon Rex</td>
<td>None</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Odds ratios (OR) and 95% confidence intervals (CI) for malignant tumours of the intestine for the most common cat breeds compared to those for the European Shorthair cat (OR=1)

<table>
<thead>
<tr>
<th>Breed</th>
<th>Malignant tumours of the intestine</th>
<th>Odds Ratio (OR) and 95% Confidence Interval (CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Shorthair</td>
<td>1 (Standard)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown Breed</td>
<td>0.90 (0.73; 1.10)</td>
<td></td>
<td>0.31</td>
</tr>
<tr>
<td>Persian</td>
<td>0.49 (0.32; 0.76)</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Siamese</td>
<td>1.92 (1.40; 2.64)</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Maine Coon</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abyssinian</td>
<td>0.67 (0.21; 2.09)</td>
<td></td>
<td>0.48</td>
</tr>
<tr>
<td>Other Breeds</td>
<td>0.50 (0.12; 2.00)</td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>British Shorthair</td>
<td>0.52 (0.13; 2.09)</td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>Birman</td>
<td>0.75 (0.24; 2.36)</td>
<td></td>
<td>0.63</td>
</tr>
<tr>
<td>Chartreux</td>
<td>2.65 (1.39; 5.02)</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Norwegian Forest</td>
<td>0.85 (0.27; 2.67)</td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td>Domestic Longhair</td>
<td>0.60 (0.15; 2.41)</td>
<td></td>
<td>0.47</td>
</tr>
<tr>
<td>Burmesian</td>
<td>1.44 (0.46; 4.54)</td>
<td></td>
<td>0.53</td>
</tr>
<tr>
<td>Turkish Angora</td>
<td>0.91 (0.23; 3.70)</td>
<td></td>
<td>0.90</td>
</tr>
<tr>
<td>Mixed Breed</td>
<td>0.49 (0.07; 3.51)</td>
<td></td>
<td>0.48</td>
</tr>
<tr>
<td>Oriental Shorthair</td>
<td>1.58 (0.39; 6.45)</td>
<td></td>
<td>0.52</td>
</tr>
<tr>
<td>Ragdoll</td>
<td>0.87 (0.12; 6.29)</td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td>Somali</td>
<td>3.41 (1.25; 9.36)</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Devon Rex</td>
<td>None</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Odds ratios (OR) and 95% confidence intervals (CI) for malignant tumours of the respiratory system for the most common cat breeds compared to those for the European Shorthair cat (OR=1)

<table>
<thead>
<tr>
<th>Breed</th>
<th>Malignant tumours of the respiratory system</th>
<th>Odds Ratio (OR) and 95% Confidence Interval (CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Shorthair</td>
<td>1 (Standard)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown Breed</td>
<td>0.93 (0.79; 1.10)</td>
<td></td>
<td>0.42</td>
</tr>
<tr>
<td>Persian</td>
<td>0.93 (0.72; 1.20)</td>
<td></td>
<td>0.56</td>
</tr>
<tr>
<td>Siamese</td>
<td>1.05 (0.76; 1.45)</td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>Maine Coon</td>
<td>0.57 (0.31; 1.08)</td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>Abyssinian</td>
<td>0.24 (0.06; 0.95)</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Other Breeds</td>
<td>1.27 (0.67; 2.39)</td>
<td></td>
<td>0.47</td>
</tr>
<tr>
<td>British Shorthair</td>
<td>0.46 (0.17; 1.25)</td>
<td></td>
<td>0.13</td>
</tr>
<tr>
<td>Birman</td>
<td>0.13 (0.02; 0.92)</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Chartreux</td>
<td>1.48 (0.82; 2.65)</td>
<td></td>
<td>0.19</td>
</tr>
<tr>
<td>Norwegian Forest</td>
<td>0.51 (0.19; 1.38)</td>
<td></td>
<td>0.19</td>
</tr>
<tr>
<td>Domestic Longhair</td>
<td>1.51 (0.80; 2.87)</td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>Burmesian</td>
<td>0.88 (0.32; 2.38)</td>
<td></td>
<td>0.80</td>
</tr>
<tr>
<td>Turkish Angora</td>
<td>0.50 (0.12; 2.02)</td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>Mixed Breed</td>
<td>0.85 (0.21; 3.48)</td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td>Oriental Shorthair</td>
<td>1.33 (0.49; 3.63)</td>
<td></td>
<td>0.58</td>
</tr>
<tr>
<td>Ragdoll</td>
<td>0.71 (0.17; 2.90)</td>
<td></td>
<td>0.63</td>
</tr>
<tr>
<td>Somali</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Devon Rex</td>
<td>None</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Odds ratios (OR) and 95% confidence intervals (CI) for malignant tumours of the mouth/pharynx for the most common cat breeds compared to those for the European Shorthair cat (OR=1)

<table>
<thead>
<tr>
<th>Breed</th>
<th>Malignant tumours of the oral cavity/pharynx</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (OR) and 95% Confidence Interval (CI)</td>
</tr>
<tr>
<td>European Shorthair</td>
<td>1 (Standard)</td>
</tr>
<tr>
<td>Unknown Breed</td>
<td>0.82 (0.69; 0.99)</td>
</tr>
<tr>
<td>Persian</td>
<td>0.86 (0.65; 1.13)</td>
</tr>
<tr>
<td>Siamese</td>
<td>0.45 (0.26; 0.75)</td>
</tr>
<tr>
<td>Maine Coon</td>
<td>0.73 (0.41; 1.31)</td>
</tr>
<tr>
<td>Abyssinian</td>
<td>0.14 (0.02; 0.98)</td>
</tr>
<tr>
<td>Other Breeds</td>
<td>0.54 (0.20; 1.46)</td>
</tr>
<tr>
<td>British Shorthair</td>
<td>0.61 (0.25; 1.50)</td>
</tr>
<tr>
<td>Birman</td>
<td>0.41 (0.13; 1.27)</td>
</tr>
<tr>
<td>Chartreux</td>
<td>0.58 (0.21; 1.55)</td>
</tr>
<tr>
<td>Norwegian Forest</td>
<td>0.56 (0.21; 1.52)</td>
</tr>
<tr>
<td>Domestic Longhair</td>
<td>0.52 (0.17; 1.63)</td>
</tr>
<tr>
<td>Burmesian</td>
<td>0.70 (0.17; 2.86)</td>
</tr>
<tr>
<td>Turkish Angora</td>
<td>1.00 (0.32; 3.15)</td>
</tr>
<tr>
<td>Mixed Breed</td>
<td>None</td>
</tr>
<tr>
<td>Oriental Shorthair</td>
<td>1.62 (0.51; 5.15)</td>
</tr>
<tr>
<td>Ragdoll</td>
<td>0.92 (0.23; 3.76)</td>
</tr>
<tr>
<td>Somali</td>
<td>None</td>
</tr>
<tr>
<td>Devon Rex</td>
<td>0.45 (0.06; 3.22)</td>
</tr>
</tbody>
</table>
4. General Discussion

Cancer is a major cause of death in man and companion animals. The prevalence of cancer continues to rise for a variety of reasons, not the least of which is related to humans and animals living longer thanks to improvements in medical care. Cancer registries are important tools for establishing cancer control and prevention strategies. They are used in epidemiological research to examine possible risk factors underlying the incidence of different types of cancer. The idea of recording information on human cancer cases in a defined population dates from the first half of the twentieth century. (Parkin, 2006, 2008; Withrow et al., 2013) Although the importance of cancer registries is known, cancer registries of companion animal tumours are rare and do not cover more than a couple of years, which is unfortunate, because they would provide an excellent opportunity for investigating many aspects of cancer, from etiology to treatment, from a comparative oncology standpoint (Vail & MacEwen, 2000; Brønden et al., 2007; Nødtvedt et al., 2011; Withrow et al., 2013). This epidemiological work, the feline cancer registry and the subsequent risk factor analyses, laid the foundation for further scientific research.

4.1 Epidemiology

Epidemiology is the study and analysis of disease in defined populations and factors that determine its occurrence. It is the cornerstone of public health, and shapes evidence-based medical and veterinary practice by identifying risk factors for disease and targets for preventive healthcare. Initially, epidemiologic knowledge advanced slowly, with large segments in time where little or no advancement in the field occurred. Hippocrates (460-377 BC) was the first known epidemiologist who attempted to describe disease from a rational perspective and introduced terms like endemic and epidemic. His proposals to observe how diseases affect populations and how diseases spread, as well as observing and describing all contributing or causal factors of disease, like seasons, place and environmental conditions are still sound epidemiological concepts (Garrison, 1913; Cumston, 1926; Hippocrates, 1988)

Historically, epidemiology was centred on the study of major epidemics like cholera, bubonic plague, rinderpest, smallpox and typhus. Through empirical approaches involving close observations of population and environment, diseases were identified and differentiated. Causal factors were distinguished and, when possible, eliminated (Timmereck, 2002).
One of the great contributors, who has been referred to by many as the Father of Epidemiology, was John Snow (1813 -1858). Many of the concepts, approaches and methods used by Snow in his epidemiologic work are still useful and valuable in epidemiologic work today (Timmereck, 2002). Throughout his medical career, Snow mainly studied cholera (pathogen: Vibrio cholera). The conventional theory at that time was that cholera was an airborne infection (miasmatic theory introduced by Hippocrates) transmitted through foul smelling odours. Snow recorded detailed scenarios of many first-hand witnessed cases of cholera, including incubation times, cause-effect relations, clinical observations and manifestations of the disease, diets, water (also microscopic observations) and the differences between healthy and sick people. The collected scientific data, led him to question miasma theories and to publish the first edition of “On the Mode of Communication of Cholera” in 1849, in which he proposed that cholera was attributable to a self-replicating agent that was excreted in the cholera evacuations and inadvertently ingested, often, but not necessarily, through the medium of water (Snow, 1855, 1988; Benenson, 1990; Timmereck, 2002). Snow conducted two major investigations of cholera outbreaks in London in the 1850s where he could test his hypothesis. A major outbreak of cholera occurred in the Soho and Golden Square districts that led to about 500 fatal attacks in 10 days. Snow calculated statistics based on dates and mortality rates, studied sources of contamination of the water and the flow of the water in the underground aquifer by assessing water from wells and pumps. He used a spot map, to identify the locations of all deaths, occurrence of new cases, sources of exposure and transmission of the disease among people and possible causation, and found that nearly all deaths had taken place within a short distance of the Broad Street pump and convinced the local council to remove the pump handle, which was largely responsible for the spread of the disease. In the second major outbreak he conducted an analytical epidemiological investigation of the cholera epidemic, in which he finally compared death rates from the disease for the two water companies that supplied different regions with water. He employed a comparison group to establish a cause-effect association and ultimately presented conclusive evidence as to the source of contamination (Snow, 1988; Benenson, 1990; Timmereck, 2002; Vinten-Johansen et al., 2003; Ramsay, 2006). The work of John Snow clearly demonstrates the importance of strict observations, descriptions and exploration of available factors. Snow made no interferences, he just described what he observed, which factors were available and if there were any correlations between these factors and the disease. He proposed hypotheses, tested the factors with correlations for causality and evaluated triggers of disease.

In the beginning, veterinary epidemiology and veterinary medicine was governed mainly by economic motives associated with the importance of domestic stock as a source of food and as
working animals. The major problems were large-scale outbreaks of infectious diseases like bovine tuberculosis or foot-and-mouth disease (Thrusfield, 2007). The inception and acceptance of the microbial theory in the 1860s, due largely to the work of Pasteur and Koch, who also confirmed Snow's work by the isolation and cultivation of Vibrio cholera, changed the face of medicine (Ford, 1911; Dunlop, 1928; Sakula, 1983; Timmereck, 2002; Waller, 2003; Thrusfield, 2007). The specific cause of an infectious disease could be defined, which led to suitable control strategies. Prevention and eradication of infectious diseases involved testing and, finally, immunization of all animals when an increasing number of vaccines became available (Thrusfield, 2007). Following the control of the major infectious diseases and the ageing of our society, non-infectious diseases like cancer have increased in importance. A landmark in cancer epidemiology was the establishment of tobacco as a carcinogen. First observational studies that suggested an association of tobacco with cancer were published as early as the 1700s (Hill, 1761). However, it took until the 1950s before strong experimental and epidemiological evidence proved that smoking was responsible for lung cancer (Doll & Hill, 1950; Wynder & Graham, 1950). The first malignant disease that was connected with a specific occupation was described by an English surgeon named Percival Pott in 1775. He observed a high incidence of scrotal cancer in young adults who worked as chimney sweeps. The cause of chimney sweeps' cancer was blamed on chronic exposure of the scrotum to soot. Sir Henry T. Butlin (1845-1912) carefully investigated the incidence of scrotum cancer abroad and found it to be extremely rare outside of England. The reasons he established were the lack of protective clothes and the disregard of personal hygiene among chimney sweeps in England (Brown & Thornton, 1957; Kipling & Waldron, 1975; Waldron, 1983; Herr, 2011).

4.2 Epidemiology of malignant lymphoma

A nice illustrative example in animal cancer epidemiology is the study of malignant lymphoma in cats. In 1963, Schneider et al (1967) drew attention to a household where an unusually large aggregation of malignant lymphoma cases occurred in cats. At this time, reports of aggregations of lymphoma existed only in humans (Johnson & Peters, 1957; Gilmore & Zelesnick, 1962) and in cattle herds (Bendixen, 1963; Croshaw et al., 1963; Theilen et al., 1964). During the 3-year study of Schneider et al. (1967), 6 out of 34 cats, all living in the same family household, died of malignant lymphoma. This was far higher than the 42 cases/100’000 cats, observed by a study from a nearby county (Dorn et al., 1967). Schneider described and analysed as many aspects as possible. During his study, the family changed their residence three times. Schneider's group observed all the houses, where they were located and the environment of the residences. He compared age, sex, food,
available vaccinations, the health of the owner, and the relations among the cats. He concluded that possibly both genetic factors and an infectious agent might be involved in the occurrence of malignant lymphoma in cats, and that the disease favoured cats born in the spring. This epidemiological study found three correlations that could explain the transmission and occurrence of malignant lymphoma, and which further could be tested for causation. Subsequent studies confirmed the hypothesis that lymphoma is transmitted through an infectious agent (feline leukaemia virus (FeLV)) either via infection or transmission from cat to kitten (Jarrett et al., 1964, 1973; Kawakami et al., 1967; Laird et al., 1968; Brodey et al., 1969; Hardy et al., 1973, 1976). These findings finally led to the development of vaccines against the virus (Jarrett et al., 1975; John et al., 1976), which have saved the lives of many cats. It has been reported that FeLV accounted for as many as 70% of the cases of feline lymphoma before a vaccine was available (Hardy, 1993). The first commercial FeLV vaccine was approved by the U.S. Department of Agriculture in November 1984 and distributed in the United States and Canada (Bart, 1985). In Switzerland, the vaccine called Leucocell was introduced in 1986 (Lutz, 1986). From the 1970s to the early 1990s, malignant lymphoma was a frequent tumour diagnosis in Switzerland, with a yearly proportion of around 30% of all tumour diagnoses. In the early 1990s its relative frequency dropped substantially and has remained at around 12% ever since (Graf et al., 2016). This substantial decrease is probably due to the introduction of the vaccine and its customary usage in Swiss cats. Louwerens et al. (2005) studied lymphoma in cats from 1983 to 2003 in California at the Davis veterinary teaching hospital and reported a decline in FeLV association to 14-25% of all cats presenting with lymphoma. They reported a median age of approximately 11 years, which is considerably higher than the median ages of 4 to 6 years reported in the FeLV era (Hardy, 1981; Couto, 1989; Cotter, 1998; Vail et al., 1998; Louwerens et al., 2005). Studies reported that FeLV associated lymphoma was more often diagnosed in younger cats. The alimentary form of lymphoma, one of the most common non–retrovirus-associated lymphomas, was reported to be increasing and mostly seen in older cats (Vail et al., 1998; Louwerens et al., 2005; Lingard et al., 2009; Gieger, 2011; Moore et al., 2011). In our study we have no reports of an association of lymphoma with FeLV. However if we analyse our data, comparing mean age at diagnosis per year with the frequency of the location gastrointestinal tract per year, the results are quite similar (Figures 1, 2). The mean ages of cats with a lymphoma in the 1960s/ early 1970s was quite high, then dropped to a low in the 1980s and afterwards increased again. This correlates well with the diagnoses of lymphomas in the gastrointestinal tract and supports our hypothesis that the introduction of the vaccine led to the reduction of FeLV associated lymphomas and to a drop in the relative frequency of lymphoma compared to all tumours (Graf et al., 2016).
4.3 Injection site sarcomas in cats

The development of vaccines in human and in animal healthcare has saved many lives, however vaccines are not always free of risks. In 1991, an increased incidence of subcutaneous feline tumours that developed at injection sites was observed in the United States (Hendrick & Dunagan, 1991). The abrupt increase in the prevalence of fibrosarcomas at injection sites was connected to the introduction of rabies and feline leukaemia virus vaccines (containing an adjuvant), strengthened in 1987 by the Pennsylvania state law requiring rabies vaccination of cats at around the same time (Hendrick & Goldschmidt, 1991; Kass et al., 1993; Macy & Hendrick, 1996). The authors observed that animals that developed a tumour at a vaccination site were younger than those with similar tumours elsewhere, and that the likelihood of sarcoma development increased with the number of injections administered. The component in the vaccine most commonly thought to be associated with the local post vaccination inflammation and subsequent sarcoma development is the adjuvant aluminium in the form of aluminium hydroxide or aluminium phosphate. Particles of aluminium were detected in postvaccinal granulomas, in some sarcomas at the vaccination site as well as in macrophages (Hendrick & Dunagan, 1991; Hendrick et al., 1992; Macy, 1999; Madewell et al., 2001). However, it is now believed that these vaccines are not the unique cause of sarcoma at injection sites. More studies that investigated the pathogenesis of injection site sarcomas have described that in addition to killed adjuvanted vaccines, other foreign material injected into the subcutis of a cat can induce an inflammatory response and ultimately neoplastic transformation. There have been reports of sarcomas developing at sites where other non-adjuvanted vaccines,
antibiotics, steroids, and anti-parasitic agents were administered, as well as due to non-absorbable
suture material (Hendrick et al., 1994; Lester et al., 1996; Burton & Mason, 1997; Esplin & McGill,
1999; McEntee & Page, 2001; Buracco et al., 2002; Kass et al., 2003; DeMan & Ducatelle, 2007;
Srivastav et al., 2012).

Despite considerable research over the last 25 years, there is currently no plausible explanation for
the development of fibrosarcomas at injection sites. The most widely accepted hypothesis suggests
that a chronic inflammatory reaction, due to the puncture, acts as trigger for possible subsequent
malignant transformation. Adjuvanted vaccines seemed to be a higher risk for the development of a
sarcoma, due to the more intense local inflammation associated with such products (Macy &
Hendrick, 1996; Hendrick, 1998; Madewell et al., 2001; Martano et al., 2011; Woodward, 2011). The
relationship between trauma, inflammation, and tumourigenesis in the cat is still not understood.
The fact that not all cats develop a sarcoma after vaccination suggests that there might be a genetic
predisposition. It has been suggested that there is a higher incidence of injection site sarcomas in
siblings of affected cats, and that some cats tend to develop more than one injection site tumour
(McEntee & Page, 2001; Martano et al., 2011; Hartmann et al., 2015). Vaccines are very important
prophylactic tools that protect against many severe diseases and the relatively low risks of injection
site sarcomas (1-10/10000 vaccinations) are undoubtedly weighted less than the benefits from
these products. However, studies have revealed that the effect of vaccinations lasts much longer
than indicated by the pharma companies’ recommended annual booster. Therefore, in many
guidelines for the vaccination of cats they recommend vaccination at longer time intervals after
basic immunization (normally 3-year periods). Although it has been known for some time now that
it is not necessary to vaccinate so often, many vets still follow the scheme of annual vaccinations
(Esplin et al., 1993; Lester et al., 1996; Scott & Geissinger, 1999; Scherk et al., 2013; Schweizerische
Vereinigung für Kleintiermedizin, 2014; Schultz, 2015; World Small Animal Veterinary Association
(WSAVA), 2016).

Our study shows a steady increase in fibrosarcomas from the beginning of data collection to the
1990s. In the 1990s, fibrosarcoma frequency increased from approximately 10% of the overall
tumour diagnoses to 20%, and has remained stable ever since. We suspect that this sudden increase
is due to the introduction of the feline leukaemia virus vaccine in 1986 (Lutz, 1986). The rabies
vaccine was already available in the 1960s and there has been no law in Switzerland requiring
vaccination of cats against rabies (Cabasso et al., 1965; Dietzgen & Kuzmin, 2012). Existing studies
found no sex or breed predilection in cats for developing a fibrosarcoma. Our data showed a small
difference between male and female cats as well as between female intact and female neutered cats.
Although these differences are significant, one should be aware that they may be due to big data and thus purely coincidental. Major significant differences were found between breeds. Most breeds had significantly lower odds of developing a fibrosarcoma than the European shorthair cat; for some breeds it was even more than five times lower. There are two possible scenarios that could explain these differences. A simple explanation would be that purebred cats are more often kept inside the house and that therefore these cats are only vaccinated with the core vaccines against the panleukopenia virus, feline calici virus and feline herpes virus. It is not absolutely necessary to vaccinate cats that never go outside against the FeLV. This explanation would indicate that the impact of the leukaemia virus vaccine on the development of injection site sarcomas is far greater than that of any other vaccine. The other explanation would be that there is indeed a breed difference and that Swiss European shorthair cats have a genetic predisposition that makes them more susceptible to tumour development at injection sites. Either way, these indications are worth studying further. In addition, the company Merial brought a new vaccine, Purevax, to the Swiss market in 2006. This vaccine against the FeLV is a recombinant vaccine that does not include any adjuvants. To determine what influence the adjuvants have in the development of fibrosarcomas, it would be worth preparing and analysing the feline data further than 2008.

In human medicine, accumulation of aluminium in the human body and its potential role in the development of certain diseases like dementia, Alzheimer’s, Parkinson’s and breast cancer is being investigated. Several studies have described pro-oxidant effects, DNA double strand breaks, modifications of the essential metal homeostasis, and altered release of some cytokines related to the main inflammatory pathways (Perl, 1985; McLachlan & Berckum, 1986; Martyn et al., 1989; Forbes et al., 1995; Zafar & Uppal, 1999; Ruipérez et al., 2012; Walton, 2012; Darbre et al., 2013; Lukyanenko et al., 2013; Mannello et al., 2013; Darbre, 2016). In human breast tumours, it has been noticed that both cancer and cysts/fibroadenomas occur with a disproportionate incidence in the upper outer quadrant of the breast. The aluminium content of the tissue from outer regions of the breast was higher than from inner regions, a finding linked to the long-term usage of aluminium salt-containing antiperspirant close to this region. However, it remains to be established whether aluminium might be a contributory factor in the development of these breast diseases (Mannello et al., 1999, 2006, Darbre, 2001, 2003, 2005a, 2005b, 2016; Exley et al., 2007; Darbre et al., 2011, 2013). The study of feline injection site sarcomas and the potential role of the aluminium containing adjuvants could help to understand the possible role of aluminium in the development of tumours in both humans and animals.
4.4 Big data in healthcare

In the 1850s, when London was frequently the scene of cholera epidemics, John Snow painstakingly recorded the locations of affected homes. This was long, laborious work that nevertheless led to the source of contamination. Today, in a world where enormous amounts of data are recorded every second, Snow might have crunched Global Positioning System (GPS) information and disease prevalence data, solving the problem within hours (Harvard Public Health, 2014). That could be one potential impact of big data on public health. Big data, a term originally introduced by NASA scientists in 1997, while they attempted to depict the difficulty of displaying data sets too large to be stored, nowadays has numerous definitions. (Cox & Ellsworth, 1997) It is however generally seen as a large volume of complex and variable data that is not easily collected, stored and analysed due to its enormous size (Mayer-Schönberger & Cukier, 2013).

In medical healthcare, with more and more genomic data available, personalized medicine and big data could reach a whole new level. The already daunting volume of existing healthcare data includes personal medical records, radiology images, clinical trial data and a continuously increasing number of genomic sequences and genomic/biometric expression profiles. In addition, medical information is generated every second through technical improvements that allow the individual to monitor an increasing number of health parameters via smartphone apps and other wearable devices (Sorensen & Brand, 2011; Brand, 2012; Raghupathi & Raghupathi, 2014; Kostkova, 2015; Merchant, 2015). The snag is that patient information is not accessible due to data protection and privacy laws (Brand, 2012; Hafen et al., 2014). There are concerns over control of the data, confidentiality and privacy of the individual (Kostkova, 2015). If one wants to convince people to open up their data, there needs to be a strict policy and regulation of sensitive data as well as open communication about the positive aspects of big data analysis, so that patients will be willing to share medical information.

Access to these massive quantities of data, not only in human but also in veterinary medicine holds the promise of supporting a wide range of medical and healthcare functions. At the clinical/population and research data level, opening up medical data and sharing large healthcare datasets would enrich data on more symptoms, diseases, diagnosis, treatments, side effects and prescriptions. It has the potential for improvements in the care of individuals and populations, resulting in a higher quality of care and in a deeper understanding of outcomes (Jupp et al., 2008; Burghard, 2012; Feldmann et al., 2012; de Lusignan et al., 2014; Raghupathi & Raghupathi, 2014;
Patients could benefit from an improved personalized precision medicine and from successful treatment plans of others. Ideally, individual and population data would inform each physician and his patient during the decision-making process and help determine the most appropriate treatment option for that particular patient. Personalized medical therapies with fewer side effects and greater success rates are not only beneficial for the patient, but also for society. They would lower costs in healthcare, as much money is still spent on ineffective and inefficient treatments, despite the obvious differences between individuals in their response to drugs and their susceptibilities to diseases (Brand, 2012; Burghard, 2012; Feldmann et al., 2012; Harvey et al., 2012; Hafen et al., 2014; Minora, 2014; Raghupathi & Raghupathi, 2014; Austin & Kusumoto, 2016). In the drug development process, the sharing of large population level data could accelerate patient recruitment, which is often a lengthy process, especially in rare diseases (Minora, 2014; Raghupathi & Raghupathi, 2014).

Big data in medical healthcare sounds very promising; however one has to be aware that with big data there is also “big noise” (Khoury & Ioannidis, 2014). Claude & Longo (2016) wrote in their paper: “the more data, the more arbitrary, meaningless and useless correlations will be found, which appear only due to the size and not the nature of data”. They imply that they can be found in randomly generated large enough databases and that therefore most correlations are spurious. Big data must be coupled with rigorous observational methods and proper testing for causality. Otherwise grave mistakes can occur when simple correlations are taken as causalities (Prasad & Jena, 2013; Lupton, 2014). Many researches believe that a p-value of 0.05 or 0.01 indicates that a result is meaningful and that their hypothesis is therefore proven right or wrong. The truth however is that the p-value value does not provide ultimate evidence of a postulated difference or relationship. The British statisticians Sterne and Smith (Sterne & Smith, 2001) postulated that results of medical research should not be reported as significant or non-significant, but should be interpreted in the context of the type of study and other available evidence, and that confounding factors and biases should always be considered for findings with low p-values. Unfortunately, many journals expect or even insist on the reporting of statistical results as being significant or not significant, and many results that are not significant end-up in the bottom drawer and are never published.

Our study also falls into the category of big data in medicine, consisting of over 50'000 cat patient data from more than 40 years. Our analyses revealed many correlations that could be analysed further for causation. We now have the privilege of choosing from this huge amount of information
those tumours we deem interesting to study further. We could plan a prospective study to confirm or dismiss certain correlations found in the retrospective study. Moreover, genetic examinations on tumour tissue concerning tumour markers are possible as well as spatial analyses with the information we extracted from the patient files. Veterinary healthcare could of course benefit from opening up patient data, medication and treatment plans from animal patients in the same way as human healthcare. Furthermore, they could benefit from each other, as many diseases are treated in the same way. It would have been marvellous if more information on the animal patient had been gathered in the past, or were to be gathered in the future. Information on eating habits, weight, age of castration, households with smokers, and other factors could reveal more possible influential variables responsible for cancer development.

4.5 One medicine, One Health

“Between animal and human and medicine, there is no dividing line---nor should there be. The object is different, but the experience obtained constitutes the basis of all medicine.” Rudolf Virchow (1821-1902) (Klauder, 1958).

Rudolf Virchow, a German physician and one of the 19th century’s foremost leaders in medicine and pathology, created the field of comparative pathology. Interested in human and animal pathogen discoveries, Virchow noted the link between diseases of humans and animals and coined the term zoonosis. He insisted that health and disease in animals and humans differed only in detail and not in kind. During his lifetime, Virchow supported veterinary research and education and formed the focus of a new field of veterinary public health. He was convinced that environmental factors were key determinants of health outcomes. However, his concept of “one medicine” was not uniformly appreciated during his lifetime (Saunders, 2000; Cardiff et al., 2008a; Schultz, 2008; Currier & Steele, 2011; Evans & Leighton, 2014; Bresalier et al., 2015). William Osler (1849–1919), a student of Virchow’s, further promoted the concepts of comparative medicine and comparative biology and the integration of human and animal health in his faculties in North America. Being a passionate comparative pathologist, Osler taught veterinary students to undertake research into the diseases of animals and asserted the value of comparative medicine. He is credited with having coined the term “one medicine” although no direct written evidence for this has been found (Cushing, 1940; Murphy, 1960; Teigen, 1984; Dukes, 2000; Zinsstag et al., 2011). Unfortunately, with the increasing accumulation of knowledge in medical, veterinary and public health, the various departments were occupied with their own fields, and the common vision of the one health concept was all but
forgotten in the early 20th century. Calvin Schwabe (1927-2006), a professor of veterinary epidemiology, was instrumental in the 1960s in reviving the theme of “one medicine”. His thorough rethinking of the concept that fully recognized the close systemic interaction of humans and animals for livelihood, nutrition and health was published in his book “Veterinary Medicine and Human Health” (Schwabe, 1964; Cardiff et al., 2008b; Zinsstag et al., 2011; Nolen, 2013; Evans & Leighton, 2014; Bresalier et al., 2015).

A milestone in the ongoing internationally coordinated activities to further develop the One Health concept was set in October 2008, when the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE) published a document entitled “Contributing to One World, One Health – A Strategic Framework for Reducing Risks of Infectious Diseases at the Animal-Human-Ecosystems Interface”. Their vision is to improve public and animal health and to protect the health of ecosystems by minimizing the global impact of epidemics and pandemics due to highly infectious and pathogenic diseases of humans and animals (FAO - WHO - OIE - Worldbank - UNICEF, 2008; Meisser et al., 2011). Another feature of the One Health concept of the 21st century is the focus on ecological processes and environmental factors as key determinants of human and animal health. One Health is a hopeful, adaptive approach to achieving health in a world where accelerating environmental changes, due to the use of all natural resources, are associated with the parallel exponential growth of the global human and domestic animal population (Cook et al., 2004; FAO - WHO - OIE - Worldbank - UNICEF, 2008; Zinsstag et al., 2011; Evans & Leighton, 2014; Bresalier et al., 2015; Cassidy, 2016). Most publications on One Health refer to cooperation in the field of zoonosis; however, the field of comparative oncology also offers a unique and major opportunity to learn more about universal cancer risk, development and therapies through epidemiology, genetic and genomic investigations (Schiffman & Breen, 2015).

4.6 One Health – one oncology

Spontaneous cancers in companion animals offer a unique model for investigating human cancer in a comparative way. In the meaning of One Health, companion animals could serve as epidemiological or etiological sentinels for the changing patterns of cancer development seen in humans. The age-adjusted overall cancer incidence per 100,000 individuals per year is comparable in humans and domestic animals, being approximately 300 in humans, 381 in dogs and 264 in cats.
Humans and their pets share the same living environment, and their tumours occur spontaneously and under natural circumstances, where interactions between a variety of causal factors may occur. Epidemiological data are therefore crucial to better understand the risk of cancer and to develop preventive measures (Dorn, 1967; Schneider, 1977; Reif, 2011). Translational oncology strongly relies on research in mice. These animals can be held in laboratories at low cost, produced in mass and manipulated easily. Cancer models such as xenografts and transgenic mouse models have been extremely useful in the study of the complexity of human cancer, providing valuable insights into cancer biology and biochemistry that cannot be accessed easily by other means (Gordon & Khanna, 2010). A table (Table 1) presented by Cekanova & Rathore (2014) that contains a list of major cancer molecular targets, with their sequence percentage identities to human proteins, shows that mice, cats, and dogs all have relatively similar sequences to humans.

| Table 1 List of major molecular targets with their sequence percentage identities to human proteins |
|------------------------------------------------|------------------------------------------------|------------------------------------------------|
| **Mouse (%)** | **Cat (%)** | **Dog (%)** |
| p53 | 77 | 80 | 79 |
| c-Myc | 91 | 93 | 94 |
| COX-2 | 87 | 90 | 90 |
| c-Kit/CD117 | 82 | 89 | 88 |
| K-RAS | 97 | 99 | 99 |
| EGFR | 88 | 89 | 89 |
| PDGFR-α | 94 | 91 | 98 |
| β-catenin | 99 | 99 | 99 |
| PTEN | 99 | 100 | 100 |
| BRCA1 | 56 | 72 | 74 |

Notes: The sequences identified in various species were compared using the Basic Local Alignment Search Tool from the National Center for Biotechnology Information. Abbreviations: BRCA1, breast cancer type 1 susceptibility protein; c-Kit/CD117, tyrosine-protein kinase Kit/cluster of differentiation 117; c-Myc, cytoplasmic-myelocytomatosis oncprotein; COX-2, cyclooxygenase-2; EGFR, epidermal growth factor receptor; K-RAS, Kirsten rat sarcoma viral oncprotein; p53, tumor suppressor p53; PDGFR-α, platelet-derived growth factor receptor-α; PTEN, phosphatase and tensin homologue.

Mouse research has led to major advances in our ability to treat a number of serious diseases and conditions. A very accurate mouse model of human disease was the genetically engineered mouse (GEM) model of acute promyelocytic leukemia (APL), which was able to define oncogenes and “druggable” targets and develop very successful targeted therapies. After identifying the two genes involved in the translocations that are responsible for this disease, they ultimately succeeded in
generating faithful models of APL in transgenic mice. They were able to demonstrate that APL models in the mouse were not only faithful to the biological and pathologic features of the human disease, but that their leukaemia behaved exactly as APL in human patients when challenged with drugs. They could advise the clinicians on how to stratify patients for clinical trials on the basis of genetic criteria, using information accrued in preclinical testing of their mouse models of APL, which had a dramatic impact on the evolution of treatment of APL. Treatments with single agents or drug combinations ultimately led to disease eradication (Pandolfi et al., 1991; Brown et al., 1997; Grisolano et al., 1997; He et al., 1997; Lallemand-Breitenbach et al., 1999; Rego et al., 2000, 2006; Nasr & de The, 2010; Nardella et al., 2011). Despite the unquestionable importance of mouse models in cancer research and preclinical testing, the efficacy of drugs seen in preclinical cancer models often cannot be reproduced in human clinical trials (Gura, 1997; European Commission, 2010; Arrowsmith, 2011; Mak et al., 2014; Thomas et al., 2016; Venkatakrishnan & Ecsedy, 2017). Possible factors could be that they are limited in their representation of some essential features that define human cancer. Depending on the mouse model (i.e. ectopic and orthotropic xenografts, genetically engineered mouse models (GEMM), patient derived xenografts (PDX)), they may lack features such as specific functions of the immune system and the significant heterogeneity in tumour cells, tumour microenvironment, and stroma seen in humans. The complex biology of cancer recurrence and metastasis is often not sufficiently reproduced in mice. Furthermore, mouse models such as PDX are very expensive and labour intensive, with limited engraftment rates and long latency for tumour development (Van Dyke & Jacks, 2002; Hansen & Khanna, 2004; Frese & Tuveson, 2007; Simon, 2008; Cheon & Orsulic, 2011; Zhang et al., 2011; Khaled & Liu, 2014; Malaney et al., 2014; Ruggeri et al., 2014; Nass & Gorby, 2015). Moreover, unlike humans, mice are standardized, including standardized husbandry and environment, as animal diversity is seen as a confounding factor rather than a research strength (Bresalier et al., 2015). Companion animals with cancer could offer a unique model with which to support the investigation of human cancer in a comparative way, in order to overcome the limitations seen in mouse models (MacEwen, 1990; Knapp & Waters, 1997). Companion animals are diverse like humans, and represent many features that define human cancer. Cancers in dogs and cats develop naturally in the context of an intact immune system, which is characterized by tumour growth over long periods of time within a syngeneic host and tumour microenvironment, as well as developing recurrence and metastases to relevant distant sites. Their response to therapy and cytotoxic agents is similar to those in humans (Vail & MacEwen, 2000; Khanna et al., 2006; Paoloni & Khanna, 2007, 2008). Companion animals with naturally occurring tumours could be useful in multiple approaches to cancer investigation: breed-specific risk can be used to discover disease pathways; human cancer pathways can be tested
for roles, and targeted for treatment in canine and feline disease, and genomic information from pet patients could help to identify cancer genes not yet identified in humans and accelerate the development of targeted therapies for the benefit of both pet patients and humans (Cadieu & Ostrander, 2007; Breen, 2009; Ostrander & Franklin, 2012; Alvarez, 2014). However, although naturally occurring tumours in animal models much more represent human cancer, one has to keep in mind that tumours of companion animals still do not completely reflect human tumours. There may be an involvement of up-or down-regulated pathways in certain human tumours, which are not associated with the animal tumour, or vice versa. If, however, the same pathways are involved or affected receptors are similar, drugs that act there can be used by humans and animals (e.g. Imatinib (Glivec®; Novartis)). Companion animals with naturally occurring tumours could therefore play a valuable role in the clinical phase of the drug development process, when drugs are tested which act on structures that are similar/the same in humans and animals.

4.7 The drug development process

Forged in the 1960s, the drug development process has remained unchanged for more than 50 years. However, modifications are required, as the process is slow, inefficient and expensive (Figure 3). The average cost of bringing a new drug to market is over one billion dollars, and the average time span for bringing a drug from bench to bedside is around 10 to 15 years. Moreover, the average success rate for bringing a drug onto the market is - for all therapeutic areas - approximately 11%, and for oncology as low as 5% (Kola & Landis, 2004; Kaitin, 2010; Hutchinson & Kirk, 2011; Turner & Hoofwijk, 2013; Phrma, 2015).

A major change in drug regulation occurred in the late 1950s/early 1960s, when thalidomide, a drug given to pregnant women to stop morning sickness, was found to produce severe birth defects. This incident forced the pharmaceutical industry to focus on drug safety. So, legislation was introduced to protect the public from potentially dangerous drugs. Drugs cannot be prescribed or sold without a licence or marketing authorisation. Regulatory agencies worldwide govern how trials are to be conducted. These agencies include the Food and Drug Administration (FDA), the European Medicines Agency (EMEA), the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) and others. In order to harmonize the requirements and standards of the development and approval process of pharmacological treatments in Europe, Japan and the United States, all of these countries approved consolidated guidelines elaborated by the International Council for Harmonisation of
Technical Requirements for Pharmaceuticals for Human Use (ICH). However, in spite of great advancements in the harmonization process, there are still cases where different regulations are imposed. Moreover, other countries may require different regulations (Hawthorn & Redmond, 2006; Bacchieri & Della Cioppa, 2007; FDA, 2010; Turner & Hoofwijk, 2013).

A significant amount of work spanning several years must be completed in the development process of a new drug before clinical trials begin. The discovery process, often occurring in academia and pharmaceutical/biotechnological research labs, generates data to develop hypotheses that the inhibition or activation of a protein or pathway will result in a therapeutic effect in a disease state. Cell lines are then chosen or developed that show properties similar to the disease under consideration. Scientists screen thousands of compounds and hope to obtain a certain number of molecules that, at the same time, are simple to synthesize, have physico-chemical properties compatible with the predicted function, and demonstrate pharmacological activity (Roche, 2013; Turner & Hoofwijk, 2013; Phrma, 2015).

Before a pharmaceutical company can file a New Drug Application with the responsible regulatory agency for first-in-human clinical trials, compounds must undergo thorough preclinical testing in living animals for safety reasons. Although biomedical research follows the guiding principles of the three R’s (replacement, reduction, and refinement) to reduce the use of animals in scientific procedures and focus more on developing alternative approaches, preclinical testing in animals is absolutely compulsory. The nonclinical safety assessment for marketing approval of a pharmaceutical usually includes toxicity studies in normally 2 different animal species (rodent and non-rodent), nonclinical pharmacokinetic pharmacodynamics studies, teratogenicity studies, fertility studies, and, for drugs that have special cause for concern or are intended for a long duration of use, an assessment of carcinogenic potential. After thoroughly checking preclinical results, regulatory agencies decide on the approval for clinical trials in humans (Russel & Burch, 1959; Bacchieri & Della Cioppa, 2007; FDA, 2010; Turner & Hoofwijk, 2013).

Phase I in clinical trials involves clinical experimentation, which starts with the first administration of the drug to humans. These studies are used to evaluate pharmacokinetic parameters and potential drug-drug interactions in a small group of healthy volunteers (scale: tens). Exceptions are cytotoxic cancer drugs with carcinogenic or teratogenic potential; they are normally carried out in patients who have failed to benefit from other therapies, and therefore have no further treatment options.
Phase 2 clinical trials are conducted in participants affected by the disease under study. In a small-scale trial (scale: hundreds), the drug’s preliminary efficacy and short-term side effects are assessed in a tightly controlled manner in the intended patient population.

Phase 3 studies are large-scale clinical trials and are both the most costly and longest trials. In large patient populations (scale: thousands), they confirm safety and efficacy, monitor adverse reactions for long-term use and assess the benefit-risk relationship, often in comparison with the current standard therapy.

After successful clinical trials, the company submits a marketing application for a new drug, which will be reviewed by a regulatory agency. The pharmaceutical company must be able to clearly demonstrate the effectiveness and safety of the drug, and must provide all of the scientific information the pharmaceutical company has collected on the specific drug.

If a drug is approved for the market, patients are still monitored for further side effects as well as for exploring the use of different treatment regimens. Research into new indications for the medicine in different disease areas may also be pursued. This research may continue for several years (Hawthorn & Redmond, 2006; Hughes et al., 2011; Roche, 2013; Turner & Hoofwijk, 2013; Phrma, 2015).
The pharmaceutical industry is currently attacking diseases of great complexity. These include cancer or psychiatric and neurological disorders, in which developments are difficult and attrition rates very high, costing the industry a great deal of money. Furthermore, more drugs fail in Phase 3 clinical studies due to lack of efficacy or for safety reasons, thereby incurring almost the full discovery and development costs as well as wasting resources and time. In oncology, the attrition rates of drugs that enter phase 3 clinical trials is as high as 60%. It is therefore crucial that the industry develops and embraces paradigms and methodologies to identify safety and efficacy factors earlier in development. The lack of efficacy affects therapeutic areas more significantly, where animal models of efficacy are notoriously unpredictable, demonstrating the need for better models. Other factors contributing immensely to the failing of drugs are irreproducible preclinical data. Although data from tumour models, in which a drug is inactive or may not completely fit an original hypothesis, are just as important as showing models in which the hypothesis was confirmed, negative data are often omitted to present a “perfect story”. We need a system that will facilitate a transparent discovery process to report troubling and negative data without fearing adverse consequences (Kola & Landis, 2004; Dimasi & Grabowski, 2007; Kaitin, 2010; Hutchinson & Kirk, 2011; Begley & Ellis, 2012).
### 4.8 Orphan drugs

The development of drugs is very expensive. Attrition of drugs late in clinical trials costs the pharmaceutical industry significant amounts of money. Moreover, the growth of this industry has slowed in recent years because of various reasons such as generic competition, patent expiration and increasingly stringent regulatory guidelines. The introduction of the orphan drug act in 1983 in the United States and the European legislation in 2000 shifted the focus of pharmaceutical companies to the new business model — niche busters, also called orphan drugs. In the European Union (EU), a disease is considered ‘orphan’ if it is a life-threatening or seriously debilitating disorder that affects fewer than 1 per 2,000 people. According to the US definition, such diseases affect less than 200,000 individuals in the United States. Today, there are over 5,000 rare diseases listed of which 80% have been identified to genetic origins. Initially, the small market for orphan drugs restrained the pharmaceutical industry from developing medicines for rare diseases. However, the legislation provides significant financial benefits to a pharmaceutical company that develops an orphan drug. They receive tax credits and fee exemptions, and most importantly they benefit from 10 years (7 years in the USA) of market exclusivity after registration. The low patient numbers make it difficult for pharmaceutical companies to recoup research and development costs, and consequently orphan drugs are generally much more expensive than non-orphan drugs. Each one of the world’s 10 most expensive drugs is an orphan drug, and some drugs have proven themselves as viable money-makers, especially if they can be used in other diseases as well. Rituximab, as one example, was initially approved as an orphan drug by the FDA for the treatment of follicular non-Hodgkin’s lymphoma, and is now used to treat a wide variety of conditions, making it one of the best-selling drugs in the world. Many orphan drugs approved for the market are for the treatment of cancer. The investigation into rare diseases can help many people by providing them with a treatment for their disease; however, the affordability of orphan drugs has become a major issue for payers because depending on the country, health systems will not cover them (FDA, ‘European Parliament, 2000; Fischer et al., 2005; Hughes et al., 2005; Dear et al., 2006; Sharma et al., 2010; Meekings et al., 2012; Helfand, 2013; Schuller et al., 2015; Onakpoya et al., 2015; Daniel et al., 2016; Hughes & Poletti-Hughes, 2016).
4.9 Companion animals in clinical trials

A possible way to improve clinical trials in oncology involves the use of companion animals with naturally occurring cancers. In addition to the already mentioned similarities in human and animal cancers, including pets with cancer in clinical trials could bring many advantages. But first of all, a clinical study that includes pets with cancer must be designed under primary consideration for the best care of the animal cancer patient, with the informed permission of the pet owner and under the guidance of an accredited and appropriate institutional animal care committee. The scientific and translational motivation of the study must be balanced against the overriding mandate for animal care. A pet owner’s decision to pursue an investigational treatment is often influenced by the risks associated with this therapy compared to conventional therapy, as well as their expectations for outcomes and reduced costs. Furthermore, many pet owners are motivated by the opportunity to contribute to the advancement of cancer treatment for future human and animal patients (Gordon et al., 2009; Khanna et al., 2009).

Clinical trials in animals are not constrained by traditional Phase I, Phase II, and Phase III trial designs and could be used to answer specific questions that are necessary for progress of the product development strategy. It allows novel agents to be offered to companion animals with naturally occurring tumours before conventional therapies or during the period of minimal residual disease, as opposed to human clinical trials where patients are enrolled who often have advanced treatment-resistant disease (Khanna et al., 2009). Unlike in human trials, where only well-defined patients are allowed and comprehensive information on a drug’s benefits and risk in a large population is only achieved in phase 3 and postmarked surveillance, animals with cancer are not restricted to certain characteristics and could therefore bring additional information according to efficacy of a cancer drug in different patients already in the early phase of the clinical trial (Figure 4). Overall survival is often regarded as the “gold standard” of endpoints. Studies designed to demonstrate an impact of treatment on overall survival need large sample sizes and a long follow-up. Dogs and cats with cancer, whose life is shorter and disease progression is faster could add additional insights. In novel targeted therapies, the conventional paradigms of toxicity studies conducted in healthy animals followed by Phase 1 and Phase 2 human trials often leave many important questions on the “best use” of these drugs unanswered. Translational drug development studies in dogs and cats with cancer could provide an opportunity to answer these questions by serving as an intermediary between conventional preclinical models and human clinical trials, provided the same pathways or receptors are affected. Patient recruitment, especially in rare
diseases, is often difficult and time consuming. Including pets with cancer in the process could provide additional valuable, not otherwise obtainable, information and a significantly larger patient population in which to evaluate new treatment strategies (Porrello et al., 2004; Hawthorn & Redmond, 2006; Bacchieri & Della Cioppa, 2007; Kummar et al., 2008; Paoloni & Khanna, 2008).

Figure 4: Companion animals in the drug development process

4.9.1 Dogs in clinical trials

Dogs with naturally occurring tumours have already contributed successfully to clinical trials. Kurzman and colleagues (1995) demonstrated the anti-tumour activity of the immune stimulator liposomal muramyl tripeptide phosphatidylethanolamine (L-MTP-PE) in dogs with osteosarcoma. These randomized, placebo-blinded studies of L-MTP-PE in dogs were part of the scientific rationale for the phase III evaluation of L-MTP-PE in osteosarcoma. Re-evaluation of the mature human data from these studies found remarkably similar results to the earlier canine studies, which eventually led to approval of L-MPT-PE (MEPACT) for osteosarcoma in children in Europe (Kleinerman, 1995; Kleinerman et al., 1995; Meyers et al., 2005). Another example of a successful comparative study was conducted in pet dogs with osteosarcoma (OS) to evaluate the safety, efficacy, and feasibility of novel inhalation therapies in the management of macroscopic pulmonary OS metastases. Inhalation
cytotoxic chemotherapy trials in dogs demonstrated that aerosolized therapies were well tolerated with no dose-limiting toxicity. Furthermore, these studies supported the expected mechanism of anti-tumour activity associated with this therapy and contributed to the clinical development of inhalation approaches in humans. These studies in dogs established a safety and efficacy profile for inhaled liposomal IL-2 therapy, demonstrated evidence of local immunomodulatory effects and provided support for subsequent early-phase trials of this novel treatment approach in humans with pulmonary metastases (Klausner et al., 1996; Khanna et al., 1997; Hershey et al., 1999; Khanna & Vail, 2003; Rodriguez et al., 2010; Rodriguez, 2014).

4.9.2 Cats as a model for human disease

In cats, the only tumour that has been examined thoroughly is mammary carcinoma. This was in an attempt to identify prognostic markers and to compare it to human breast cancer. However, weaknesses in study design and different methodologies made comparisons difficult. Expanded molecular evaluation of feline mammary tumours are necessary in order to allow targeted specific therapies to be used in cats, and would enhance the value of feline mammary tumours as a model of human breast cancer (Zappulli et al., 2015). So far, over 250 hereditary genetic diseases have been described in cats, and approximately half of these diseases have established homology with human genetic defects, which makes the cat an interesting natural model (O’Brien et al., 2002; Menotti-Raymond & O’Brien, 2008). The cat possesses several advantages from a comparative genomics perspective. The first genetic map of the cat, a physical map generated from a somatic-cell hybrid panel, shows that the feline genome, which is composed of 19 chromosome pairs, is highly conserved in gene content (conserved synteny) and G-banded chromosome appearance. The extent of chromosome segment conservation between the human and cat genomes is among the highest observed between mammals. The feline genome assembly is 3 to 4 times less rearranged relative to the human genome than are the genomes of mice and rats (Rettenberger et al., 1995; Wienberg et al., 1997; Modi & O’Brien, 1998; O’Brien & Nash, 1998; O’Brien et al., 1999, 2002, Murphy et al., 2000, 2001). However, there are still few studies with cats in genetic comparative oncology. One drawback was that although a completed draft whole genome sequence of an Abyssinian cat named Cinnamon was published in 2007, the sequence contained significant gaps and errors, which slowed efforts to map genes (Pontius et al., 2007). This obstacle has now been overcome, as a high-quality version of Cinnamon’s genome was published in late 2014 (Tamazian et al., 2014). Moreover, the feline genetics laboratory of Professor Leslie Lyons (University of Missouri), whose research focuses
on the genetics of the domestic cat, started an initiative called “99 lives - Cat Whole Genome Sequencing”. Their goal is to map 20,000 genes in 99 cats of various breeds in order to construct a complete genetic portrait of felines, which is important for the understanding of genetic diseases, for the discovery of mutations that cause inherited diseases and for the development of diagnostic and screening tests that will improve disease treatment. With sequencing many cats of various breeds, they would like to identify normal and abnormal genetic variations and improve coverage of the cat genome. By making the data publicly available they enable all members of the research community to benefit in a non-competitive and collaborative manner. So far, 50 cats have been sequenced (Lyons).

The popularity of cats around the world, and the intensive medical care provided by the owner, improves the interest in feline diseases and treatments. However, the popularity of cats also makes them a disliked scientific object because people do not like to hear about experiments on cats. This obstacle may be the reason for the limited number of publications involving cats, with the omission of negative results (publication bias) being a particular concern. Comparison of diseases and treatments in humans and cats could be beneficial for both. Cats with naturally occurring tumours in clinical trials could gain from a cancer treatment, and could thereby help other cats with cancer.

In the United States of America, twenty academic comparative oncology centres have formed a network, the Comparative Oncology Trials Consortium (COTC), to provide the infrastructure and resources needed to integrate clinical trials for pets with naturally occurring cancers into development pathways for new drugs, devices, and imaging techniques for human cancers. Trials conducted by the COTC are directly integrated into the design of current human Phase I and II clinical trials, with the goal being to support the development, validation, and assessment of pharmacokinetic and pharmacodynamic end-points (Gordon et al., 2009). However, the cancer research community has not yet succeeded in communicating the value of companion animals in clinical trials, and their useful integration into these trials still proves challenging. The Institute of Medicine’s National Cancer Policy Forum hosted a workshop held in Washington, D.C. on June 2015 to examine the rationale and potential for integration of companion animals into translational cancer research and development, and discussed potential opportunities for overcoming existing challenges to that integration. Their proposals include: the development of Food and Drug Administration guidance to clarify regulatory oversight and processes in clinical trials with pets, the elaboration of ethical questions and concerns by considering the needs of both the pet and the owner, the improvement of communication among interested stakeholders and the establishment of a clinical trials registry for pet patients similar to the registry for human trials. To meet these goals
and maximize the value of spontaneous animal tumours, it is essential to continue to validate animal cancers as a model for human cancer and to show their possible potential in the improvement of clinical trials (National Academies of Sciences Engineering and Medicine, 2015).

### 4.10 Novel cancer therapeutics

Ludwik Fleck (1896-1961), a Polish physician, researcher and philosopher of science, published various works on cognition as a collective activity. He claims that people with a similar experimental and theoretical background look at, or deal with a problem in a specific way and defines this as a thought collective. In 1927, he published (in Polish) his first work in the philosophy of medicine: “Some Specific Features of the Medical Way of Thinking”, in which he characterized the peculiar approach of doctors’ maintenance of medical disease models. Unlike scientists who examine typical normal phenomena, doctors study atypical pathological phenomena. Disease patterns are extremely diverse, and one hardly resembles the other. They are described as states of higher order, ignoring several observed factors, building hypotheses on the basis of assumed causalities. The disease types described in the medical taxonomy are therefore idealized fiction that never precisely describes a patient’s disease state. Doctors cannot therefore simply rely on book knowledge; they have to include their personal experience in medical diagnostics and therapies (Fleck, 2011). In cancer research, they use these idealized model types as well in preclinical studies. Cancer studies in preclinical models are conducted in mice that are standardized as many individual characteristics and external influences as possible are eliminated. By choosing standardized models, they want to see a certain mechanism that is not influenced by external factors to prove their hypotheses or their results from in vitro models. However, cancer is such a diverse disease and influenced by many factors that it is hard to predict whether a drug effect seen in preclinical models shows the same results in patients. During the past two decades, cancer treatment has evolved from relatively nonspecific cytotoxic agents (chemotherapies) that kill rapidly dividing cells, to selective, mechanism-based therapeutics. Cytotoxic drugs remain the backbone of current treatment, but significant toxicities, a narrow therapeutic index, and frequently acquired resistance limit them. Through improved understanding of cancer pathogenesis, new treatment options, including targeted agents and cancer immunotherapy, have been developed (Vanneman & Dranoff, 2012). Targeted drugs work only on a fraction of patients depending on the kind of protein expression on the cancer cells, and in most cases only a small fraction of patients show benefits from a particular
immunotherapy. This shows even more that there is no one generalizable cancer patient, but that patients are as diverse as their cancers. It will also be challenging for these novel therapies to create or find appropriate preclinical models that express the same clinical target or respond to immunotherapies in a similar way, especially since many cancer mouse models also have an impaired immune system.

4.10.1 Targeted cancer therapy

Targeted cancer therapies are drugs or other substances that block the growth and spread of cancer through different approaches. Many different targeted drugs have been approved for use in cancer treatment including signal transduction inhibitors, apoptosis inducers, gene expression modulators, apoptosis inducers, angiogenesis inhibitors and toxin delivery molecules. Most targeted therapies are either small molecules or monoclonal antibodies (mABs).

Targets for mABs can be proteins on cells that are overexpressed on cancer cells and that are simultaneously responsible for the cancer cells' growth and ability to spread. An example is the drug Trastuzumab (Herceptin®), which targets the extracellular domain of EGFR2 protein (HER2) and thereby mediates antibody-dependent cellular cytotoxicity in cancer cells. It is used in breast and stomach cancer patients.

Vemurafenib (Zelboraf®) targets a mutant (altered) protein (known as BRAF V600E) that drives cancer progression. This drug is approved to treat patients with inoperable or metastatic melanomas whose cancer expresses this altered BRAF protein.

Abnormalities in chromosomes that are present in cancer cells can result in the creation of a fusion gene. Such fusion genes may drive cancer development, and are potential targets for cancer therapies. For example, Imatinib mesylate (Gleevec®) targets the BCR-ABL fusion gene that is found in certain leukaemia cells.

Monoclonal antibodies can also be attached to particles. Radiolabeled antibodies have small radioactive particles attached to them. Ibritumomab tiuxetan (Zevalin®) is an example of a radiolabeled mAb. This antibody delivers radioactivity directly to cancerous cells and can be used to treat some types of non-Hodgkin's lymphoma.

Antibodies labeled with a highly potent cytotoxic agent, also called antibody-drug-conjugates (ADCs), bind to their target antigens and are internalized through receptor-mediated endocytosis. This facilitates the subsequent release of the cytotoxin, which eventually leads to apoptotic cell
death of the cancer cell. ADCs that are currently on the market are brentuximab vedotin (Adcetris) to treat relapsed or refractory Hodgkin’s lymphoma, and refractory systemic anaplastic large cell lymphoma and trastuzumab emtansine (T-DM1; Kadcyla®) for breast cancer.

Targeted therapies show significant improvement in progression-free and overall survival in selected patients. However, these therapies are restricted to patients with specific gene mutations that code for the target. Regressions are commonly followed by the development of progressive disease owing to the emergence of drug-resistant variants, limiting their overall clinical benefit (National Cancer Institute; Green et al., 2000; Schrama et al., 2006; Sensi & Anichini, 2006; Lambert, 2012; Scott et al., 2012; Vanneman & Dranoff, 2012; Peters & Brown, 2015; American Cancer Society, 2017).

### 4.10.2 Immunotherapy

The idea of immunotherapy, which uses the patient’s immune system to treat cancer, relies on the insight that the immune system can eliminate malignant cells during initial transformation (immune surveillance). Tumours arise through a combination of genetic and epigenetic changes. Cancer cells manage to escape immune recognition and subsequent destruction. To achieve this, tumours develop multiple resistance mechanisms, including induction of tolerance, local immune evasion and systemic disruption of T cell signalling. Furthermore, through immune editing they achieve less immunogenic and more apoptosis-resistant neoplastic cells.

Immunotherapy aims to boost or restore the ability of the patient’s immune system to fight cancer. Immunotherapeutic strategies include cancer vaccines, oncolytic viruses, adoptive transfer of ex vivo activated T and natural killer cells, and administration of antibodies or recombinant proteins that either co-stimulate cells or block the so-called immune checkpoint pathway.

Oncolytic viruses (OV) are native or engineered viruses that are injected locally into the tumour. They have the ability to infect, multiply within and subsequently lyse cancer cells. Moreover, they initiate systemic antitumor activity. Talimogene laherparepvec (T-VEC) is one drug that has been approved by the FDA for the treatment of advanced melanoma. Overall survival is superior compared to control treatment, but the drug has low efficacy in patients with more advanced diseases.
Cancer vaccines should stimulate the patient’s immune system. However, all attempts have had rather poor efficacy and response thus far. The first cellular immunotherapy sipuleucel-T approved in 2010 for metastatic prostate cancer has led to an approximately 4-month improvement in overall survival.

Adoptive Cellular Therapy (ACT) attempts to reverse the functional impairment of the tumour-specific T cells that reside within the tumour, caused by the immune suppressive tumour microenvironment. Isolated lymphocytes from the patient are grown outside the body to produce a large amount of high avidity effector T cells that are reinfused back into the patient. Lymphodepleting enhances efficacy. This treatment is restricted to melanoma and has a high risk of adverse effects, lack of long-lasting responses in many patients, and is very expensive.

The immune system has the ability to discriminate between normal cells in the body and those it sees as “foreign.” For this, it uses “checkpoints” – molecules on certain immune cells that need to be activated (or inactivated) to start an immune response. Cancer cells sometimes find ways to use these checkpoints to avoid being attacked by the immune system. PD1 is a checkpoint protein that can be targeted by monoclonal antibodies to boost the immune response against cancer cells. For the treatment of metastatic melanoma, the drugs Pembrolizumab (Keytruda) and Nivolumab (Opdivo) have been approved. However, these drugs have immune-related adverse events, and while only a relatively small fraction of patients obtain clinical benefits, the drugs do provide the possibility for long-term survival in some patients.

For the majority of patients that respond to immunotherapy, monotherapy may be relatively ineffective. In order to achieve complete remission and cures for patients with cancer, the combination of multiple therapeutic approaches may be required and holds significant potential for improving treatment outcomes. Several combinational treatments are under investigation.

Unfortunately, immunotherapies are sometimes risky, leading to a wide range of adverse events, with only a fraction of patients responding to a particular immunotherapy. Improving this situation will require the identification and validation of reliable surrogate biomarkers, in order to provide an early indication of response or predict clinical benefit to avoid treatment-related toxicity and cost in patients that are unlikely to benefit (Mahoney et al., 2015; Rosenberg et al., 2008; Dimberu & Leonhardt, 2011; Sharma et al., 2012; Vanneman & Dranoff, 2012; Weiner et al., 2012; Pardoll,
4.11 Outlook

Genetic predisposition and exposure to specific risk factors are usually regarded as the main variables in comparative disease epidemiology. Several factors (i.e. radiological, chemical, genetic, viral, UV radiation and industrial pollutants) influence the development of tumours in animals and humans (Dorn, 1967; Reif, 2011). The Swiss canine and Swiss feline cancer registries contain data that would allow investigations in spatial epidemiology (currently being evaluated). Spatial cancer epidemiology aims to examine and interpret cancer incidences with regard to their geographic distribution (Lawson, 2006). The North American Association of Central Cancer Registries (NACCR) routinely maps national human cancer rates and works with spatial analysis for cluster detection (Du et al., 2010; Sherman et al., 2014; ’NAACCR, 2017). As humans and animals share the same environment and are exposed to the same risk factors, a spatial perspective in veterinary epidemiology could provide a better understanding of shared risk factors related to specific environmental settings (Scotch et al., 2009). Moreover, as the time lag between exposure to carcinogens and tumour development is much shorter in animals than in humans, particular interest lies in the role of companion animals as sentinels for human disease (Vastag, 1999). A spatial analysis comparing cancer data from dogs and humans was conducted by O’Brien et al. (2000), however their data was very limited.

When the cat genome project will be finished and a complete genetic portrait of felines will be available, more research on genetic diseases and mutations will be possible (Lyons). With the overall increase in cat lifespans and improved medical care, cancer in cats has become increasingly important. Cats are often seen as family members and owners demand equal medical care for their pets as for themselves. Many novel cancer medications act on receptors /pathways that are affected by the disease. Cancer research on mutations and affected pathways in cat tumours are therefore necessary for an improved cancer treatment. Research on somatic mutations and genome alterations in cats would also be useful in humans as it improves the understanding of this complex disease (Cadieu & Ostrander, 2007; Breen, 2009; Ostrander & Franklin, 2012; Alvarez, 2014).

The feline cancer registry lays the groundwork for possible further analyses. It illustrates the most important cancers in cats and reveals correlations between higher risk of certain tumours in breeds or sexes, which could be studied further for probable genetic or hormonal influences. Annual trends
on tumour occurrences could be used to narrow down possible influential factors on tumour
development (e.g. Chernobyl disaster), which could also be compared to human cancer incidences. A
continuation of the companion animal cancer registries in parallel to the human cancer registry
would be desirable.

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