Chapter 9
Canine and Feline Spontaneous Mammary Tumours as Models of Human Breast Cancer

Hugo Vilhena, Ana Catarina Figueira, Fernando Schmitt, Ana Canadas, Raquel Chaves, Adelina Gama, and Patrícia Dias-Pereira

Abstract The frequency of cancer presents an increasing trend in humans and companion animals, and despite recent advances in diagnosis and treatment, it remains a major cause of morbidity and mortality in human and veterinary medicine. The epidemiological and clinicopathological similarities between spontaneous tumours of companion animals and their human counterparts make them suitable natural models for human cancer research. Moreover, the faster progression of cancer in dogs and cats in comparison with humans, associated with the shorter life span of companion animals, enables faster data retrieval than in human malignancies. Furthermore, the health effects associated with exposure to environmental hazardous materials, including cancer, occur similarly in companion animals and humans; consequently, in an epidemiological context, dogs and cats can also be useful as sentinels of human malignancies. For these reasons, comparative oncology, which can be defined as the study of spontaneous cancers in animals as models for human disease, has gained increasing importance over the last decades. Breast cancer represents the most prevalent cancer among women worldwide and the leading cause of cancer-related mortality in women. Mammary gland tumours are

H. Vilhena (✉)
Center for Investigation Vasco da Gama (CIVG), Department of Veterinary Medicine, Vasco da Gama Universitary School, Coimbra, Portugal

Baixo Vouga Veterinary Hospital, Águeda, Portugal

Animal and Veterinary Research Centre (CECAV), University of Trás-os-Montes e Alto Douro, Vila Real, Portugal

A. C. Figueira
Center for Investigation Vasco da Gama (CIVG), Department of Veterinary Medicine, Vasco da Gama Universitary School, Coimbra, Portugal

University Veterinary Hospital of Coimbra, Coimbra, Portugal

F. Schmitt
Institute of Molecular Pathology and Immunology, University of Porto (IPATIMUP), Porto, Portugal

Medical Faculty, University of Porto, Porto, Portugal

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also among the most frequent tumours in female dogs and cats. Canine and feline mammary tumours present similar incidence, relative age of onset, risk factors, biological behaviour, metastatic pattern, histological, molecular, and genetic features, and response to therapy to human breast cancer; thus, they are recognized as suitable natural models for human breast cancer studies. The comparative "One Health" approach allows advances in knowledge of the diseases in order to obtain an improvement in clinical outcomes for affected humans and animals.

Keywords Breast cancer · Canine · Comparative oncology · Feline · Mammary tumours · Natural animal models · One Health

9.1 Introduction

Domestic animals develop several spontaneous diseases, including cancer, that in many aspects parallel human morbidities; hence, they are considered appropriate natural models of human diseases (MacEwen 1990; Porrello et al. 2006; Roman et al. 2013). These spontaneous models of cancer have several advantages over the classic in vitro tumour cell lines and the in vivo xenograft models, namely, the evaluation of the animal's immune response to the tumour, the ability to reproduce interactions between the neoplastic cells and the microenvironment, and the capacity to reproduce the metastatic behaviour of the neoplasm (Vargo-Gogola and Rosen 2007; Pinho et al. 2012; Nguyen et al. 2018). Moreover, the shorter life span and faster progression of cancer in dogs and cats allow an earlier data collection than in human malignancies (Cannon 2015). Furthermore, companion animals share the same environment as humans, and the health effects associated with exposure to hazardous materials, such as cancer, might also be detected in animals; consequently, in an epidemiological context, animals can act as sentinels of human

A. Canadas · P. Dias-Pereira
Department of Pathology and Molecular Immunology, Institute for the Biomedical Sciences Abel Salazar, University of Porto (ICBAS-UP), Porto, Portugal

R. Chaves
Department of Genetics and Biotechnology (DGB), University of Trás-os-Montes e Alto Douro (UTAD), Vila Real, Portugal

Laboratory of Cytogenomics and Animal Genomics (CAG), University of Trás-os-Montes e Alto Douro (UTAD), Vila Real, Portugal

Biosystems & Integrative Sciences Institute (BioISI), Faculty of Sciences, University of Lisboa, Lisboa, Portugal

A. Gama
Animal and Veterinary Research Centre (CECAV), University of Trás-os-Montes e Alto Douro, Vila Real, Portugal

Department of Veterinary Sciences, University of Trás-os-Montes e Alto Douro, Vila Real, Portugal

malignancies (Misdorp 1996; Porrello et al. 2006). Changes in the canine cancer incidence ratios, and probably also in feline tumours, were described to precede by 2 years similar changes in human incidence rates, which might be useful for predicting changes in cancer patterns in humans (Garbe 1988).

Spontaneous canine and feline mammary tumours share several similarities with their human counterpart, including incidence, relative age of onset, risk factors, biological behaviour, metastatic pattern, histological, molecular, and genetic features, and response to therapy; thus, they are recognized as suitable natural models for human breast cancer studies (Vail and MacEwen 2000; Zappulli et al. 2005; Nguyen et al. 2018; Abadie et al. 2018).

9.2 Epidemiology and Risk Factors

Breast cancer represents the most prevalent cancer among women worldwide, and despite the recent advances in diagnosis and treatment, it remains the leading cause of cancer-related mortality in women (Ferlay et al. 2013, 2015; Ghoncheh et al. 2016). Furthermore, a trend for an increase in breast cancer incidence is observed worldwide (Glass et al. 2007; Arnold et al. 2015). According to the World Health Organization, 2.1 million women are diagnosed with breast cancer every year, with an estimation of 627,000 breast cancer-related deaths in 2018, corresponding to approximately 15% of all cancer-related deaths in women (WHO 2018). The incidence of breast cancer increases in women over 40 years of age, with a median age at diagnosis of approximately 50–60 years, depending on geographical location and tumour type (Bray et al. 2004; Song et al. 2014; Corbex et al. 2014; Monticciolo et al. 2017). Breast cancer also occurs in men; however, male breast cancer is considered a rare disease, corresponding to 1% of all breast cancer diagnoses and approximately to 0.1% of all male cancer-related deaths (Fentiman 2016; Ferzoco and Ruddy 2016). Nonetheless, a trend to an increase in incidence has also been observed in the last years (Giordano et al. 2014; Howlader et al. 2017). Several differences in epidemiology and clinical features of male and female human breast cancer have been described (Fentiman 2016; Deb et al. 2016).

Mammary tumours are also among the most frequent neoplasias in female dogs and cats (Vascellari et al. 2009; Egenvall et al. 2010; Grüntzig et al. 2016; Baioni et al. 2017). Canine mammary gland tumours represent more than 50% of all tumours in female dogs, with an estimated incidence of approximately 100–250 cases per 100,000 dogs per year (Dobson et al. 2002; Vascellari et al. 2009, 2016; Grüntzig et al. 2016; Baioni et al. 2017). Feline mammary tumours account for 17% of all tumours in female cats, with an incidence of approximately 25 cases per 100,000 female cats per year (Morris 2013). However, the prevalence and incidence of mammary tumours in companion animals vary geographically, being lower in areas where females are routinely neutered at younger ages (Beauvais et al. 2012; Salas et al. 2015). As in humans, canine and feline mammary tumours are rare in males. Female dogs present a predisposition 62 times higher than males to develop

mammary tumours, and most tumours in males are benign (Euler 2010; Bearss et al. 2012). In felines, approximately 1% of all mammary tumours occur in tomcats, with no sex-related differences of biologic behaviour or clinical signs (Hayes Jr et al. 1981; Skorupski et al. 2005; Gregório et al. 2012).

The relative ages of female dogs and cats with mammary tumours are similar to those described for women with breast cancer (Metzger 2005). Mammary tumours occur mainly in middle-aged to older bitches and are rare, namely, the malignant tumours, in dogs under 5 years of age; the mean age at diagnosis of malignant mammary tumours is of 9–11 years and of benign neoplasms of 7–9 years (Sorenmo et al. 2009, 2013). As in women, the incidence increases with age, with a peak at 11–13 years of age (Schneider 1970; Egenvall et al. 2005). In queens, the incidence of mammary tumours also increases with age and also occurs mainly in middle-aged to older queens, with a mean age at diagnosis of 10–12 years (Millanta et al. 2006; Morris 2013; Figueira et al. 2015).

Hormonal influence is another common feature of humans' and companion animals' mammary gland tumours (Schneider et al. 1969; Overley et al. 2005; Farhat et al. 2013; Finlay-Schultz and Sartorius 2015). The endocrine environment, defined by the length of exposure to the sex hormones oestrogen and progesterone, has been suggested to have a role in the development of canine and feline mammary carcinomas (Rutteman and Misdorp 1993; Overley et al. 2005; Queiroga et al. 2015). Evidences indicate that the steroid hormones act at the early stages of tumour development and that oestrogen receptor and progesterone receptor levels are decreased in carcinomas when compared to benign tumours, which may indicate a hormone-independent growth at the advanced stages of malignancy (Rutteman et al. 1991; Rutteman and Misdorp 1993; Martín De Las Mulas et al. 2000; Millanta et al. 2005b). In female dogs, the risk to develop mammary tumours is reduced to 0.5%, 8%, and 26% if the ovariohysterectomy or ovariectomy is performed before the first, before the second, or after the second estrus, respectively, with no risk reduction if performed after the second estrus (Schneider et al. 1969). Queens neutered before six months and one year of age are reported to have a 91% and 86% reduction risk, respectively, for the development of the disease when compared to intact queens (Overley et al. 2005). The administration of progestogens to prevent estrus increases the risk of mammary tumour development by a dose-related carcinogenic effect (Misdorp 1991; Misdorp et al. 1991; Rutteman and Misdorp 1993). This outcome appears to be more evident if these drugs are given regularly for long periods of time rather than intermittently (Misdorp et al. 1991), and male cats present a similar risk if treated with progestogens (Jacobs et al. 2010).

Besides the ovarian hormones, also the pituitary hormones prolactin and growth hormone have been associated with carcinogenesis of human breast cancer and canine and feline mammary tumours (Mol et al. 1995; van Garderen et al. 1997; Queiroga et al. 2014; Wang et al. 2016; Subramani et al. 2017).

Although any pure-breed or cross-breed dog or cat can develop mammary tumours, a genetic predisposition has been suggested in some canine and feline breeds. In dogs, mammary tumours are more frequent in pure-breed than in cross-breed dogs, and small and medium breeds are more commonly affected than

large and giant breeds (Moe 2001; Egenvall et al. 2005; Sorenmo et al. 2013; Salas et al. 2015; Grüntzig et al. 2016; Baioni et al. 2017). Moreover, different predispositions to mammary tumours have been described in dogs from the same breed but from different lineages, reinforcing the genetic influence in disease development (Schafer et al. 1998). A genetic predisposition is also suspected in cats, with Siamese, Oriental, and Domestic shorthair breeds appearing to be associated with a higher risk for the development of mammary neoplasias (Hayes Jr et al. 1981; Novosad 2003; Sorenmo et al. 2013). A familial genetic predisposition for breast cancer development is well established in human medicine, with different genes and gene mutations being associated with an increased risk for the disease (Lalloo and Evans 2012; Adank et al. 2013; Brewer et al. 2017). Similar genetic basis has been described in human and in companion animal breast cancer (Im et al. 2013; Enginler et al. 2014; Canadas et al. 2018b, c) and will be discussed later in this chapter.

Overweight and obesity are associated with a higher risk for human breast cancer, and among affected women, associated with more aggressive tumours and with a worst prognosis (Carmichael and Bates 2004; Jiralerspong and Goodwin 2016). Obesity has also been associated with canine mammary tumour development, mainly juvenile obesity, with female dogs with overweight or obesity at 9–12 months presenting a higher risk of mammary tumour development (Sonnenschein et al. 1991; Pérez Alenza et al. 1998). Obesity at 1 year before diagnosis of mammary masses was also associated with a higher prevalence of canine mammary tumours and dysplasias (Pérez Alenza et al. 1998). Moreover, as in women, overweight or obese diseased bitches tended to have more aggressive tumours than lean or ideal weight dogs (Lim et al. 2015a, b). Furthermore, the ingestion of homemade meals, namely, with a high content of red meat, was also associated with a higher risk for mammary tumours (Pérez Alenza et al. 1998).

9.3 Clinical Course of Disease

Approximately 50–75% of mammary tumours in bitches are malignant, and 25–50% are benign (Hellmén et al. 1993; Salas et al. 2015; Rasotto et al. 2017; Canadas et al. 2018a). At presentation, approximately 20–30% of malignant cases present regional lymph node metastases, and although less frequently, distant metastases might also be present, mainly in the lungs, but also in the liver, bone, and other organs (Sorenmo et al. 2013; Santos et al. 2013a; Gundim et al. 2016; Canadas et al. 2018a). Recent studies reported an overall median survival time of 11 months after mastectomy, that approximately 30% of cases developed local recurrence and/or distant metastases and that 25–40% of dogs died or were euthanized within two years after diagnosis due to disease progression, and a two-year overall survival rates ranging from 36.4% to 48% (Santos et al. 2013a; Nguyen et al. 2018; Canadas et al. 2018a). However, the clinical course of the disease varies significantly according to different clinical and tumour features, including clinical staging, tumour histological type and grade, mode of growth, immunophenotype, and molecular and genetic features

(Yamagami et al. 1996; Santos et al. 2013a; Nguyen et al. 2018; Abadie et al. 2018; Canadas et al. 2018c; Canadas et al. 2018a).

A characteristic feature of mammary gland tumours in dogs is the common presence of multiple nodules at diagnosis, with benign and malignant tumours coexisting in the same patient (Santos et al. 2010a, b; Vascellari et al. 2016). This fact suggests that benign and malignant mammary tumours might not be separate entities; instead they may be part of a continuum process in which the malignant invasive carcinomas correspond to the advanced stages of the process. In this sense, canine mammary cancer provides an adequate model to study mammary gland carcinogenesis and progression, with direct application in human breast cancer research (Sorenmo et al. 2013).

In cats, approximately 80–90% of mammary tumours are malignant, and most of these present an aggressive behaviour and a poor prognosis (Hayes Jr et al. 1981; Ito et al. 1996; Millanta et al. 2002; Figueira et al. 2014). Feline mammary carcinomas are usually characterized by rapidly growing, highly infiltrative, and invasive nodules, with extensive necrotic areas, skin ulceration, and metastases (Misdorp and Weijer 1980; Martín De Las Mulas and Reymundo 2000), features associated with a poor prognosis (Weijer and Hart 1983; Amorim et al. 2006). At the time of diagnosis, approximately 25% of the cats with mammary carcinomas present neoplastic vascular invasion, and distant metastases are also often detected, ultimately leading to high morbidity and mortality rates (Misdorp and Weijer 1980; Zappulli et al. 2005; Sorenmo et al. 2013). The most common sites of metastization are the regional lymph nodes (83%), lungs (83%), pleura (22%), and liver (25%), and although less frequently, metastases to the adrenal glands, diaphragm, and kidneys are also described (Hayes Jr et al. 1981; Weijer and Hart 1983; Hahn et al. 1994). Feline malignant mammary tumours are generally more aggressive than canine mammary neoplasms, with reported survival times ranging from a few months to a few years; the main prognostic factors of canine malignancies act in a similar way in feline mammary cancer (Morris 2013).

9.4 Histopathological and Molecular Features of Mammary Tumours

9.4.1 Canine Mammary Tumours

Histopathology constitutes the gold standard method for mammary tumour diagnosis (Sorenmo et al. 2011; Rasotto et al. 2012; Goldschmidt et al. 2017). It is usually impossible to distinguish between benign and malignant mammary neoplasia at the clinical setting, and the accuracy of cytological differentiation is relatively low in canine mammary tumours; therefore, histopathology plays a central role in providing an accurate tumour diagnosis, as well as prognostic information (Goldschmidt et al. 2017).

The mammary gland is a modified apocrine sweat gland, histologically characterized by a tubuloalveolar structure (Sorenmo et al. 2011). The epithelium is composed by a dual-cell population of luminal epithelial and basal myoepithelial cells, juxtaposed to a basement membrane (Sorenmo et al. 2011). The gland is a hormone-dependent organ, and physiological changes are histologically identified throughout the distinct phases of the estrous cycle (Rehm et al. 2007; Santos et al. 2010b).

Routine histopathology allows recognition and distinction of a myriad of proliferative entities in the mammary gland, from hyperplasia to benign or malignant tumour lesions. Histological classification systems for canine mammary tumours published by the World Health Organization (WHO) were primarily based on descriptive morphology and to a lesser degree on prognosis (Hampe and Misdorp 1974; Misdorp et al. 1999; Misdorp 2002). In 2011, a revised classification has been proposed, based on morphological and prognostic features, incorporating several new histological subtypes (Goldschmidt et al. 2011; Rasotto et al. 2012). This new WHO classification subdivided the proliferative alterations of the canine mammary gland into eight distinct groups: hyperplasias/dysplasias; benign neoplasms; malignant epithelial neoplasms; malignant epithelial neoplasms, special types; malignant mesenchymal neoplasms (sarcomas); carcinosarcoma, malignant mixed mammary tumour; neoplasms of the nipple; and hyperplasia/dysplasia of the nipple (Goldschmidt et al. 2011). A complete description of the histological types is beyond the scope of this chapter, and a comprehensive review can be found in references (Misdorp et al. 1999; Goldschmidt et al. 2011).

Canine mammary neoplasms are characterized by a diverse morphology, originating from the proliferation of epithelial, myoepithelial, and/or mesenchymal cells (Misdorp et al. 1999; Goldschmidt et al. 2011). Myoepithelial cell proliferation constitutes one of the most distinctive features of canine mammary tumours, being frequently observed both in benign and malignant lesions. For tumour nomenclature purposes, simple type refers to the proliferation of one epithelial cell type (luminal epithelial or myoepithelial cells) and complex type to the proliferation of two epithelial cell types (luminal epithelial and myoepithelial cells) (Misdorp et al. 1999; Misdorp 2002; Goldschmidt et al. 2011, 2017).

Complex adenoma and benign mixed tumour represent the predominant benign tumour histotypes; both are characterized by the proliferation of luminal and myoepithelial cells, with benign mixed tumour being associated with the presence of metaplastic elements, such as bone and/or cartilage (Fig. 9.1a, b) (Misdorp et al. 1999; Goldschmidt et al. 2011).

The majority of malignant tumours have epithelial origin (carcinoma), with different morphological types identified – tubular, tubulopapillary, solid, and anaplastic (Fig. 9.1c) (Misdorp 2002; Sorenmo 2003; Goldschmidt et al. 2011; Sleeckx et al. 2011). The current proposed classification includes several new morphological subtypes, such as micropapillary invasive carcinoma, comedocarcinoma, ductal carcinoma, intraductal papillary carcinoma, and carcinoma and malignant myoepithelioma (Fig. 9.1d) (Goldschmidt et al. 2011; Rasotto et al. 2012). The application of this new modified classification revealed that it is a valuable tool for predicting the metastatic potential of canine mammary carcinomas (Rasotto et al. 2012).

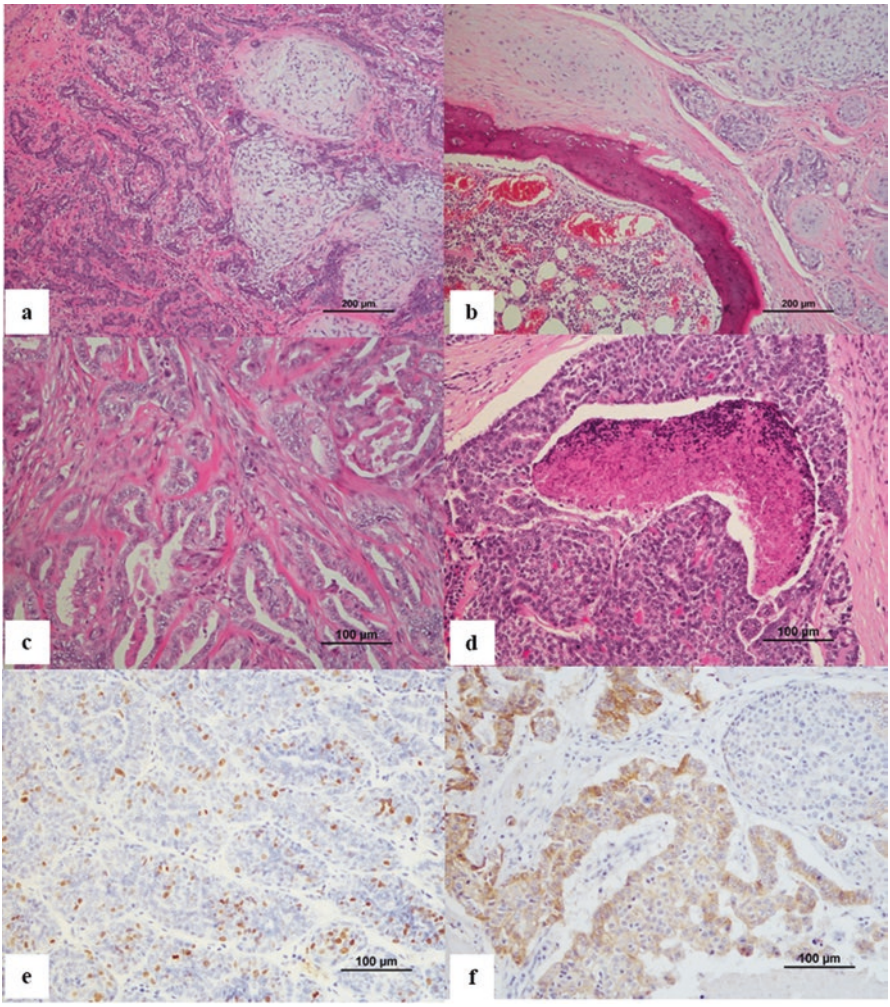

Fig. 9.1 Canine mammary gland tumours: (**a**) complex adenoma, benign proliferation of epithelial and myoepithelial cells. Myoepithelial cells present a fusiform to stellate form and are surrounded by a basophilic mucinous matrix (10×); (**b**) benign mixed tumour, proliferation of epithelial and myoepithelial cells associated with osseous differentiation. Note the presence of bone marrow (10×); (**c**) tubulopapillary carcinoma, neoplastic epithelial cells arranged in a tubular and papillary pattern (20×); (**d**) comedocarcinoma, neoplastic epithelial cells showing a central area of necrosis (20×); (**e**) solid carcinoma showing nuclear Ki-67 positive immunostaining (20×); (**f**) tubulopapillary carcinoma with reduced membrane expression of E-cadherin (20×); (**a**–**d**) hematoxylin and eosin; (**e**–**f**) streptavidin–biotin complex method. (Gill's hematoxylin counterstain)

With regard to simple carcinomas, an increase in the metastatic potential was observed from tubular to tubulopapillary, to solid, to anaplastic carcinoma (Rasotto et al. 2012), corroborating previous studies (Bostock 1975; Misdorp et al. 1999; Chang et al. 2005). Micropapillary invasive carcinoma, comedocarcinoma, and carcinoma and malignant myoepithelioma subtypes were also recognized as having significant metastatic potential (Gama et al. 2008a; Rasotto et al. 2012). In contrast to carcinoma and malignant myoepithelioma (characterized by the proliferation of malignant luminal epithelial and myoepithelial cells) (Rasotto et al. 2012; Goldschmidt et al. 2011), complex carcinomas (characterized by the proliferation of malignant luminal and benign myoepithelial cells) are commonly associated with a better prognosis (Misdorp et al. 1999; Misdorp 2002; Goldschmidt et al. 2011).

Special types of malignant epithelial neoplasms are less frequent, including squamous cell carcinomas, adenosquamous carcinomas, mucinous carcinomas, lipid-rich carcinomas, and spindle cell carcinomas (malignant myoepithelioma, squamous cell carcinoma–spindle cell variant, and carcinoma–spindle cell variant) (Goldschmidt et al. 2011, 2017).

Mesenchymal malignant tumours are unusual, but several sarcoma types are described, including osteosarcoma, chondrosarcoma, and fibrosarcoma, among others. Osteosarcoma is by far the most commonly diagnosed, being associated with a poor prognosis (Goldschmidt et al. 2011). Malignant mixed mammary tumour (known as carcinosarcoma) is uncommon, being characterized both by a carcinomatous and sarcomatous component, frequently associated with metastatic spread (Misdorp 2002; Goldschmidt et al. 2011).

With regard to human counterpart, WHO released a new and updated classification of breast tumours in 2012 (Lakhani et al. 2012). Fibroadenoma represents the most common benign breast tumour type, usually diagnosed in younger women (Yang et al. 2014); the most frequent type of breast cancer is the invasive carcinoma of no special type (IC-NST) (previously known as invasive ductal carcinoma not otherwise specified, NOS), which is a diagnosis of exclusion as it includes a heterogeneous group of carcinomas that fail to exhibit sufficient features to achieve classification as a specific histological type of carcinoma, such as lobular or tubular carcinoma (Lakhani et al. 2012).

Special types of human breast cancer have distinctive morphological characteristics and account for up to 25 % of all invasive breast cancers (Horlings et al. 2013); human classification includes several specific entities, namely, invasive lobular (5–15%), tubular (2%), cribriform (0.3–0.8%), metaplastic (0.2–5%), medullary (less than 1%), papillary (1–2%), and micropapillary (0.9–2%) carcinomas (Lakhani et al. 2012). Differing from canine mammary gland, lesions showing myoepithelial differentiation are uncommon in human breast; myoepithelial lesions are characterized by a varied morphology, including adenomyoepithelioma, myoepithelial carcinoma (malignant myoepithelioma), and epithelial–myoepithelial carcinoma (Lakhani et al. 2012). The prognosis for patients with myoepithelial neoplasia is usually good, with the exception of myoepithelial carcinoma (Foschini and Eusebi 1998; Rakha et al. 2006; Buza et al. 2010). As in canine species, this less aggressive nature of neoplasms with myoepithelial differentiation might be justified by the

tumour-suppressive properties of normal myoepithelial cells (Sternlicht et al. 1997; Jones et al. 2003; Reis-Filho et al. 2006).

Besides histological type, the histopathology report includes additional information relevant for prognosis such as the histological grade (Rasotto et al. 2012; Ehrhart et al. 2013). Several systems have been proposed for the grading of canine mammary tumours (Misdorp 2002; Clemente et al. 2010; Karayannopoulou et al. 2005; Goldschmidt et al. 2011), mainly based on the Elston and Ellis system for human breast invasive carcinomas (Elston and Ellis 1991). In women, histological grade is a powerful prognostic factor, and invasive breast carcinomas are routinely graded applying Elston and Ellis grading system (Lakhani et al. 2012). This numeric system is based on the assessment of tubule formation, nuclear pleomorphism, and mitotic counts, classifying carcinomas in grade 1 (well-differentiated), grade 2 (moderately differentiated), and grade 3 (poorly differentiated) (Elston and Ellis 1991; Lakhani et al. 2012). Recently, Peña et al. (2013) adapted Elston and Ellis system to canine mammary cancer, taking into account their heterogeneity, as well as the assessment of the frequent myoepithelial and mixed lesions; a prospective prognostic study revealed that this updated system constitutes a useful tool for predicting prognosis (Peña et al. 2013).

In addition to histological type and grading, the presence of stromal infiltration (Rasotto et al. 2012), lymphovascular invasion, and lymph node status have been found to be of prognostic significance (Kurzman and Gilbertson 1986; Sarli et al. 2002; Chang et al. 2005).

Although most mammary neoplastic lesions can be diagnosed by routine histopathology alone, some cases require the application of immunohistochemistry (IHC) to reach a definitive diagnosis; common scenarios that demand the use of immunohistochemical diagnostic markers both in human and canine settings include the identification of specific histological subtypes, the assessment of invasion, or the detection of lymph node micrometastases (Hicks 2011; Goldschmidt et al. 2011; Sorenmo et al. 2011; Liu 2014; Peña et al. 2014).

Carcinoma and malignant myoepithelioma and myoepithelial carcinoma diagnosis require immunohistochemistry to confirm the presence of myoepithelial cell proliferation, given that they usually lack their classic morphological appearance (Rasotto et al. 2012; Peña et al. 2014). Similarly, immunohistochemical cell differentiation markers are useful to classify unusual woman breast lesions, namely, adenomyoepithelial cell tumours, to differentiate radial scars from tubular carcinomas and for the diagnosis of breast papillary lesions (Dewar et al. 2011; Hicks 2011; Walker et al. 2012).

In human breast pathology, IHC is also routinely used in invasive carcinomas to assist in prognosis and to direct to specific treatments, through the evaluation of oestrogen (ER) and progesterone (PR) receptors and epidermal growth factor receptor 2 (HER2), which constitute targets and/or biomarkers of effective therapies (Payne et al. 2008; Lakhani et al. 2012).

Microarray-based gene expression studies revealed that human breast cancer encompasses a heterogeneous group of diseases, characterized by distinct molecular features (Badve et al. 2011; Guiu et al. 2012). Different breast cancer “intrinsic”

subtypes were identified (luminal A and B, basal-like, HER2 overexpressing, normal-like), resulting in a molecular taxonomy with prognostic significance (Perou et al. 2000; Sorlie et al. 2001, 2003). Surrogate immunohistochemical panels have been used to identify these subgroups, including hormone receptors, HER2, and proliferative and basal cell differentiation markers, with triple-negative (hormone receptor and HER2 negative) and basal-like (triple-negative positive for basal cell differentiation markers) carcinomas being associated with poor prognosis (Nielsen et al. 2004; Matos et al. 2005; Cheang et al. 2009; Blows et al. 2010). Although an IHC panel was adopted by the St. Gallen Consensus Committee for early breast cancer molecular subtyping leading to therapeutic and prognostic stratification (Goldhirsch et al. 2011, 2013; Nielsen and Perou 2015), controversies on the definition of IHC-defined taxonomy still prevail (Guiu et al. 2012). A current challenge is the distinction between luminal A and luminal B (HER2-negative) carcinomas, which has therapeutic implications (Goldhirsch et al. 2011). The value of using Ki-67 labelling index (Fig. 9.1e) for subgrouping these tumours has been questioned, due to the high degree of inter-laboratory variation, and experts have recently recommended the use of multi-gene expression assays (if available) to define high-risk signatures in ER-positive and HER2-negative carcinomas (Goldhirsch et al. 2013).

In the canine species, several studies applied the human molecular classification, with contradictory results (Gama et al. 2008c; Sassi et al. 2010; Kim et al. 2013; Im et al. 2014; Abadie et al. 2018), probably associated with differences in immunohistochemical cell markers, criteria, and sample selection (Peña et al. 2014). Even so, basal-like and triple-negative mammary carcinomas were frequently identified in the female dog, usually associated with an aggressive phenotype (Gama et al. 2008c; Im et al. 2014) and lower survival rates (Gama et al. 2008c; Kim et al. 2013; Abadie et al. 2018); these findings suggest canine mammary carcinomas as natural models for the study of triple negative and human basal-like breast carcinomas (Gama et al. 2008c; Abadie et al. 2018).

The use of IHC in canine mammary cancer has increased tremendously in the last decades in the search for relevant prognostic markers. Besides hormone receptors (Geraldes et al. 2000; Nieto et al. 2000; Martin et al. 2005), HER2 (Rungsipipat et al. 1999; Martin et al. 2003; Dutra et al. 2004; Hsu et al. 2009) and cell proliferation markers (Peña et al. 1998; Sarli et al. 2002; Matos et al. 2006), other molecular markers have been investigated, such as adhesion molecules (Brunetti et al. 2005; Matos et al. 2006; Gama et al. 2008), among others (Pinho et al. 2007).

The acquisition of an invasive epithelial phenotype has long been associated with functional loss or downregulation of epithelial (E-) cadherin-mediated adhesion, which is considered a hallmark of epithelial to mesenchymal transition (EMT) (Fig. 9.1f) (Cano et al. 2000). Both in canine and human breast cancer, numerous studies have focused on E-cadherin expression (Gamallo et al. 1993; Oka et al. 1993; Siitonen et al. 1996; Brunetti et al. 2005; Matos et al. 2006; Gama et al. 2008). In canine mammary carcinomas, E-cadherin loss or reduced expression was frequently associated with poor differentiation (Reis et al. 2003; Gama et al. 2008), invasion (Sarli et al. 2004; Brunetti et al. 2005; Matos et al. 2006, 2007; Gama et al.

2008), lymph node metastasis (Matos et al. 2007; Gama et al. 2008), or prognosis (Gama et al. 2008), corroborating human findings (Gamallo et al. 1993; Oka et al. 1993; Siitonen et al. 1996; Yoshida et al. 2001). However, results are not consensual in both cancer models, and the proposed tumour-suppressive role of E-cadherin in human breast cancer has been questioned (Hugo et al. 2017). In addition to E-cadherin, several studies highlighted the importance of associated catenins, such as β-catenin; its reduced expression in canine mammary carcinomas was found to be associated with high grade and invasion by some authors (Brunetti et al. 2005; Gama et al. 2008).

P-cadherin is a cell–cell adhesion molecule associated with tumour-promoting effects in human breast (Vieira and Paredes 2015); P-cadherin overexpression is found in a subset of human breast carcinomas, being associated with aggressive biological behaviour and poor outcome (Palacios et al. 1995; Peralta Soler et al. 1999; Paredes et al. 2002, 2005). In the female dog, P-cadherin is also frequently overexpressed in mammary carcinomas, being associated with tumour cell invasion (Gama et al. 2008). As in human breast cancer (Matos et al. 2005; Paredes et al. 2007), P-cadherin expression is primarily found in the basal-like subtype of canine mammary carcinomas, which is associated with poor prognostic features (Gama et al. 2008c; Gama and Schmitt 2012).

At present, no prognostic/predictive immunohistochemical marker is recommended for routine diagnosis of canine mammary cancer due to the absence of marker-associated therapies, contradictory results on biomarker prognostic value, and lack of standardized methodologies (Peña et al. 2014; Goldschmidt et al. 2017). Recently, supportive guidelines on the most useful immunohistochemical markers for canine mammary tumours have been provided, in an attempt to standardize their use and interpretation, ultimately leading to accurate and reproducible results (Peña et al. 2014).

9.4.2 Feline Mammary Tumours

The most widely accepted system for histological classification of feline mammary tumours is the WHO classification (Misdorp et al. 1999). More recently, an updated version has been proposed, including some new morphological subtypes (Goldschmidt et al. 2017). Hyperplastic/dysplastic mammary lesions are common in feline species and comprise several specific categories, while benign neoplasms are not frequent in queens. Most feline mammary tumours (80–90%) are rapidly growing malignant lesions, with an aggressive biological behaviour. Definition of the histological subtype of feline mammary carcinomas is based mainly on the cell types involved (luminal epithelial and/or myoepithelial cells) and on the arrangements adopted by the neoplastic cells – tubular, papillary, cystic, cribriform, and/or solid (Fig. 9.2a–c). As in women, malignant mammary tumours in queens usually encompass only luminal epithelium, being thus classified as simple carcinomas; myoepithelial involvement and metaplastic features (chondroid or osseous ele-

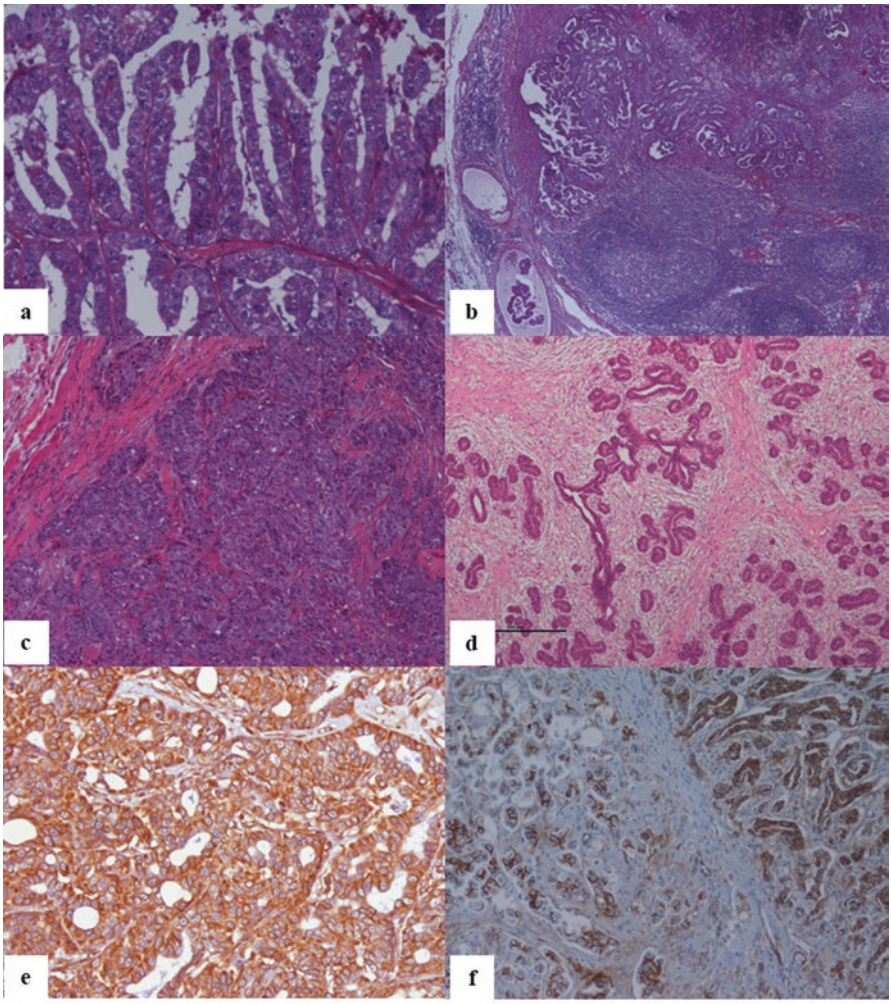

Fig. 9.2 Feline mammary gland tumours: (**a**) tubulopapillary carcinoma, neoplastic epithelial cells arranged in a tubular and papillary pattern (40×); (**b**) lymph node metastasis and intravascular neoplastic emboli of a tubulopapillary carcinoma (same case of fig. **a**, 4×); (**c**) solid carcinoma, neoplastic epithelial cells arranged in a solid pattern (40×); (**d**) fibroadenomatous change, benign ductular proliferation surrounded by an extensive stroma rich in mucin and collagen fibres. (4×); (**e**) tubulopapillary carcinoma showing vimentin positive immunoexpression (20×); (**f**) tubulopapillary carcinoma with reduced membrane expression of β-catenin (10×); (**a**–**d**) hematoxylin and eosin; (**e**–**f**) polymer-based system. (Mayer's hematoxylin counterstain)

ments) are uncommon findings. Generally, neoplastic epithelial cells exhibit a large nucleus, with prominent nucleoli and numerous mitotic figures (Misdorp et al. 1999; Goldschmidt et al. 2017). Histological grading of feline mammary carcinomas is established according to the same morphological criteria as for human and canine breast cancer, namely, tubular differentiation, nuclear pleomorphism, and mitotic

counting (Elston and Ellis 1991). Similarly to humans, histological grade is considered a valuable prognostic factor for feline mammary carcinomas, constituting a good independent predictor of disease-free interval and overall survival (Castagnaro et al. 1998; Seixas et al. 2011; Hughes and Dobson 2012; Zappulli et al. 2015). Recently, lymphovascular invasion and nuclear form were proposed as additional histological features in feline mammary carcinoma grading (Mills et al. 2015).

The histological presentation of several feline mammary hyperplasic, benign, and malignant lesions closely parallels those of human breast disease, enhancing the value of this animal species as a model for the study of their analogous lesions in women. That is the case of fibroadenomatous change and fibroadenoma, (Goldschmidt et al. 2017). Fibroadenomatous change is a large, rapidly growing, hormone-dependent, hyperplasic lesion. It is typical of young intact queens and can be also found during pregnancy. Microscopically, fibroadenomatous change is characterized by ductular proliferation surrounded by an extensive stroma rich in mucin and collagen fibres (Fig. 9.2d). Fibroadenoma is a benign neoplasm consisting of multiple tubules lined by a cuboidal/columnar epithelium, surrounded by an exuberant stroma of loose connective tissue (Misdorp et al. 1999; Goldschmidt et al. 2017). Both lesions share several morphological features with benign fibroepithelial tumours of the human breast, particularly with fibroadenoma, which comprises the vast majority of benign breast tumours, usually occurring in young women (Yang et al. 2014; Tan and Tan 2018). Histologically, human fibroadenoma is characterized by biphasic proliferation of both epithelial and stromal elements, closely resembling feline fibroepithelial lesions.

As previously performed in human breast cancer (Park et al. 2012; Goldhirsch et al. 2013), recent immunohistochemical studies allowed the establishment of a molecular-based classification for feline mammary carcinomas, with several recognized subtypes, namely, luminal A, luminal B, HER-2 overexpressing, and triple-negative basal-like and triple-negative normal-like carcinomas, some of which clearly mimic their human counterparts. This molecular-based categorization, which relies on the assessment of the immunoexpression of hormonal receptors, HER-2, luminal epithelial/basal markers, and proliferation markers, supports the identification and characterization of different feline mammary carcinoma subtypes, associated with specific clinicopathological features and with different clinical outcomes (Brunetti et al. 2013; Soares et al. 2016b).

Currently, the assessment of breast cancer molecular profile, namely, ER and PR status and HER-2 expression, is essential for diagnosis, classification, and treatment of the human disease (Perou et al. 2000; Peppercorn et al. 2008; Falck et al. 2013). Most human breast cancers are hormone receptor-positive carcinomas, of the luminal subtypes, that tend to respond well to endocrine therapy, presenting a good prognosis (Park et al. 2012; Goldhirsch et al. 2013). Other breast cancer subtypes (HER-2 overexpressing) benefit from treatment with humanized monoclonal antibodies, such as trastuzumab (Yin et al. 2011). However, part of breast cancer cases lack hormone receptors, are less endocrine sensitive lesions, miss other specific therapeutic targets, or develop resistance to endocrine/HER-2 targeted therapy. These breast cancer cases are usually characterized by a poorly differentiated,

highly aggressive phenotype and constitute a major clinical challenge, being associated with a worse prognosis (Bosch et al. 2010; Esteva et al. 2010; Toft and Cryns 2011; Elizalde et al. 2016; Liu et al. 2017).

The molecular-based classification of feline mammary carcinomas demonstrated their molecular heterogeneity, and several of the molecular subtypes identified present similarities with some aggressive forms of the human disease. Most feline mammary carcinomas are highly aggressive, hormone-independent tumours with an unfavourable clinical outcome. Several investigations have demonstrated a progressive decrease in hormonal receptor expression from feline normal mammary tissue to hyperplasic/dysplastic lesions and from benign to malignant tumours (Rutteman et al. 1991; Martín De Las Mulas et al. 2000; Cardazzo et al. 2005; Millanta et al. 2005b; Burrai et al. 2010; Caliari et al. 2014). This hormonal independence of feline mammary carcinomas has also been associated by some authors to high histological grade of carcinomas, vascular invasion, and lymph node metastases, being thus considered a reliable predictor of poor prognosis (Millanta et al. 2006; Soares et al. 2016c). Some reports have documented HER-2 overexpression in around 30–60% of FMC and associated this feature with poorly differentiated tumours, low disease-free survival, and short overall survival (De Maria et al. 2005; Millanta et al. 2005a; Brunetti et al. 2013; Soares et al. 2016b). Furthermore, Soares et al. (2016b) have recently demonstrated that triple-negative basal-like mammary carcinomas in cats are associated with large tumour size and vascular invasion, also showing the lowest overall survival and the shorter disease-free interval, clearly resembling their human counterpart. The correspondence observed between the molecular-based taxonomy of feline mammary carcinomas and human breast cancer emphasizes the potential comparative value of these lesions in the development of innovative and alternative therapeutic strategies for breast cancers unresponsive to conventional medical treatment and in predicting biological behaviour of mammary neoplasia.

More recently, a claudin (CLDN)-low molecular breast cancer subtype was reported; it is defined by an aggressive biological behaviour and high metastatic capacity, being frequently refractory to conventional chemotherapeutic protocols and associated with a bad prognosis (Kim et al. 2008; Prat et al. 2010; Lu et al. 2013). Similarly, a decreased expression of CLDN-1, CLDN-2, and CLDN-7 was also reported in feline mammary carcinomas, and CLDN-2 and CLDN-7 under-expression was significantly associated with metastization (Flores et al. 2014a, b). These findings clearly support the involvement of CLDN down-expression in mammary carcinogenesis and metastization in feline species and underline the importance of this animal species as a model in pursuing for new therapeutic regimens focused on this distinctive breast cancer subtype.

Feline mammary carcinomas are characterized by under-expression of low-molecular-weight cytokeratins (typical of well-differentiated epithelial tissues) and by the expression of basal high-molecular-weight cytokeratins (namely, CK5/6 and CK14) and vimentin (Fig. 9.2e) in neoplastic cells (de las Mulas et al. 1994; Espinosa et al. 1999; Peñafiel-Verdu et al. 2012; Brunetti et al. 2013; Caliari et al. 2014; Soares et al. 2016b). These features are more frequent in invasive carcinomas and have been significantly associated with a poor prognosis (Peñafiel-Verdu et al. 2012;

Soares et al. 2016b). Such findings resemble some aggressive forms of human breast cancer, which have been associated with invasive behaviour, metastasis, and increased drug resistance (Sommers et al. 1992; Gilles et al. 2003).

Like in human breast cancer, feline mammary carcinomas typically exhibit significant changes in mechanisms of cell adhesion, such as those involving the cadherin–catenin complex. E-cadherin down-expression was described by some authors in feline mammary carcinomas (Dias Pereira and Gärtner 2003; Zappulli et al. 2012; Figueira et al. 2014) and was associated with lymph node metastases (Peñafiel-Verdu et al. 2012). This feature was also reported in breast cancer cases, in which it is associated with high histological grade (Gamallo et al. 1993). On the other hand, P-cadherin overexpression was recently documented in feline mammary carcinomas, being related to high histological grade, infiltrative growth pattern, and vascular invasion (Figueira et al. 2012, 2014). Likewise, in human breast cancer, this immunostaining pattern is associated with recurrence and distant metastasis and with poor prognosis, namely, short overall survival and reduced disease-free interval (Liu et al. 2012). Furthermore, N-cadherin expression was also documented in mammary carcinomas in queens and associated with lymph node metastasis (Buendia et al. 2014), similarly to data from breast cancer (Bock et al. 2014). Feline mammary malignant tumours are also characterized by reduced membrane expression of α-, β-, and p120-catenin, as well as by abnormal subcellular localization of β- and p-120 catenin (Fig 9.2f) (Peñafiel-Verdu et al. 2012; Zappulli et al. 2012; Figueira et al. 2015). Peñafiel-Verdu et al. (2012) associated β-catenin under-expression to the development of metastases. Similarly, α-, β-, and p120-catenin abnormal/reduced expression in breast cancer was reported and related to a poor prognosis (Yoshida et al. 2001; Nakopoulou et al. 2002; Talvinen et al. 2010).

In addition, data from recent research demonstrated that feline mammary carcinomas emulate the EMT process, which has been described in human breast cancer and related to tumour invasiveness and metastatic capability (Fedele et al. 2017). Epithelial to mesenchymal transition is a program of phenotype transformation characterized by (1) loss of epithelial traits, in which neoplastic cells typically lose intercellular adhesion proteins, namely, E-cadherin, and exhibit downregulation of epithelial markers, such as low-molecular-weight cytokeratins, and (2) acquisition of mesenchymal-like features, with gain of several mesenchymal-associated markers, like vimentin and N-cadherin, and development of a fibroblast-like morphology through cytoskeleton reorganization. This process of epithelial plasticity leads to loss of intercellular contact and changes in cell shape and polarity, favouring the conversion of a stationary to a migratory phenotype, thus increasing the invasive potential of the neoplastic cells (Sarrió et al. 2008; Foroni et al. 2012; Wu et al. 2016). As described above, feline mammary carcinomas encompass a series of immunophenotypic changes (decreased E-cadherin and low-molecular-weight cytokeratin expression, along with vimentin, P-cadherin, N-cadherin, and basal high-molecular-weight cytokeratin overexpression) that clearly resemble EMT, endorsing the importance of this animal species in the study of tumour progression, invasion, and metastasis.

These extensive immunophenotypic changes that characterize feline mammary carcinomas and permit the definition of several different subtypes corresponding to distinct clinical entities (often mirroring their human counterparts) support the cat as an appropriate model for the study of some specific forms of aggressive breast cancer.

9.5 Genetics

Genetic homology between canine and feline mammary tumours and human breast cancer is well recognized and accepted (Lutful Kabir et al. 2015; Adega et al. 2016). Moreover, the remarkable progress in the development of molecular tools which allowed the coverage of the canine and feline genome, canine and feline DNA microarray use, and proteomic analyses is factual and in continuous evolution (Rivera and von Euler 2011; Thomas 2015). However, genetic basis of canine and feline mammary tumours remains poorly characterized when compared to its human counterpart. In fact, there is still a need to further understand canine and feline cancer genetics, in basic and clinical areas, in order to obtain robust models which could be reproducibly and effectively used to develop and test new therapeutic tools for humans and also for animals (Kim et al. 2004).

Recent molecular analyses have shown that rather than a single disease, breast cancer is a mixture of several diseases with different biological behaviours, which should direct to customized treatments for each patient (Verma 2012; Rivenbark et al. 2013). The understanding of individual genetic profiles in breast cancer enabled the implementation of guidelines and clinical practices. These are based on preventive measures such as prophylactic surgeries and family follow-up and specific or individual treatments, which are the core of the so-called personalized medicine (Sabatier et al. 2014; Stover and Wagle 2015). In women, almost 30% of breast cancer cases are considered hereditary, and up to 25% of these are due to a mutation in one of the few rare but highly penetrant identified genes, including BRCA1, BRCA2, PTEN, TP53, CDH1, and STK11 (Antoniou and Easton 2006; Walsh et al. 2006). An additional 2–3% of cases are due to a mutation in rare, moderate penetrant genes, such as CHEK2, BRIP1, ATM, and PALB2 (Shiovitz and Korde 2015). Several other candidate genes predisposing to breast cancer, such as FGFR2, LSP1, MAP3K1, and TOX3, have also been reported (Ripperger et al. 2009). Besides the susceptibility to develop breast cancer, the influence of genetic profiles in clinicopathological features is also well documented in numerous studies, including genome-wide association studies (Han et al. 2004; Long et al. 2007; Giess et al. 2010; Chan et al. 2012; Sirisena et al. 2018).

Being canine and feline mammary tumours a model for human breast cancer (Vail and MacEwen 2000; Burrai et al. 2010; Queiroga et al. 2011; Adega et al. 2016; Abdelmegeed and Mohammed 2018), the awareness of concrete genetic variations such as mutations, deletions, insertions, and genetic polymorphisms can be essential in canine and feline disease diagnosis, prognosis, and treatment and potentially lead to implementation of an individualized approach also in veterinary medicine (Lloyd et al. 2016; Pang and Argyle 2016).

9.5.1 Genetics of Canine Mammary Tumours

In 1989, a disease-causing mutation was identified for the first time in dogs (Evans et al. 1989), and 10 years later, the first germline mutation associated with canine mammary tumours was reported in the p53 tumour suppressor gene, which has long been classified as an important cancer catalyst in humans (Veldhoen et al. 1999). Since then, mutations have been described for over 130 diseases, and the vast majority of these (107) are inherited based on an autosomal recessive pattern (Slutsky et al. 2013). Furthermore, two of them have been successfully used for gene therapy in humans (Switonski 2014). Currently, over 130 molecular genetic tests are available for dogs, most of these being breed-specific mutations and single-nucleotide polymorphisms (SNPs), which emphasizes the nature of hereditary diseases in canine medicine (Slutsky et al. 2013). This great progress allowed the identification of genetic profiles of specific tumours, in addition to the recognition of clinically relevant constitutional genomic alterations in dogs. This recent evidence led to a new approach to mammary pathogenesis (Klopfleisch et al. 2011). The emerging studies show promising results regarding the significance of genetic profiles in cancer susceptibility and clinicopathological features.

Genetic approach to canine mammary tumours has been covering both somatic and germline genetic variations, alongside with the analyses of structural aberrations at the subchromosomal level, including interchromosomal rearrangements or chromosomal instability. The identification of genetic variants in tissue samples such as mutations and SNPs, among others, has been conducted by comparing normal and neoplastic mammary tissue or by comparing different histological types of tumours. In this field, several genetic variations have been identified, and homology has been studied and compared between canine and human genes, specially focusing both BRCA1 and BRCA2 genes (Szabo et al. 1996; Bignell et al. 1997; Ochiai et al. 2001; Yoshikawa et al. 2005; Goebel and Merner 2017).

Individual genetic background, emphasizing constitutional genetic variations, has also been the aim of recent studies. In canine species, the high incidence of mammary tumours in certain breeds suggests a genetic component effect, similar to familiar breast cancer. In fact, breeds showing the highest predisposition to develop mammary tumours are Poodles, Spaniels, Pulis, English Setters, German Shepherds, Yorkshire Terriers, and Doberman Pinschers (Egenvall et al. 2005). In 2009, Rivera et al. selected 10 canine orthologues of genes either known or predicted to increase the risk of human breast cancer, including BRCA1, BRCA2, CHEK2, ERBB2, FGFR2, LSP1, MAP3K1, RCAS1, TOX3, and TP53. Four to nine common SNPs were selected per gene, totalizing 63 genotyped SNPs. Haplotypes in BRCA1 and BRCA2 genes were significantly associated with an increased risk of developing mammary tumours (with a stronger association to BRCA1 in malignant cases) in English Springer Spaniel female dogs (Rivera et al. 2009). In 2011, Borge et al. included 64 SNPs from 11 candidate genes, namely, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EGFR, ESR1, HER2, PTEN, STK11, and TP53, from 8 different breeds, divided into “high risk” and “low risk” groups. The authors highlighted

potential pathogenic variants that appear to be associated with canine mammary tumours (Borge et al. 2011). Later, they also found a correlation with the ESR1 gene, revealing its influence in the susceptibility to mammary tumour development (Borge et al. 2013). In 2014, a case-control study surveyed female dogs from several breeds for genetic differences, specifically in BRCA1 and BRCA2. The latter was found to be associated with risk of mammary tumour development (Enginler et al. 2014). Recently, a study described the first canine mammary tumour genome-wide association study, including approximately 130,000 SNPs, comprising only English Springer Spaniel dogs (Melin et al. 2016). The authors revealed a new gene, namely, CDK5RAP2, involved in cell cycle regulation, with a possible key role in the development of mammary tumours (Melin et al. 2016). The most recent study, considering the risk of mammary tumour development, included 67 canine SNPs from 14 genes including HER2, EGFR, TP53, STK11, BRCA1, BRCA2, RAD51, CHECK2, PTEN, BRIP1, ESR1, PGR, PRLR, and COMT (Canadas et al. 2018b). From this study, RAD51 and STK11 genes emerged as being involved in the risk of mammary tumour development (Canadas et al. 2018b). Additionally, genetic variants, such as polymorphisms related to the hormonal environment, demonstrated to be pertinent in different clinicopathological features (Dias Pereira et al. 2008, 2009; Canadas et al. 2018c). In this context, an association between age at onset of mammary tumours and tumour recurrence has been reported (Dias Pereira et al. 2008, 2009). Later, prognostic features were found to be associated with the individual's genetic profile, specifically with histological grade and vascular invasion (Canadas et al. 2018c). These results emphasize the importance of genetic variations on recognized prognostic factors for mammary tumours in dogs.

Several features of human breast tumours involving genomic aberrations have been identified in canine mammary tumours (Beck et al. 2013; Liu et al. 2014; Borge et al. 2015; Santos et al. 2017). Beck et al. (2013) detected copy-number aberrations in five sequenced tumour genomes and analysed the representation of copy-number imbalances in the plasma cell-free DNA. A recurrently deleted region at the proximal end of chromosome 27 was found in four out of the five tumour genomes and was proven to be significantly related with higher Ki-67 scores (Beck et al. 2013). Liu et al. (2014) explored the genetic differences between simple and complex carcinomas. Their findings indicated that canine simple carcinomas probably arise from genomic aberrations, whereas complex carcinomas originate from epigenomic alterations. Aligned with Beck et al. (2013), Borge et al. (2015) also identified copy-number aberrations, fundamentally in PTEN and MYC genes that often occur during mammary tumour development, with increased frequency of aberrations and loss of heterozygosity being positively correlated with increased malignancy in terms of histopathological diagnosis. Lately, due to the known evidence on the heterogeneity in canine mammary tumours, a pilot study that included synchronous multiple tumours from the same animals reported different clonal genetic profiles between tumours, providing preliminary evidence for a probable independent pathogenesis of the different tumours of dogs presented with multiple mammary tumours (Santos et al. 2017).

9.5.2 Genetics of Feline Mammary Tumours

The study of the genetics of feline mammary tumours is of crucial importance allowing the data acquired to be effectively translated into the women's breast cancer. Indeed, the extraordinary homology between the human and the cat genomes allows the translation of the genetic data of the cat into the human counterpart, highlighting the use of the cat as a model of human breast cancer.

The genetic alterations that occur in cancer can serve as cancer biomarkers for diagnosis and prognosis and for choosing the adequate therapeutic program or also as markers to assess tumour response to therapy. As in the dog, also in the cat, the genes or chromosome alterations involved in mammary tumour carcinogenesis are far from being characterized.

The first published work regarding a cytogenetic study in feline mammary tumours goes back to 1991, where the loss of several chromosomes in two feline mammary cell lines were identified, namely, A3, B4, D2, F1, and F2, and also detected the gain of chromosome C2 (Minke et al. 1991). Further works were published, but most probably due to technical difficulties, several marker chromosomes were detected with the putative involvement of chromosomes B1, B2, and D4 (Mayr et al. 1995b, 1999; Santos et al. 2006). Numerous highly reshuffled karyotypes with recurrent losses of chromosome B2-material and E3-material were reported in feline mammary gland neoplasms (Mayr et al. 1999). More recently, several different aneuploidies in different passages of a feline mammary cancer cell line (FkMTp) were identified (Borges et al. 2016). These cell lines demonstrated to have a high degree of genome instability with several chromosome rearrangements involving different chromosomes (unpublished work). Interestingly, some of these chromosomes are the same as the ones involved in the previous cytogenetic works done by Minke et al. (1991) and Mayr et al. (1995b, 1999), demonstrating the recurrent use of these chromosomes in the tumorigenesis of feline mammary tumours. It is also important to highlight that some of these chromosomes, which seem to be involved in feline mammary tumours, are syntenic to human chromosome regions reported to be associated with the human breast cancer (Bièche et al. 1997; Popescu and Drazen 2002; Wessels et al. 2002; Bergamaschi et al. 2006; Korkola and Gray 2010).

Data regarding the key cancer-related genes that were associated with initiation or progression of feline mammary tumours was extensively reviewed by Adega et al. (2016). In this report, only the feline cancer genes that currently present more promising results to be used as models of human breast cancer in a near future will be focused. At the primary sequence DNA level, the genes that are being analysed more extensively in feline mammary tumours are the TP53 suppressor gene and the growth factor genes, such as the epidermal growth factor receptor, the EGFR family, mainly the erb-B2 receptor tyrosine kinase 2 (usually named ERBB2, EGFR2, HER2, or NEU) (Ignar-Trowbridge et al. 1992; Buerger et al. 2000; Santos et al. 2012a, 2013b).

The mutations detected in TP53 gene in human breast cancer, among other gene mutations, seem to be associated with the most aggressive triple-negative breast cancer (Walerych et al. 2012). Some mutations in this gene have also been reported

in cats with mammary tumours (Mayr et al. 1995a, 1998, 2000). In feline mammary carcinoma tissues, Nasir et al. (2000) detected a mutant p53 protein similar to what was reported for human breast cancer.

One of the most important genes for human breast cancer is the HER2 gene. In cats, HER2 gene at its DNA sequence was recently analysed for the first time (Santos et al. 2012a, 2013b) and was found that has no amplification with in situ hybridization techniques (Soares et al. 2013). The studies on HER2 expression in feline mammary tumours are more abundant (Adega et al. 2016). Some of these reports suggested that feline mammary tumours are a potential valuable model for HER2-negative human breast cancer, specifically those with a homologous gene behaviour and the recurrent occurrence of low HER2 expression levels in feline mammary tumours (Santos et al. 2013b). Moreover, it seems that feline mammary tumours can also be used as model for the HER2-positive human breast cancer (Soares et al. 2016a), since approximately 30% of feline mammary tumours test positive for the human epidermal growth factor receptor 2, which promotes the growth of cancer cells. However, Soares et al. (2016a) found that the HER2 protein in feline serum and in tumour tissue was associated with features of lower aggressiveness, contradicting what is described for humans. In fact, all these findings, together with the non-amplification of the HER2 gene (Soares et al. 2013), reinforce the need for more studies in order to clarify the biological role of this protein in feline mammary tumours.

Genetic investigation is quintessential and has been gradually increasing over the last years. The study of specific genetic variations in genes known to be involved in mammary carcinogenesis will undoubtedly contribute to a wider understanding of this complex disease. This subject holds great promise in human breast cancer and in canine and feline mammary tumours' clinical management because of its potential application in a preventive, diagnostic, and prognostic context and will certainly open new perspectives in determining potential targets for individual therapeutic approaches – the emerging trend called "theranostics" (Blomme and Spear 2010).

9.6 Conclusions

The "One Health" approach to oncologic diseases, including mammary tumours and other neoplasias, provides advances in the knowledge of malignancies and potentially an improvement in clinical outcomes for diseased humans and animals. The similar epidemiological, clinical, histological, molecular, and genetic features shared between human breast cancer and canine and feline mammary tumours described in this review represent important information to be used in research and in the clinical practice. However, despite the recent advances in diagnosis and treatment, breast cancer remains the leading cause of cancer-related mortality in women and also one of the most important causes of morbidity and mortality in canine and feline oncology. Future studies, using the "One Health" approach, might contribute to obtaining relevant knowledge in the clinical management of this disease.

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