Canine mammary cancer: clinical implications with specific focus on the HER-2 gene

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Abstract

Canine mammary cancer (CMC) is one of the most common neoplasms in intact females in comparison to other species. Several risk factors have been identified, including breed, genetic predisposition, age, reproductive history, hormonal influence, diet, and body condition, in addition to previous lesions to the mammary gland, such as mammary atypical hyperplasia. An understanding of the genetic markers for the disease and a clinical approach are important for establishing a specific therapy that can allow adequate patient survivorship. Overexpression of the HER-2 gene in canines and humans is associated with a poor clinical prognosis, mainly short survivorship, although the clinical relationship is not clear. The incidence of HER-2 in female dogs can range from 29.7% to 38%. However, overexpression of HER-2 is not necessarily associated with malignancy processes of the mammary tissue, although it participates in cellular proliferation. Finally, canines remain one of the most important models for comparative oncology with humans due to the great similarity in the spontaneous presentation and development of cancer, and in the high homology in the amino acid sequence.

Key words: *c-erbB2; diagnostic; malignant mammary tumour; prognosis; risk factors*

Overview

The use of animal models for research on genetic human pathologies poses multiple advantages, including the greater size of laboratory specimens that facilitates their management (Lindblad-Toh et al., 2005; Uva et al.,

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2009), highly similar tissue development and architecture, and the involvement of similar genes. The latter enables us to identify and understand the clinical, pathological, and genetic mechanisms involved in the onset and development of cancer (expression). Studies using canines represent an ideal solution to reduce the gap between animal models with naturally developed diseases and facilitate extrapolations to human medicine (Rowell et al., 2011).

Mammary cancer (MC) is a highly complex disease due to its heterogeneous histopathology, biological behaviour, and responses to systemic interventions (Geleick et al., 1990; Viale, 2012). Furthermore, it is considered a worldwide public health issue (Uribe et al., 2013). Canine mammary cancer (CMC) is one of the most important pathologies in veterinary medicine, particularly in non-spayed female dogs (Schneider et al., 1969; Sleeckx et al., 2011; Beck et al., 2013). Given the multifactorial origin of the disease, prevention and treatment is complex (Perez-Alenza et al., 2000). CMC is among the main causes of mortality in females and this tumour pathology has the greatest incidence compared to other domestic species (Cruz, 1999). CMC corresponds to almost 50% of all canine tumours (Misdorp et al., 1999; Dhami et al., 2010), with an incidence estimated to be three times higher than in women (Kumaraguruparan et al., 2006; Dhami et al., 2010). In addition, 50% to 70% of canine mammary tumours (CMT) are considered malignant (Moe, 2001; Merlo et al., 2008; Salas et al., 2015).

Canines as a model for naturally occurring human breast cancer (BC)

Canines are the most common pet worldwide, and it is estimated that 33% people over 15 years old own a dog. This is the most common pet in Latin America, Asia and Oceania, and second most common in Europe (GfK, 2016). This is due in part to ongoing social changes in recent years, which have led to the role of pets as "family members" (Sharpe, 2017), even influencing the owners' finances (Pet Census, 2016). As a consequence, companion animals, particularly canines, are an excellent model for studying complex human diseases (Rowell et al., 2011).

At the genome level, canines share ~650 Megabases (Mb) of ancestral sequence with humans (Lindblad-Toh et al., 2005; Pang and Argyle 2009). Also, many uni- or multifactorial physiological disorders constitute unique models for human diseases (Yang et al., 1999; Starkey et al., 2005). Nearly 400 hereditary diseases in canines have an equivalent in humans, many of which have been described and named in the same manner (Starkey et al., 2005). Therefore, as with murine models, there is increasing interest in undertaking comparative oncology research with canines (MacEwen, 1990; Pinho et al., 2012). In canines, the evolution period of cancer is significantly less than in humans, as is the response to treatment, enabling preclinical studies in cancer development (Uva et al., 2009; Peruzzi et al., 2010). As such, the time period for evaluating cancer treatment success in canines is 18 months, while at least seven years are required in humans (Paoloni and Khanna, 2008).

Canines can develop MC spontaneously (Macewen et al., 1982; Jaillardon et al., 2015) or it can be hereditary, though there is insufficient evidence despite the evident homologies with humans (Szabo et al., 1996; Goebel and Merner, 2017). The underlying genetic complexity of tumour development (Aguirre-Hernández et al., 2009), biological behaviour, growth patterns, morphology, tumour progression, metastasis patterns, histological

types, and therapeutic response are highly similar in humans (Starkey et al., 2005; Paoloni and Khanna, 2008; Pang and Argyle, 2009; Tamburini et al., 2009; Peruzzi et al., 2010; Tang et al., 2010; Gupta et al., 2012). The epidemiological characteristics are also similar between the two species (Cassali, 2013; Vascellari et al., 2016), although for some cancer types, disease progression is more aggressive in canines than in humans (Meirelles, 2010; García, 2013). Therefore, the establishment of oncology research protocols for the early detection of cancer in canines will enable its future extrapolations, followed by advantages for medicine and for human and animal survivorship.

CMC risk factors and pathogenesis

Different factors influence CMC development, including breed and genetic predisposition, age, reproductive history, hormonal activity, diet, and obesity (Sleeckx et al., 2011). Previous lesions, such as mammary atypical hyperplasia, can also increase the risk of CMC presentation (Dupont et al., 1993; Page et al., 2003; Ferreira et al., 2014).

Breed and genetic predisposition: Purebreds show a higher predisposition (Hemanth et al., 2015; Sahabi et al., 2015). French Poodle, English Springer Spaniel, English Spaniels, Cocker Spaniels, German Shepherds, Maltese, Yorkshire Terrier, and Dachshunds display a high incidence of CMC (Borge et al., 2011; Sleeckx et al., 2011; Caicedo et al., 2012; Burrai et al., 2015; Campos et al., 2015). Dhami et al. (2010) and Hemanth et al. (2015) reported other breeds that are highly susceptible to CMC development, including the Doberman, Labrador Retriever, Great Dane, Pomeranian, and Spitz (Dhami et al., 2010; Hemanth et al., 2015). Meanwhile, other breeds have been identified as low risk: Border Collie, Shetland Sheepdog, Bernese Mountain, and Saint Bernard (Borge et al., 2011). However, these results could be biased by the ownership popularity of certain breeds compared to others (Vidales and Eslava 2007; Dhami et al., 2010). Yet, there is a consensus regarding a higher cancer predisposition of small breeds compared to large breeds (Chang et al., 2005; Hsu et al., 2009; Sahabi et al., 2015).

Age: In addition to genetic predisposition, age also plays a fundamental role. CMC presentation is more frequent in mid to older age females, and an average age of six years has been defined as the "cancer age" (Perez-Alenza et al., 2000; Dhami et al., 2010; Shinoda et al., 2014). In addition, a high incidence is also observed between 9 and 10 years (Støvring et al., 1997; Hsu et al., 2009; Caicedo et al., 2012; Campos et al., 2015., Sahabi et al., 2015). However, there are also reports of age averages under 8.4 years (Chang et al., 2005), while authors such as Hemanth et al. (2015) found a higher age range of 6 to 10 years, with a reduction in frequency after 12 years.

Reproductive history: Non-spayed females are more susceptible to CMC than spayed females (Chang et al., 2005; Sleeckx et al., 2011; Hemanth et al., 2015; Sahabi et al., 2015). Females spayed before their first oestrous cycle have approximately a 0.5% risk of developing CMC, while ovariohysterectomy after the second cycle increases the risk to 8%, and to 26% after three cycles (Schneider et al., 1969). Therefore, ovarian hormone ablation through ovariohysterectomy performed during early life dramatically decreases dose-dependent steroid exposure, thus reducing the risk of early mammary tumour development (Sorenmo et al., 2011). Additionally, ovariohysterectomy increases the survival index when established as a therapeutic measure for CMC (Hsu et al., 2009), since the survival index of females with CMC that undergo ovariohysterectomy has been found to

nearly double compared to non-spayed females (Chang et al., 2005). Nevertheless, there are differences among cancer types regarding the therapeutic impact of ovariohysterectomy, e.g. in females with complex carcinoma compared to simple (Chang et al., 2005).

Hormone influence: Ovarian steroid hormones and products with medroxyprogesterone acetate (MPA) produce a proliferative effect on the mammary tissue, thus stimulating growth and increasing the risk of mammary tumour development (Sleeckx et al., 2011). Steroid hormones (mainly oestrogens and progesterone) participate in the normal development of the mammary tissue and play a key role in the early stages of CMC pathogenesis (Sorenmo et al., 2011). Therefore, an ovariohysterectomy after the second oestrous cycle does not guarantee full protection from possible tumour development (Schneider et al., 1969). This can be explained by the fact that both oestrogen receptors (ER) and progesterone receptors (PR) are present in high amounts in normal tissues and benign lesions, leading to accumulation and availability in the mammary tissue (Macewen et al., 1982; Rutteman et al., 1988; Clamp et al., 2003; Rao, 2008), as compared to cancerous or metastatic tissues. Nevertheless, there is a notable presence of 17β-[^{3}H] oestradiol (Macewen et al., 1982). Furthermore, MPA, a progestin used to prevent oestrous or treat false pregnancy, is known to increase the risk of CMC development (Rutteman et al., 1988; Støvring et al., 1988). MPA induces overproduction of the growth hormone (GH), which induces the development of dysplasia and benign tumours (Perez-Alenza et al., 2000). The interaction of the GH in the mammary tissue stimulates the insulin-like growth factor 1 (IGF-1).

Prolactin (PRL) is a 199 amino acid peptide with a molecular weight of 23 kDa (Freeman et al., 2000), synthesized by the anterior pituitary gland. This peptide displays a luteotrophic action that is especially important during the second half of pregnancy (Verstegen-Onclin and Verstegen, 2008; Rufo et al., 2016), participates in cellular development and differentiation of the canine mammary gland (Jöchle, 1997; Rufo et al., 2016), and carries out lactogenic activity (Michel et al., 2012a), among other functions. Although the role of PRL in tumour development in the canine mammary gland is still under debate, several studies have proposed that tumour genesis in the pituitary gland is associated with decreased secretory activity (El Etreby et al., 1980). This agrees with later studies that reported a reduced expression of the prolactin receptor (PRLR) (Michel et al., 2012b). In addition, findings have shown high levels of PRL in CMC compared to benign lesions or hyperplasias (Queiroga et al., 2005). These authors indicate that most PRL present in cancerous tissues is not of pituitary origin. This has been demonstrated in humans (Ginsburg and Vonderhaar, 1995), where there might be an autocrine and paracrine effect (Ben-Jonathan et al., 2002; Clevenger et al., 2003).

Diet: Homemade food, such as those rich in fat and beef and pork, increase susceptibility to CMC compared to diets rich in poultry or balanced diets (Alenza et al., 2000; Sleeckx et al., 2011).

Overweight and obesity: Body fat ranges from 15 to 25% in healthy animals, while more than 30% is considered obesity (Burkholder et al., 2000). However, this relationship tends to be narrower as age increases (German, 2006). Body mass and overweight status can be assessed through morphological analysis with determination of body fat (Burkholder et al., 2000), e.g. the Canine Body Mass Index (IMCC) (Muller et al., 2008) or Escore of Body Condition (ECC) (Laflamme, 1997). Adipocytes are

the functional unit of fatty tissue (Khan et al., 2015). They have high metabolic activity and are highly sensitive to nervous, nutritional and hormonal control (Stephens, 2012) and about 95% of the cell weight is represented by triglycerides (Khan et al., 2015). However, being overweight alters the release of certain substances, including leptin (German et al., 2010). This protein hormone specific to adipocytes of 167 amino acids, has been known for its appetite control effects (Facey et al., 2017) and is linked to the regulation of body mass (Hassink et al., 1996).

In dogs and humans, an increase in leptin has been found when adipose tissue is more abundant (Maffei et al., 1995; Gayet et al., 2004; Kil and Swanson, 2010), implying cell proliferation by stimulation of the IGF-1 or somatomedin and promotion of angiogenesis (Renehan et al., 2006). In BC, the leptin receptor (ObR) and Human Epidermal Growth Factor Receptor type 2 (HER-2) can be co-expressed, which reduces the effectiveness of HER-2 treatments (Fiorio et al., 2008), since ObR can mediate HER transactivation-2 (Soma et al., 2008), although this is controversial (Santillán et al., 2012). The positive relationship between ObR and HER-2 has also been observed in animals (rodent models) with mammary tumour (García-Robles et al., 2013), although this interaction is not yet clear (Lim et al., 2015).

In female dogs, obesity during the first year of life markedly increases the risk of cancer, since several carcinogenic events occur in the mammary gland during this period, although there is no clarity on this mechanism (Sonnenschein et al., 1991; Perez-Alenza et al., 2000; Sorenmo et al., 2011; Lim et al., 2015). Several findings have shown that the risk is similar if a female is obese at least one year prior to being diagnosed with CMC (Shofer et al., 1989).

Clinical aspects and diagnosis of CMC

Clinically, tumour masses are the main warning of abnormality in the mammary glands of female dogs. The size of these masses can range from 0.5 cm to 21 cm in diameter (Chang et al., 2005; Hsu et al., 2009). Consequently, the clinical significance of canine tumour masses indicates that small and hard masses are more likely benign, while larger masses generally display ulceration and are histologically malignant (Hemanth et al., 2015). Thus, the latter result in a more unfavourable prognosis (Hsu et al., 2009).

All mammary glands can be involved in the development of CMC, whether initially one gland is involved or a combination of them, and these can show the same or different histological features (Perez-Alenza et al., 2000; Goebel and Merner, 2017). There is no tendency towards one side more than the other (Chang et al., 2005; Hsu et al., 2009; Hemanth et al., 2015), though findings have shown that the caudal mammary glands (glands 3, 4 and 5) are more affected than the thoracic pairs (1 and 2) (Chang et al., 2005; Hsu et al., 2009). In consequence, the inguinal zone is most affected, while the least affected is the caudal thoracic sector (Hemanth et al., 2015).

Additionally, lymphatic drainage in healthy females is ipsilateral (towards the same side) and there is no evidence of drainage towards the contralateral lymph nodes (LN) (Pereira et al., 2003; Pereira et al., 2008), which is one of the differentiating factors in neoplastic glands (Patsikas et al., 2006). However, not all CMC types behave in the same manner, e.g. epithelial type neoplasms, such as carcinomas, generate metastasis through the lymphatic system, while mesenchymal neoplasms, such as sarcomas, achieve metastasis through capillaries and veins (Sorenmo et al.,

2011). There are correlations between CMC patient survival and the number of affected LN, where average survivorship decreases with increasing number of affected LN (Carter et al., 1989; De Araújo et al., 2015). Tumour size and LN condition are independent prognostic factors; however, they are additive (Carter et al., 1989), since a larger tumour diameter is related to metastasis to the lymph node (Chang et al., 2005). This fact indicates a direct relation between these two factors.

CMC and genetic markers

In hereditary human BC, alterations of the suppressor gene p53 and mutations in suppressor genes BRCA1 and BRCA2 (Breast Cancer 1, 2) are mainly involved (Overgaard et al., 2000; Honrado et al., 2006; Olivier et al., 2006; Pérez-Losada et al., 2011). In sporadic MC, there is an involvement of modulators of cellular proliferation, including alterations in ER, which are classified into three groups: classic ERα, ERβ, and the most recently described, GPR30 (G protein-coupled receptor 30) (Prossnitz et al., 2007; Hazell et al., 2009; Prossnitz and Maggiolini, 2009). The first two ER groups belong to the superfamily of nuclear receptors that regulate elements at the nuclear level through MAPK-type responses (*Mitogen-Activated Protein Kinases*), PI3K (*Phosphoinositide (PI) 3-Kinase*), and cAMP (*cyclic adenosine monophosphate*). Alterations in these two receptors lead to cellular proliferation, growth, and survival. ER are implied in high resistance to treatments and development of metastasis, in co-expression with the HER-2 gene (Filardo et al., 2006). Another group consists of *Transforming growth factor* (TGF β), which includes three members (TGF β I-III). A reduction in the expression of TGF β enables the development of MC and eventual metastasis (Landis et al., 2005; Dong et al., 2007). In addition, PGDF (Platelet-Derived Growth Factor) receptors include two types, PGDFR α and β, which are related to cellular proliferation and differentiation. Tumour invasion capacity has been correlated with co-expression of PGDFR α and HER-2 (Carvalho et al., 2005). Finally, the Protease-activated receptor (PAR) participates in the modulation of cancer growth (Ceballos and Hernández, 2008). PAR1 mediates calcium signalling, transcription processes, and mitogenesis (Coughlin, 2000). HER-2 contributes to PAR1 activation, therefore, providing high prognostic value (Ceballos and Hernández, 2008).

In canines, mutations in genes with high or low penetrance in cancer considerably increase the risk of CMC presentation. Single Nucleotide Polymorphisms (SNP) in coding regions can lead to alterations in protein structure or function (Borge et al., 2011). Genes that show different risk levels have been the most studied, including breast cancer susceptibility genes 1 and 2 (BRCA1, BRCA2), tumour protein p53 (TP53), phosphatase and tensin homolog (PTEN), checkpoint kinase 2 (CHEK2), ataxia telangiectasia mutated (ATM), and human epidermal growth factor receptor-2 (HER-2) (Hsu et al., 2009; Borge et al., 2011).

CMC and clinical implications of the HER-2 gene

In women with BC, the overexpression of HER-2 (HER-2 positive state) is found between 20% and 30%, and is generally correlated with a high phenotypic aggressiveness and resistance to cytotoxic and endocrine therapies (González et al., 2007; Fehm et al., 2007; Savino et al., 2009; Park et al., 2014). The latter leads to a poor clinical prognosis, mainly short survivorship (Slamon et al., 1987; Gambini et al., 2003; Ross et al., 2003),

and in both humans and canines, the prognosis is reserved for up to two years after surgery (Ressel et al., 2013).

The oncogene HER-2/*neu* was initially isolated from neuroectodermal tumours in rats and compared to its homologues in humans and rabbits; therefore, *neu* corresponds to neuroblastoma (Shih et al., 1981). In humans, HER-2/*neu* maps to chromosome 17q 12-21.32 (Akiyama et al., 1986; Fukushige et al., 1986; Popescu et al., 1989; Fehm et al., 2007; Finn et al., 2009; Krishnamurti and Silverman, 2014). In canines, the gene is located on chromosomes 9 and 5 (Yang et al., 1999); however, it has also mapped to chromosome 1q13.1 through fluorescence *in situ* hybridization (FISH) (Murua Escobar et al., 2001). HER-2/*neu* is a membrane protein of 185-kDa (Manguire et al., 1989), conformed by three domains: a transmembrane lipophilic domain, an extracellular domain (ECD) (105 -kDa), and an intracellular tyrosine kinase domain (Ha et al., 2015; Di Gioia et al., 2015). HER-2 carries out an important role in regulating cellular growth and differentiation (Yarden, 2001). However, it has gained importance given its participation in the physiopathological progression of the mammary tumour and low response to treatments (Akiyama et al., 1986; Lüftner et al., 2003).

In humans, the clinical significance of HER-2 is relevant, because it is overexpressed in early stages of cancer development. In consequence, it has become a therapeutic target (Hanna, 2001; Yarden, 2001; Wilson et al., 2002; Reddy et al., 2004; Finn et al., 2009; Krawczyk et al., 2009; Onitilo et al., 2009; Page et al., 2011; Soares et al., 2016). Yet, unlike the other receptors (HER-1, HER-3, and HER-4), HER-2 oncogenesis is attributed to an increase in the expression of a non-mutated receptor. As a result, there is an increase in tyrosine-kinase activity, which induces cellular transformation (Siegel et al., 1994; Biscardiet et al., 2000; Yarden 2001; Stefano et al., 2004; Moasser, 2007). Therefore, HER-2 is closely related with the rate of cancer progression (González et al., 2007). This is due to a deletion in exon 16 of the extracellular domain (Siegel et al., 1994) and a polymorphism in codon 655 (Papewalis et al., 1991). Hence, MC with overexpression of HER-2 highly correlates with metastasis in regional lymph nodes and, for this reason, HER-2 is used as a prognosis marker in relation to other proteins p53, Ki67, ER, and PR (Selvarajan et al., 2004).

There is a 29.7% incidence of HER-2 overexpression in female canines diagnosed with malignant mammary tumour (Hsu et al., 2009). Later studies showed incidence rates of 28.6% (Ressel et al., 2013), 38% (Shinoda et al., 2014), 37.5% (Burrai et al., 2015) and 32.1% (Campos et al., 2015). However, the results regarding HER-2 expression levels are not yet clear (Hsu et al., 2009; Ressel et al., 2013). HER-2 overexpression is seemingly not strictly associated with the initial stages of atypical cellular proliferation (Ferreira et al., 2014), indicating a high complexity in terms of establishing the most adequate prognosis and therapy for each type of CMC (Resssel et al., 2013).

In canines, it is likely that HER-2 only participates in proliferation and not in the malignancy process of the mammary tissue during tumour formation (Hsu et al., 2009; Ressel et al., 2013). Nevertheless, this can vary, since there have been reports of CMC processes with amplification or overexpression of HER-2 (Rungsipipat et al., 1999), and of others with no association to HER-2 (De las Mulas et al., 2003). This poses a challenge for prognosis (Dutra et al., 2004), as findings are not clear regarding the effects of HER-2 on the survivorship rate in comparison to other genes (Hsu et al., 2009; Shinoda et al., 2014). However, a HER-2 positive state means an unfavourable prognosis, both for women (Savino et al., 2009) and

in most canine female cases (Hsu et al., 2009; Ressel et al., 2013).

HER-2 as a tumour marker in CMC

A tumour marker (TM) is a molecule (glycoprotein, generally) that can be produced by normal cells and tumour cells, although levels are higher in the presence of cancer (Hermida et al., 2016). In cancer, concentrations of TM can be produced by both normal cells and cancer cells, and these substances are detectable in biological fluids (Romero et al., 2002; Almeida et al., 2007). TMs may be tumour-specific proteins (tumour antigen specific), nonspecific protein tumour markers associated with malignant cells, or specific proteins overexpressed in malignant cells (Lindblom and Liljegren, 2000; Romero et al., 2002). No TM is totally sensitive and specific, but together with other clinical procedures can take specific therapeutic decisions (Koshida et al., 1996; Lindblom and Liljegren, 2000; Hermida et al., 2016).

HER-2/*neu* (HER-2) is a proto-oncogene that encodes a glycoprotein that stimulates cell proliferation and differentiation in normal epithelial cells (Yarden and Sliwkowski, 2001; Farzadnia et al., 2010). In humans, overexpression of the HER-2 protein has been found in 20 to 30% of invasive breast cancer cases (Slamon et al., 1987; Wolff et al., 2013). The concentration in serum has an important prognostic value (Andrulis et al., 1998; Sjögren et al., 1998; Agrup et al., 2000) and it has high influence on treatment decisions (Leyland-Jones, 2002).

In human breast cancer (HBC), HER-2 levels in blood serum have been studied in metastatic cancer (Jensen et al., 2003). Serum concentrations of 18.5% have been reported (Carney et al., 2003), and 13.4% with significant correlation with tumour size and clinical grade by immunohistochemical analysis (IHC) (Harris et al., 2001) and ELISA in primary HBC (Pallud et al., 2005). Other studies have not found a positive correlation between clinical-pathological variables and elevated serum levels (Kong et al., 2006). The cut-off value for serum measurements of HER-2 should be determined for each type of population (Ellis et al., 2000; Rakha et al., 2015) due to the little relation that there could be with the amplification of the gene or the overexpression of the protein (Kong et al., 2006).

The BLAST alignment of HER-2 reveals a 92% homology in the amino acid sequence between humans and canines (Singer et al., 2012). However, the use of human test kits for enzyme-linked immunosorbent (ELISA) to measure concentrations of HER-2 in dogs did not significantly differentiate between healthy patients and those with cancer (Campos et al., 2015). However, the correlation of serum levels of HER-2 with tumour size, high histological grade, mitotic index and nuclear polymorphism indicated a poor prognosis (Dutra et al., 2004; Hsu et al., 2009; Muhammadnejad et al., 2012; Kaszak et al., 2018), although this relationship is controversial (Kim et al., 2011; Ressel et al., 2013). Additionally, reduced expression has been reported in the presence of aggressive tumours such as ducal carcinoma *in situ* (DCIS) (Silva et al., 2014), unlike that found in feline mammary cancer (FMC) (Soares et al., 2016).

Currently, it has been difficult to determine the similarities or differences in the overexpression of HER-2 between humans and canines. In canines, we find the deletion of exon 16 or the absence of polymorphism of codon 655, yet there is a polymorphism in exon 14 (Hsu et al., 2009). Nonetheless, it is important to differentiate between diagnostic methods with high sensitivity, in order to clearly establish similarities and relations in

this gene between humans and canines (Savino et al., 2009).

Conclusions

The differences between the overexpression of HER-2 in human BC and CMT are not yet clear. Despite recognizing the importance of HER-2, the clinical usefulness of its detection in animal medicine is still unclear, since the relationship between overexpression of HER-2 and CMC may be due to the interaction of several genes and not to the activity of the gene itself. In addition, care must be taken to determine HER-2, since it is overexpressed in other types of tumours, therefore it is necessary to supplement the clinical correlation with other clinical analyses. In humans, high levels of ECD in primary BC have a high diagnostic, prognostic and therapeutic value, while in canines, the pattern of presentation is not clear and survival findings are controversial. Given the high complexity involved in monitoring HER-2 in female dogs, it is important to develop studies with simple, minimally invasive methods that would allow for early detection.

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Tumor mliječne žlijezde kuja: kliničke implikacije sa specifičnim fokusom na HER-2 genu

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Tumor mliječne žlijezde kuja je jedna od najčešćih neoplazija u ženki u usporedbi s drugim vrstama. Ustvrđeno je nekoliko čimbenika rizika uključujući pasminu, genetsku predispoziciju, dob, reproduktivnu anamnezu, hormonalni utjecaj, hranidbu i tjelesnu kondiciju uz prethodne lezije mliječne žlijezde kao što su primjerice atipična hiperplazija mliječne žlijezde. U cilju uspostavljanja specifične terapije koja bi omogućila prihvatljivo vrijeme preživljavanja pacijenata važno je razumijevanje genetskih markera za spomenutu bolest kao i klinički pristup. Prekomjerna ekspresija HER-2 gena u kanida i ljudi povezana je s nepovoljnom kliničkom prognozom, uglavnom s kratkim vremenom preživljavanja, premda nije jasna njihova klinička povezanost. Incidencija HER-2 u kuja može biti u rasponu od 29,7 % do 38 %. Međutim, prekomjerna ekspresija HER-2 nije nužno povezana sa zloćudnim procesima u tkivu mliječne žlijezde, premda ima ulogu u staničnoj proliferaciji. Naposljetku, kanidi su i dalje najvažniji modeli za komparativnu onkologiju u odnosu na ljude zbog velike sličnosti u spontanom izgledu i razvoju tumora kao i u visokoj homologiji u slijedu aminokiselina.

Ključne riječi: *c-erbB2, dijagnostika, zloćudni tumor mliječne žlijezde, prognoza, čimbenici rizika*