Preventive Veterinary Medicine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Preventive Veterinary Medicine

journal homepage: www.elsevier.com/locate/prevetmed

Incidence of mammary tumors in the canine population living in the Veneto region (Northeastern Italy): Risk factors and similarities to human breast cancer

Marta Vascellari[a,*], Katia Capello[a], Antonio Carminato[a], Claudia Zanardello[a], Elisa Baioni[b], Franco Mutinelli[a]

[a] Istituto Zooprofilattico Sperimentale delle Venezie, Viale dell'università 10, 35020 Legnaro, PD, Italy
[b] Istituto Zooprofilattico Sperimentale del Piemonte Liguria e Valle d'Aosta, Via Bologna, Torino, Italy

ARTICLE INFO

Article history:
Received 14 January 2015
Received in revised form 10 February 2016
Accepted 27 February 2016

Keywords:
Dog
Incidence
Mammary tumors
Population
Risk factors

ABSTRACT

Although mammary gland tumors (MT) are the most-common type of tumor in intact female dogs, there is little information about their incidence in dog population. Data on MT in female dogs was retrieved from the Animal Tumor registry of dogs and cats of Venice and Vicenza provinces during 2005–2013 and was analyzed to visualize crude incidence rates by breed and across age categories. Overall, 2744 mammary tumors were reported accounting for 54% of all tumors in female dogs. The annual incidence rate (IR) was 250 cases per 100,000 dogs. The most frequent malignant tumors were complex carcinomas, consisting of both epithelial and myoepithelial tissues (IR = 71.89), and simple carcinomas (IR = 62.59). The MT incidence rate increased through the study period; particularly in the last 4 years, and malignant neoplasms occurred more frequently (70%) than the benign counterparts (30%). Seventy-four percent of tumors were diagnosed in intact females, and the mean age at diagnosis was significantly higher for spayed dogs than for intact ones. MT were less frequent in dogs younger than 6 years and increased up to approximately 60% for ages between 8 and 13 years. The purebred dogs had a higher probability to have a malignant neoplasm than mixed-breed dogs, particularly in dogs younger than 7 years, and the Samoyed, Dobermann, Schnauzer and Yorkshire Terrier breeds were more inclined to develop malignant MT. The incidence of MT in dogs is increasing, and IRs are comparable to that in women. The epidemiological similarities between dogs and women support the validity of canine MT as a model for human breast cancer.

1. Introduction

Dogs develop mammary gland tumors (MT) spontaneously, and some epidemiologic, clinical, and prognostic features are similar to human breast cancer (Owen, 1979; Misdorp, 2002; Vail and MacEwen, 2000; Mohammed et al., 2011). Despite the fact that MT are the most-common type of tumor in intact female dogs (Sleeckx et al., 2011), there is little information about their incidence in the dog population. Most of the information is based on data obtained from hospitals in which the population is only represented by cases referred to veterinary clinics, or biopsied and necropsied dogs (hospital-based registry). The scarcity of population-based canine registries is partly due to expense and difficulties in acquiring such data. Among commonly cited studies, Schneider (1970) reported an incidence of 145 per 100,000 dogs-year at risk amongst female dogs in California, USA. Some European studies showed an incidence rate of approximately 200 per 100,000 dogs-year (Dobson et al., 2002; Merlo et al., 2008; Vascellari et al., 2009). In general, more than 40% of tumors in female dogs are MT (Merlo et al., 2008; Vascellari et al., 2009; Dorn et al., 1968), and approximately 30–50% of canine MT are malignant (Dorn et al., 1968; Sorenmo et al., 2000). Many factors are known to influence the incidence of MT, such as breed, age, and spayed status. Results from different studies showed that the incidence rates of MT in purebred dogs are significantly higher than in mixed-breed (Merlo et al., 2008) and depending on the study, different breeds seem to have an increased risk of developing MT (Jitpean et al., 2012; Moe, 2001; Borge et al., 2011). As in humans, advanced age increases the risk of MT development in dogs, with a median age at diagnosis of approximately 8–10 years (Sleeckx et al., 2011). Furthermore, development of canine MT is hormone

* Corresponding author.
E-mail address: mvascellari@izsvenezie.it (M. Vascellari).

http://dx.doi.org/10.1016/j.prevetmed.2016.02.008
0167-5877/

dependent. Schneider et al. (1969) reported that ovariohysterectomy before the first, second, or third estrus cycle significantly reduces the relative risk of developing MT, while ovariohysterectomy later in life had no significant effect.

Breast cancer is also one of the most common cancers in women living in Western countries (Youlden et al., 2012). Excluding skin cancers, breast cancer is the most common malignancy and the second leading cause of cancer death among women in the United States (Desantis et al., 2011). In 2002, the estimated age-standardized rate of breast cancer was equal to 40.4 new cases per 100,000 people worldwide (Parkin et al., 2005), and it increased to 42.3/100,000 in 2008 (Ferlay et al., 2010). After adjusting the number of new cases for population size and age, it emerged that incidence rates were almost 2.5 times higher in the more developed countries than in less developed ones (71.7/100,000 and 29.3/100,000, respectively) (Ferlay et al., 2010). A range of factors relating to lifestyle in more developed countries, such as having fewer children, giving birth at an older age and being less likely to breastfeed, may influence the incidence rate. Higher levels of obesity combined with lower levels of physical activity, increased alcohol consumption, and use of oral contraceptives and hormone replacement therapies, may also affect incidence (Youlden et al., 2012). Globally, 89% of breast cancers are diagnosed from the age of 40 onwards (Ferlay et al., 2010; Youlden et al., 2012).

The main objective of this study was to describe the incidence of MT in female dogs living in the Venice and Vicenza provinces during 2005–2013 and to measure the incidence by breed and across age categories. The descriptive epidemiological data obtained have been compared with those obtained by the human cancer registries in the same area and globally.

2. Material and methods

In April 2005 the Animal Tumor Registry (ATR) of Vicenza and Venice provinces of Veneto region (northern Italy) was established (Vascellari et al., 2009). This incidence registry, is based on an active surveillance program and includes both malignant and benign neoplasia. A network of collaboration with the veterinary clinics in Veneto region was established, inviting to submit any suspected neoplasm from dogs and cats living in the Vicenza and Venice provinces. The histopathology lab of the IZSVe, provides free cytological and histopathological evaluation to practitioners in the area of the registry. A standardized case-report form, specifically designed for the collection of canine and feline tumor cases, was made available to all veterinarians (Vascellari et al., 2009). MTs were classified according to the World Health Organization International histological classification of tumors of domestic animals (Misdorp et al., 1999), in order of malignancy in the following types: non infiltrating (in situ) carcinoma, complex carcinoma, simple carcinoma (tubulopapillary, solid, anaplastic), special types of carcinoma (spindle cell carcinoma, squamous cell carcinoma, mucinous carcinoma, lipid-rich carcinoma), sarcoma (fibrosarcoma, osteosarcoma), and carcinosarcoma. Benign tumors were classified into simple and complex adenoma, basaloid adenoma, fibroadenoma, benign mixed tumor, and duct papilloma.

2.1. Statistical analysis

Crude and specific incidence rates (IRs) were calculated by dividing the number of cases by the estimate of the canine population of the registry catchment area, multiplied by the number of years. The estimate of the canine population was obtained by applying the Lincoln-Petersen version of the capture-recapture method (Seber, 1982): the capture sample was represented by the official Canine Demographic Registry established in Veneto region, while the recapture sample was obtained by a telephone survey of households of the Veneto Region (Capello et al., 2015). The canine population estimated in 2011, was 137.006 (95% CI 127.603–149.302), and it has been considered stable through the study period. The lower and upper limits of the 95% confidence interval of the population estimate were used as the denominator to provide the intervals of the IRs, later called "range". The trend of IRs during the study period was evaluated after having split the observation period into 4 periods of 24 months each. The chi-squared test was used to compare the proportion of benign and malignant tumors and the proportion of complex and simple carcinomas during the study period. The Student's *t*-test was used to assess differences in the mean age between dogs with malignant and benign tumors and between neutered and entire subjects. The Satterthwaite approximation was used to allow for variance heterogeneity. A logistic regression analysis was used to evaluate the association of spayed status, age, breed (pure and mixed-breed), and their interaction on the occurrence of malignant and benign tumors. The same statistical method was applied to malignant tumors and, particularly, to compare complex versus simple carcinoma (other types of malignant neoplasms were not considered in the analysis, given the low number of cases). For both models, the p-values obtained using type 3 analysis were used to evaluate the significance of the main effects. The odds ratios (OR) with 95% confidence intervals (95%CI) were used to summarize the results. To assess the distribution of cases among breeds, standardized morbidity ratios (SMRs) with 95% confidence intervals were calculated using the Canine Demographic Registry of the Veneto region as the reference population for the distribution of breeds in the general dog population. The SMR for a specific breed was obtained using the formula: $SMR_b = \frac{o_b/C}{n_b/N}$ where o_b and n_b are the number of cases and the number of dogs for a specific breed, respectively, while C and N are the total number of cases in the ATR and the number of dogs in the reference population, respectively.

3. Results

Overall 2744 MT were reported in 2359 dogs, accounting for 33% of all tumors in the whole population, and 54% in females. The annual incidence rate was 250 cases per 100,000 dogs, ranging from 229.74 to 268.80 per 100,000 dogs, given the confidence interval of the population estimate. Malignant tumors (1636, 60%, IR = 149.26 range: 136.97–160.26) were more frequent than benign neoplasms (1108, 40%, IR = 101.09 range: 92.77–108.54). The most frequent malignant tumors were complex carcinomas consisting of both epithelial and myoepithelial tissues (788, IR = 71.89, range: 65.97–77.19), and simple carcinoma (686, IR = 62.59, range: 57.43–67.20). Other tumors were special types of carcinoma (61, IR = 5.57, range: 5.11–5.98), carcinosarcoma (24, IR = 2.19, range: 2.01–2.35) and in situ carcinoma (17, IR = 1.55, range: 1.42–1.67). Fifty-eight tumors of mesenchymal origin (fibrosarcoma/osteosarcoma/other sarcomas) were collected (IR = 5.29, range: 4.86–5.68). Among benign tumors the most frequent were complex adenoma (485, IR = 44.25, range: 40.61–47.51), simple adenoma (320, IR = 29.20, range: 26.79–1.35) and mixed benign tumors, which are a combination of epithelial and mesenchymal tissues (251, IR = 22.90, 95%CI: 21.01–24.59). The MT incidence rate increased through the study period (Fig. 1), ranging from 178.82 (range: 164.10–192.00) to 313.12 (range: 287.34–336.20). A significant association between the classification of benign and malignant tumors and the 4 investigated periods was observed (p-value < 0.001, Table 1), highlighting different trends between the two groups of tumors. At the end of the study period, malignant neoplasms occurred more frequently (70%) than the benign counterparts (30%). Focusing on the most frequent types of malignant

Please cite this article in press as: Vascellari, M., et al., Incidence of mammary tumors in the canine population living in the Veneto region (Northeastern Italy): Risk factors and similarities to human breast cancer. PREVET (2016), http://dx.doi.org/10.1016/j.prevetmed.2016.02.008