Mammography and Ultrasound Imaging of Preinvasive and Invasive Canine Spontaneous Mammary Cancer and Their Similarities to Human Breast Cancer

S.I. Mohammed1, G.B. Meloni2, M.L. Pinna Parpaglia4, V. Marras3, G.P. Burrai4, F. Meloni2, S. Pirino4, and Elisabetta Antuofermo4

Abstract

Understanding the evolution of proliferative breast disease such as atypical hyperplasia and carcinoma in situ is essential for clinical management of women diagnosed with these lesions. Therefore, an animal model that faithfully represents human breast disease in every aspect from spontaneity of dysplasia onset, histopathologic features, and genetics to clinical outcome is needed. Previously, we studied canine spontaneous atypical hyperplasia and ductal carcinoma in situ (low, intermediate, and high grade) and reported their similarities to human lesions in histopathologic and molecular features as well as prevalence. To further validate the resemblance of these lesions to humans, we examined their mammographic and sonographic characteristics in comparison with those of human’s as well as the potential of the human Breast Imaging Reporting and Data System (BI-RADS) to predict canine disease. Nonlesional, benign, and malignant mammary glands of dogs presented to Sassari Veterinary Hospital were imaged using mammography and ultrasonography. The images were then analyzed and statistically correlated with histopathologic findings and to their similarities to humans. Our results showed that canine mammary preinvasive lesions, benign, and malignant tumors have mammographic abnormalities, including the presence, pattern, and distribution of macrocalcification and microcalcification, similar to their human counterparts. BI-RADS categorization is an accurate predictor of mammary malignancy in canine, with 90% sensitivity and 82.8% specificity. The similarities of mammographic images and the ability of BI-RADS to predict canine mammary malignances with high specificity and sensitivity further confirm and strengthen the value of dog as a model to study human breast premalignancies for the development of prognostic biomarkers. Cancer Prev Res; 4(11); 1790–8. ©2011 AACR.

Introduction

Most invasive breast cancers are thought to originate from proliferative breast disease such as atypical hyperplasia and carcinoma in situ lesions. These lesions are currently diagnosed more often because of increased public awareness and routine mammographic screening (1–3). Approximately 54,010 new cases of ductal carcinoma in situ (DCIS) are expected to be diagnosed in 2010 (4). Despite the technological advances in detecting these lesions, their biological significance and natural history are not well understood. Five percent to 10% of women diagnosed with DCIS who are treated with lumpectomy alone develop invasive cancer within 5 years and a similar group develops subsequent DCIS (5). Although adjuvant treatment with radiation and tamoxifen has reduced the rates of subsequent breast cancer, these treatment regimens have not affected death rates from breast cancer (6, 7). Studies that attempted to identify women at high risk of developing invasive cancer were not successful, thus creating uncertainty in how aggressively clinicians would treat women diagnosed with DCIS (8).

As a result, many animal models of mammary tumorigenesis such as rodents were developed to examine pathogenesis and progression of human breast cancer (9–11). Therefore, rodent models may not accurately represent human breast cancer pathogenesis or reproduce many aspects of the human disease (12, 13).
In contrast to rodents, dogs develop mammary cancer spontaneously with similar epidemiologic, clinical, morphologic, and prognostic features as human breast cancer (14–18). Mammary tumors constitute about half of all canine mammary tumors. About 30% to 50% of canine mammary tumors are malignant (19, 20). Furthermore, as in humans, development of canine mammary tumor is hormone dependant. Ovariectomy before the first, second, or third estrus cycle reduces the relative risk of developing mammary tumors to 0.5%, 8%, or 26%, respectively. Ovariectomy later in life had no significant effect on risk of developing mammary tumors. As in humans, advanced age also increases the risk of mammary tumor in dogs. The median age for the dog to develop mammary tumors is about 10 to 12 years (21).

Most important, dysplasias develop spontaneously before tumors in canine mammary tissue (18–22). Intraepithelial lesions (IEL) are common in tumor-bearing glands and in nontumor-bearing glands in female dogs. In previous study in our laboratory, within dogs without mammary tumors evaluated for prevalence of IEL, half had at least one type of IEL, including ductal hyperplasia, atypical ductal hyperplasia, low-grade DCIS, intermediate-grade DCIS, and high-grade DCIS. One fourth of the dogs examined had 2 or more different IEL types. Furthermore, we have shown that these lesions are remarkably similar in histopathologic morphology and in expression patterns of estrogen receptor-α, progesterone receptor, and HER2 to those of the human breast (22, 23).

Human DCIS are currently detected by X-ray mammography as mentioned earlier (3–24). The ability of mammogram to identify these lesions is based on the presence of microcalcification. Microcalcifications are present in 42% to 72% of DCISs (25, 26). About 90% of nonpalpable DCISs were diagnosed on the basis of microcalcifications alone (27). The American College Radiologists recommendation, Breast Imaging Reporting and Data System (BI-RADS), classifies mammogram findings into following 3 categories: typical benign, intermediate concern, higher probability of malignancy according to morphology and distribution of calcifications (28).

Mammographically detected DCIS is usually excised immediately, and, currently, it is not possible to estimate the fraction of untreated lesions that would progress to invasive cancer (8). Despite the increase in detection of DCIS, the probability of definitive studies in human to show whether detection of DCIS by mammography would contribute to the reduction of breast cancer mortality is very slim (8). For this reason, our laboratory focus is to characterize the dog as a model for preinvasive and invasive breast cancer.

Therefore, to complement our previous work, the purpose of this study was to determine whether the routinely used imaging techniques in human, mammography and sonography, as well as interpretations of their results according to BI-RAD, could be used to detect and discriminate between preinvasive, benign, and malignant mammary lesions in the dog. Our results showed that canine mammary preinvasive lesions, benign, and malignant tumors have mammographic abnormalities, including the presence, pattern, and distribution of macrocalcifications and microcalcifications, similar to their human counterparts. BI-RADS categorization is an accurate predictor of mammary malignancy in canine with high sensitivity and specificity. Mammographic image similarities and the ability of BI-RADS to predict canine mammary malignances with high accuracy and sensitivity further confirm and strengthen the value of dog as a model to study human breast premalignancies. This is important for the development of prognostic biomarkers to stratify women diagnosed with DCIS according to risk of developing subsequent disease.

Materials and Methods

Animals

This study was conducted ex vivo in 88 excised mammary glands from 40 female dogs that underwent mastectomy at Sassari Veterinary Hospital during 2006–2008. Dogs belonged to the following breed: poodle (4), Dachshund (2), mixed breed (13), Yorkshire (12), one each of Bobtail, German hounds, German shepherd, Giant Schnauzer, Mastiff, Dalmatian, Doberman, Siberian husky, and English setter. The age of dogs ranged from 5 to 15 years (median age = 10), of which 36 were adult spayed and 4 were intact females. Mammary tissues were surgically removed. Fresh samples were mammographically and ultrasonographically imaged and subsequently processed for histopathology. All procedures from handling, anesthesia, and surgeries were in accordance with the Sassari University Animal Care and Use Committee guidelines.

Mammographic experiment

Eighty-eight mammary specimens were imaged with the Diamond Premier Analog DMR Mammography System (General Electric). Images were examined by 2 radiologists (human and veterinarian), and calcifications were assessed according to the BI-RADS categories. Mammographic features of 78 lesions and 10 normal-looking mammary glands were described according to BI-RADS lexicon. Assessment of categories were based on the description of shape (round, oval, lobular, irregular) and margins (circumscribed, indistinct) of mammary masses and shape (popcorn-like, round, pleomorphic, amorphous, linear branching) and distribution (regional or diffuse) of macro- and microcalcifications.

Ultrasound experiments

Forty-six of 88 mammary specimens that were mammographically imaged were also examined by ultrasonography. All ultrasound scans were done with Esaote MyLab
BI-RADS
All lesions examined by mammography and ultrasonography were classified in consultation between both human and veterinary radiologists according to the American College of Radiology BI-RADS lexicon, which provide standardized classification for mammographic and ultrasound reporting (28). This system classifies findings into 6 assessment categories and provides 4 management outcomes. These assessment categories have been shown to correlate with the likelihood of malignancy in human breast cancer (29, 30). Depending on the level of suspicion, the lesions can be placed on the following BI-RADS categories: category 0 when additional image evaluation is recommended; category 1 when there is no abnormality to report; category 2 for benign findings; category 3 for likely benign lesions where 6-month follow-up is recommended; category 4 for suspicious abnormality; and category 5 for highly suspicious lesions or diagnostics of malignancy.

Histopathologic evaluation
Mammary gland samples were formalin fixed and paraffin embedded. Cut sections (5 μm) were stained with hematoxylin and eosin (H&E). Tumors were classified according to WHO Histological Classification of Mammary Tumors of the Dogs and Cats (31). Mammary glands were also evaluated for the presence of IELs in tumor-bearing glands and in nontumor-bearing glands as previously described (22, 23). Lesions were imaged with Nikon Eclipse 80i, and digital computer images were recorded with a Nikon Ds-fi1 camera.

Statistical analysis
Accuracy of mammogram interpretation using the BI-RADS final assessment was determined by means of sensitivity, specificity rates, and positive and negative predictive values (PPV and NPV) to differentiate between benign and malignant lesions. Histologic findings were used as the gold standard. Statistical measures for overall lesions were calculated considering BI-RADS categories 1–2–3 as reporting of benign findings and categories 4–5 as malignant findings according to the methodology included in the BI-RADS guideline. In addition, PPVs were calculated for each BI-RADS category as follows: the number of lesions in one of the categories with malignant diagnosis divided by the total number of lesions classified into this category. All statistical calculations were done with statistical software (Stata software, version 11.2).

Results

Mammography and ultrasonography
The mammographic features such as macrocalcifications, microcalcifications, mass shape and margin, and their correlation with histologic diagnosis were assessed in 78 of 88 mammary glands, and the results are shown in Table 1. Normal mammographic appearance of 10 mammary gland were confirmed at histology.

Calcification was identified in 42 of 78 (54%) lesions examined, of which 19 of 78 (24%) contained macrocalcifications and 23 of 78 (29%) had microcalcifications. Of the 19 lesions with macrocalcifications, 11 (57%) were popcorn-like with regional (4/19; 21%) and diffuse (7 of 19; 36%) distribution whereas 8 of 19 (42%) were round with regional localization. Lesions with macrocalcifications were diagnosed as IELs without atypia and as benign and malignant tumors mostly of complex type. On the other hand, lesions with microcalcifications (23 of 78; 29%), generally were either pleomorphic regional and diffuse (14 of 23; 61%), amorphous/indistinct (5 of 23; 22%), or linear branching (4 of 23; 17%) and were associated mostly with atypical IELs and malignant tumors.

In addition, we evaluated mass shape and margins by mammography in 54 of 78 (69%) lesions. Of the 26 benign lesions, 21 (81%) were round or oval masses and 12 of 26 (46%) had circumscribed margins. Twelve of 25 malignant lesions (48%) displayed irregular shape, and 22 of 25 (88%) had indistinct margins. Figure 1 shows canine and human proliferative lesion (ductal hyperplasia, atypical ductal hyperplasia, and DCIS) mammograms and their corresponding histopathology.

Similarly, we correlated the ultrasound abnormalities of 46 of 78 mammary lesions with histologic findings. Calcifications were found in 19 of 46 (41%) lesions, whereas 11 of 19 (53%) were associated with malignant tumors. The oval shape was the most common form of masses and was found in 25 of 40 (62.5%) either in benign (12) or malignant (11) tumors. Benign lesions were usually with well-circumscribed margin (14 of 18; 78%), whereas malignant lesions were typically indistinct in margin (16 of 20; 80%). Figures 2 and 3 show the mammograms and ultrasound images of benign and malignant canine tumors.

Histopathologic evaluation and BI-RADS classification
Tissues from mammary glands (88) were examined histologically and included normal tissues (n = 10) and tissues that carried abnormal histology (n = 78). These lesions were classified as IELs (n = 11), benign lesions (n = 37), and malignant mammary tumors (n = 30). In addition, we diagnosed other 9 IELs (5 ductal hyperplasias, 2 atypical ductal hyperplasias) associated with benign lesions and 2 high-grade DCISs associated with invasive carcinoma (comedo type). Fifty-eight of 78 lesions (30 were classified as benign and 28 as malignant tumors) were palpable masses, whereas 20 of 78 were nonpalpable masses.
The correlation of BI-RADS categories with histologic diagnosis of IELs, benign tumors, and malignant tumors is illustrated in Table 2. Lesions were classified and placed into BI-RADS category 1 (i.e., without positive finding): 10 of 25 were normal mammary gland, 7 of 25 palpable lesions [intraductal papilloma \( (n = 2) \), tubular adenoma \( (n = 2) \), sclerosing papilloma \( (n = 1) \), fibroadenoma \( (n = 1) \), and benign mixed tumor \( (n = 1) \); and 8 of 25 were nonpalpable masses [duct ectasia \( (n = 2) \), intraductal papilloma \( (n = 2) \), adenosis \( (n = 2) \), and ductal hyperplasia \( (n = 2) \)]. The PPV for this category was 0%; no malignant lesions were identified by histologic evaluation and all lesions were benign. For BI-RADS category 2 (which indicate that the lesions are benign), 4 of 7 lesions were palpable [benign mixed tumor \( (n = 3) \), intraductal papilloma \( (n = 1) \), and atypical ductal hyperplasia \( (n = 1) \)]. The PPV for category 2 was also 0% (i.e., no lesion was identified as malignant). For BI-RADS category 3 (which denote that the lesions are probably benign), 16 of 19 lesions were benign and also palpable [complex adenoma \( (n = 5) \), benign mixed tumor \( (n = 4) \), intraductal papilloma \( (n = 2) \), tubular adenoma \( (n = 1) \), fibroadenoma \( (n = 1) \), complex carcinoma \( (n = 2) \), and tubular carcinoma \( (n = 1) \)]; and 3 of 19 were benign not palpable [adenosis \( (n = 1) \), atypical ductal hyperplasia \( (n = 1) \), and complex adenoma \( (n = 1) \)]. The PPV for this category was 16% because 3 of 19 lesions were pathologically malignant. For BI-RADS category 4 (which means that it is a suspicious lesion for malignancy and further action should be taken), lesions were mostly palpable \[29 of 35; complex adenoma \( (n = 6) \), tubular carcinoma \( (n = 6) \), carcinoma comedo type \( (n = 7) \), carcinosarcoma \( (n = 4) \), complex carcinoma \( (n = 2) \), squamous cell carcinoma \( (n = 1) \), fibrosarcoma \( (n = 1) \), liposarcoma \( (n = 1) \), and osteosarcoma \( (n = 1) \)], except 6 lesions \[where 1 was ductal hyperplasia, 2 were atypical ductal hyperplasia, 1 complex adenoma, and 2 tubular carcinomas\]. This category consisted mostly of malignant lesions \(25 of 35\), and 10 of 35 were benign lesions. The PPV for category 4 was 71% because 25 of 35 lesions were malignant lesions. For BI-RADS category 5 (lesions which are highly suggestive of malignancy), 2 of 2 malignant lesions were carcinoma comedo type. The PPV for this category was 100%. For all lesions, the PPV was 73% (95% CI: 55.9–86.2) and the NPV was 94.1% (95% CI: 83.3–98.8). The mammographic test compared with histopathologic findings and used as the golden standard showed 90% sensitivity (95% CI: 73.5–97.9) and 82.8% specificity (95% CI: 70.6–91.4).

### Table 1. Correlation of mammographic features and histopathology of IELs, benign tumors, and malignant tumors

<table>
<thead>
<tr>
<th></th>
<th>IELs ( (n = 11) )</th>
<th>Benign ( (n = 30) )</th>
<th>Benign NP ( (n = 7) )</th>
<th>Malignant ( (n = 28) )</th>
<th>Malignant NP ( (n = 2) )</th>
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<td>4</td>
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</tr>
<tr>
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<td>11</td>
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<td>3</td>
<td>17</td>
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<td>2</td>
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<td>3</td>
<td>23</td>
<td>3</td>
<td>24</td>
<td>1</td>
<td>54</td>
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**Abbreviation:** NP, nonpalpable lesions.
Discussion

We showed for the first time that mammography and ultrasound imaging, as well as interoperation of their findings according to the BI-RADS, can be used to detect IELs (atypical ductal hyperplasia and DCIS) as well as benign and invasive mammary lesions in dogs. Currently, mammography is the gold standard for screening and diagnosing breast abnormalities (25). The ability of mammography to detect these abnormalities is based on the presence of microcalcifications (26, 27). Thus, this study confirms that as in humans, canine malignant mammary lesions are associated with microcalcifications, underscoring the physiologic similarities between the dog and human breast disease. Until now, there has been no animal model of human breast malignancies that showed reproducible microcalcifications. Although many were developed using MMTV vectors or BRCA1/BRCA2 knockouts, however, calcification in the resultant tumors is rare and unpredictable (32, 33). Usually, suspicious microcalcifications vary in size and shape and form clusters in linear or segmental patterns that signify that the tissue may be malignant whereas benign calcifications or macrocalcification tend to be large with round or oval shape and scattered in the breast (34–36). Thus, calcifications are considered to be one of the most important diagnostic markers of both benign and malignant lesions (26–37). Correlation of mammographic features with histopathology, in this study, revealed that calcifications were present in 54% of canine mammary cases. Macrocalcifications were present in 24%, whereas microcalcifications occurred in 29% of mammary cases. Similarly, in a study conducted by Sickles (38) that evaluated mammographic features in human breast cancers, more than half of breast cancers examined had mammographically visible calcifications whereas tumor mass was the sole mammographic finding in another 26% of breast cancers. However, another 20% of cancers showed neither mass nor calcifications (38). In another study of 1,261 occult breast abnormalities, 50.4% lesions were found to have calcification and 18.8% were malignant (39).

Macrocalcification are associated with benign lesions as well as some malignant tumors in dogs (Table 1). Of these lesions, 58% were popcorn-like with diffused or regional localization. Ovoid shape with regional calcifications was seen in 32% of samples. These were mostly IELs without atypia (11%) and benign tumors (37%). Ten lesions (52%) belonging to this group (lesions with macrocalcification) were malignant but of complex type. These tumors had

Figure 1. A and D, mammography shows the presence of round regional microcalcification in dog and women (BI-RADS 2). G and L, histologic diagnosis of adenosis in dog and blunt duct adenosis in woman. Ductules lined by epithelial proliferating cells with occasional variation in nuclei size. A luminal eonophilic material (secretory calcification) is also present. H&E stain, scale bar, 10 μm. B and E, mammography with scattered pleomorphic/granular microcalcification in dog and in women (BI-RADS 3). H and M, histologic diagnosis of atypical hyperplasia. Part of enlarged duct lined by more than 3 columnar cell layers showing atypical features (loss of polarity, nuclear pleomorphism). A cluster of irregular calcifications is clearly evident. H&E stain, scale bar, 10 μm. C and F, mammography with diffuse pleomorphic/linear branching microcalcifications in dog and in women (BI-RADS 5). I and N, histologic diagnosis of in situ carcinoma within an invasive carcinoma comedo type. Ductal proliferation of malignant epithelial cells with large atypical nuclei. Centrally located necrotic epithelial debris. H&E stain, scale bar, 50 μm.
epithelial and myoepithelial origin and were characterized by the presence of cartilaginous metaplasia and chondroid matrix depicted as dense calcifications by mammography (17). Typical benign calcifications in human are similar to that we have seen in the dog and are large, smooth, popcorn-like, round, dense, and scattered over a large area. These lesions in human do not need further investigations or close follow-up (26, 34).

About 47% of malignant tumors in this study showed microcalcification. Likewise, microcalcifications occur in about 30% to 50% of human breast cancers (26). In our study, only 14% of nonpalpable benign lesions showed microcalcification, consistent with what is observed as microcalcifications seen in 14.5% of 198 and 4.5% of 1,818 benign cases of asymptomatic and symptomatic women, respectively. Also, microcalcifications occurred in 83% of atypical IELs in dogs. These lesions were identified histopathologically to be atypical ductal hyperplasia and DCIS. Similar to what we observed in the dog, the incidence of calcification in human DCIS ranges between 42% and 72% (26–40). Up to 90% of DCIS lesions in human are detected on the basis of mammographically visible microcalcifications (26–41). All canine DCISs were associated with comedo-type carcinoma and contained microcalcification and, interestingly, were mammographically detected.

In addition to the presence of microcalcifications, we examined the types and patterns of microcalcifications. Distributions and type of microcalcifications seen in human proliferative lesions (42) that are suggestive of malignancy also occurred in canine lesions (Fig. 1). Microcalcifications present in canine DCIS and cancer tissues were predominantly pleomorphic/granular diffuse or linear/branching.

Mammographic features other than calcifications that were examined in this study included mass shape and margin. About 50% of palpable and nonpalpable malignant lesions in dogs have irregular shape and indistinct margin consistent with findings reported in human (38), whereas majority of benign tumors were ovoid or round with circumscribed margin (Table 1).

On the other hand, sonography plays an important role in the differentiation of solid and cystic masses. It is used for evaluating palpable masses in radiographically dense breast as well as young women susceptible to radiation. It used in combination with mammography to reduce the negative to positive biopsy ratio (43). Features that characterize an invasive carcinoma by ultrasonography include irregular shape, irregular margin, internal hypoechoigenicity, and nonuniform distribution of internal echo texture (44). Reviewing the sonogram of canine mammary palpable masses, we found that the sonographic features of these lesions correlated with their histopathologic as well as mammographic findings (Fig. 2). Lesions with well-circumscribed margins were found to be mostly benign (78%), whereas lesions with indistinct margin were found...
to be malignant (80%). These results were in accordance to what is observed in humans where oval shape and well-circumscribed margins are most predictive of a benign diagnosis, whereas irregular shape and noncircumscribed margins indicate malignant features (44, 45).

Our results showed that mammography can be successfully applied to nonpalpable mammary lesions in dog to detect cancer at early stages. In human medicine, mammography detects occult breast cancer with high sensitivity, which ranges from 71% to 98% for annual screening mammography (46). However, there are variations in interpretation of findings between radiologists. To reduce the discordance in the interoperation of mammographic findings and to standardize terms for reporting, the American College of Radiology has developed the BI-RADS. This system provides specific final assessment category that correlate with the likelihood of malignancy in human breast cancer. Under the Mammography Quality Standards Act (MQSA) in the United States, all screening mammograms must be interpreted by BI-RADS final assessment categories (47, 48). Therefore, we calculated the PPV for each BI-RADS assessment category to determine whether BI-RADS categorization is a good predictor of malignancy in our canine model. On the basis of the presence or absence of a mass, the BI-RADS categories can range from 1 to 5.

Table 2. Correlation of mammography BI-RADS categories with histopathogy of IELs, benign tumors, and malignant tumors

<table>
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<tr>
<th>Lesions</th>
<th>BI-RADS mammographic categories</th>
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<tr>
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<td>Normal mammary gland</td>
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<tr>
<td>IELs</td>
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</tr>
<tr>
<td>Benign tumors</td>
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</tr>
<tr>
<td>Malignant tumors</td>
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</tr>
<tr>
<td>Total</td>
<td>25</td>
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<tr>
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<tr>
<td>NPV%</td>
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absence of masses and calcification characteristics, we were able to classify our findings according to BI-RADS, which were then confirmed by pathology. The PPVs for BI-RAD category 1, 2, 3, 4, and 5 are 0%, 0%, 15.79%, 71.43%, and 100% respectively (Table 2). According to BI-RADS category in our study, the sensitivity and specificity of diagnostic mammography were 90% and 83%, respectively, making this system an excellent predictor of mammary malignancy in palpable and nonpalpable mammary canine disease. This is the first time that BI-RADS categories are applied to species other than humans.

This study shows that the dog mammary neoplasm forms micro- and macrocalcifications similar to humans. The findings of this study also suggest that the process of cancer pathogenesis may be similar in these two species. Furthermore, mammographic and sonographic features of canine mammary IELs and benign and invasive cancer correlate with the histopathologic findings and the BI-RADS classification is a good predictor of malignancies in the dog. This further provides more evidences to the value of dogs as a model for breast cancer. The research might allow examination of breast premalignancies for the development of prognostic biomarkers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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