American Journal of Biomedicine and Pharmacy
https://biojournals.us/index.php/AJBP
ISSN: 2997-7177

Differences and Diagnosis of Mammary Tumors in Mammals: A Scientific Review

Huda Hameed Kadhim Alabbody
Center for Market Research and Consumer Protection, University of Baghdad, Iraq

Received: 2024, 15, Dec
Accepted: 2025, 21, Jan
Published: 2025, 15, Feb

Annotation: The aim of review is to discuss the incident of tumors in the mammary glands of three type female mammals (canine bovine and human) and to know the susceptibility of these species to take tumors. Usually, the diagnosis of mammary tumors is based on the case history, clinical findings, and ultrasound examination. Mammary gland lesions diagnosis is confirmed by staining the tissue sections and reading the cancerous or precancerous cellular changes. It is also preferable to use immunohistochemistry tests with tumor markers, which can be diagnostic, therapeutic and informative of tumor behavior at the same time such as BRCA1 and Ki67. The review showed that female dogs are more susceptible to mammary tumors which are often classified into adeno, lipo and carcinoma. Women have also been found to have different types such as ductal carcinoma in situ, lobular carcinoma in situ, or fibroadenomas. In cows, studies find masses in the mammary glands so rarely. The conclusion is that carnivores like female dogs are more susceptible to mammary tumors than women, while herbivores such as cows are the most resistant. Therefore, the review recommends further studies to focus on the variation among animal species in order to reduce the incidence of mammary tumors in mammals, especially humans and canines.

Keywords: Mammary tumors, Canine, Bovine, Human.

Introduction

The incidence of mammary tumors varies greatly among species. In women, breast cancer is one of the most common cancers worldwide and causes nearly half a million deaths worldwide each year (1). Canine mammary tumors (CMTs) are malignant and common tumors in female dogs. About half of all tumors in dogs occur in females and half are malignant. In female dogs mammary tumors develop with age and rarely occur before 5 years of age. However, previous studies found that mammary tumors in dogs and humans are hormone-dependent (2). In contrast, mammary tumors are rare in cows, mares, ewes, and goats. The low tumor growth rate in ruminants may be due to the fact that daily examination of the udders by palpation or milking would make tumors less frequent or detectable sooner. The morphological appearance of the bovine mammary gland is more similar to that of humans than that of rodents therefore, cows have been used for tumor studies (3). There are several factors that may influence the high rate of female tumor development such as diet, lifestyle, reproductive history, general physiology and metabolism (4). On the other hand, the udder of a dairy cow is subject to cyclic growth and is affected by hormones that produce large amounts of milk, making the udder susceptible to mastitis instead of tumors, which is very striking. Although the lifespan of a dairy cow is rather short (6-8 years), some animals also reach an age of 15 years without developing cancer (5).

The Clinical pathological facts

Most malignant mammary tumors arise from epithelial elements and are classified almost as carcinomas. Mammary cancers are a diverse group of lesions that differ in microscopic appearance and biological behavior. Cancers may be given a clinical stage before surgery and are based on the results of physical examination and imaging tests. The TNM staging system is a system for describing the amount and spread of cancer in a patient's body. T describes the size of the tumor and any spread of cancer into nearby tissue; N describes spread of cancer to nearby lymph nodes; and M describes metastasis (spread of cancer to other parts of the body) (6). This system was created and updated by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC). The TNM staging system is used to describe most types of cancer. Also called AJCC staging system. In some cases, when the tumor size cannot be determined symbolizes (TX) or the tumor cannot be found (T0) or the tumor size is classified as T 1 (tumor <3 cm in greatest diameter), T 2 (>3 cm but <5) and T3 >5 cm in greatest diameter (7).

Materials and Methods

The main lab diagnostic methods

Histopathology

Histopathology techniques include fixation, processing, sectioning, and staining the tissue. Fixation techniques are needed for hardening, keeping the cell death process from continuing, and keeping structural molecules from being damaged. Tissue processing aims to remove water from the intra cell and replace it with a medium that can harden the cell structure to make it easy to cut. Tissue sectioning refers to cutting the prepared specimen into several slices. Finally, tissue staining aims to color the cell and tissue structures with specific staining according to the examination's purpose (8, 9). Available specimens (mammary tumors, affected skin, subcutaneous tissue, and muscle) were subjected to histopathological examination. Mammary tumors were diagnosed according to the WHO classification system (10). In each tumor, the histopathologic grade of malignancy was determined by tubule formation, nuclear pleomorphism, and mitotic rate from 1 to 3 points, according to a grading system. Microscopic examination of the skin was performed to study the possible neoplastic infiltration and other histological alterations (11).

Results and Discussion

Immunohistochemistry: BRCA$_1$ & Ki-67 tumor markers as a models of diagnosis

BReast CAncer gene 1 & a prognostic parameter in mammary cancer

After histopathologic technique cancer was confirmed by Immunohistochemistry staining using their respective monoclonal primary antibodies. Then, streptavidin-biotin complexes were peroxidized using a high-temperature antigen-unmasking protocol. Peroxidase activity, which may cause non-specific staining, was blocked by incubation with 3% H2O2, for 10 min. Usually Primary antibodies were used as monoclonal mouse anti-human BRCA$_1$ (clone GLK-z) and monoclonal mouse anti-human Ki-$_{67}$ (clone MIB1), from Immunotech@ and was diluted to 1:50 and 1:25, respectively. The antibodies then were incubated for 1 h at room temperature. Then, after washing to remove the accessing antibodies, the slides were incubated with a biotinylated anti-mouse secondary antibody Dako Eo4233, dilution 1; 200) for 20 min at room temperature. All slides were incubated with peroxidase-conjugated streptavidin (Zymed P5o242, 1:400) for 30 min at room temperature. All washings and dilutions were performed in Tris-buffered saline (TBS) (pH 7.4). The slides were then developed with a chromogen solution containing 3-3-diaminobenzidine tetrachloride (Sigma Chemical Co. DSoSg) and H2O in TBS and finally counterstained with hematoxylin (Sigma GH5-2-16). Interpretation of BRCA1. The immunohistochemical results were evaluated as follows: BRCA1 expression was highly heterogeneous and mainly localized within the cytoplasm and nucleus. The cells were scored according to the percentage of malignant cells as follows: less than 10 % tumor staining was scored as 0 (negative), 10 -40% was scored as 1 (+), 40- 70 % was scored as 2 (++), more than 70% were scored as 3 (+++). In general, tumor cells were positive for BRCA1 when more than 10 % staining was shown (12).

The Ki-67 score is calculated based on the average percentage of positively stained nuclei among tumor cells. The scoring system is as follows: 0 for <5% positive cells, 1 for 5% to 10% positive cells, 2 for 10 %-20% positive cells , 3 for 20 %-30% positive cells, 4 for 30% -50% positive cells, and 5 for >50% positive cells. Positive and negative control slides are also used. In each case, the Ki-$_{67}$ index is calculated as the average percentage of positive nuclei in representative fields (13).

Increasing evidence suggests that cancers are often heterogeneous, and that response to treatment depends on the fine details of the tumor. For example, in dogs, the mammary cancer susceptibility protein BRCA1 contributes to the risk of CMTs in English Springer Spaniels, where 36% of this breed are affected by CMTs, suggesting that dogs can be a good model for investigating breast cancer in humans (Patricio et al., 2009). In the same context, the morphological features of the bovine mammary gland are very similar to those of women, especially at the molecular level (14). Thus, the determination of the expression of BRCA$_1$ and Ki-67 proteins by immunohistochemistry in human and canine tumors would serve as useful biomarkers for survival and selection of new targeted therapy. It is worth noting that the nuclear antigen Ki-67 is actively expressed in cycling cells, but not after mitosis, and this marker is often used to identify tumor cell proliferation (15).

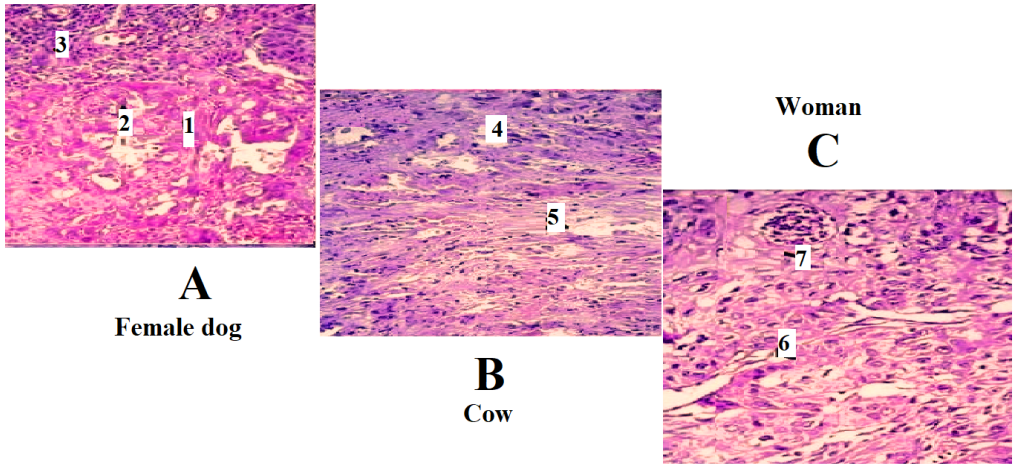

Figure 1. Three sections of mammary tumors from archived cases of the author's work and research.

A: Inflammatory carcinoma in the mammary gland of a female dog shows luminal projections of cancerous cells: 1: a lipid-rich material, 2: infiltrate of tumor cells in vascular dermal tissue, 3: heavy inflammatory cells…200X H&E

B: Mammary gland of a cow shows metastatic fibrosarcoma. 4: dense fibrous stroma, 5: pleomorphic hyperchromatic nuclei of tumor cells embedded in a fibrous stroma. Apparently phagocytosed material has many densely staining nuclei and are surrounded by a net of light color fibers compactly cellular and consisting of interweaving bands of spindly cells (200X H&E).

C: Mammary gland of woman shows abnormal acini cells and pleomorphic lobular breast carcinoma. 6: hyperchromatic nuclei of tumor cells with numerous mitotic evidence of malignancy round to oval vesicular nuclei and variable nuclear size, 7: ductile lined by a single layer of flattened cells full of macrophages and degenerated cells (400X H&E).

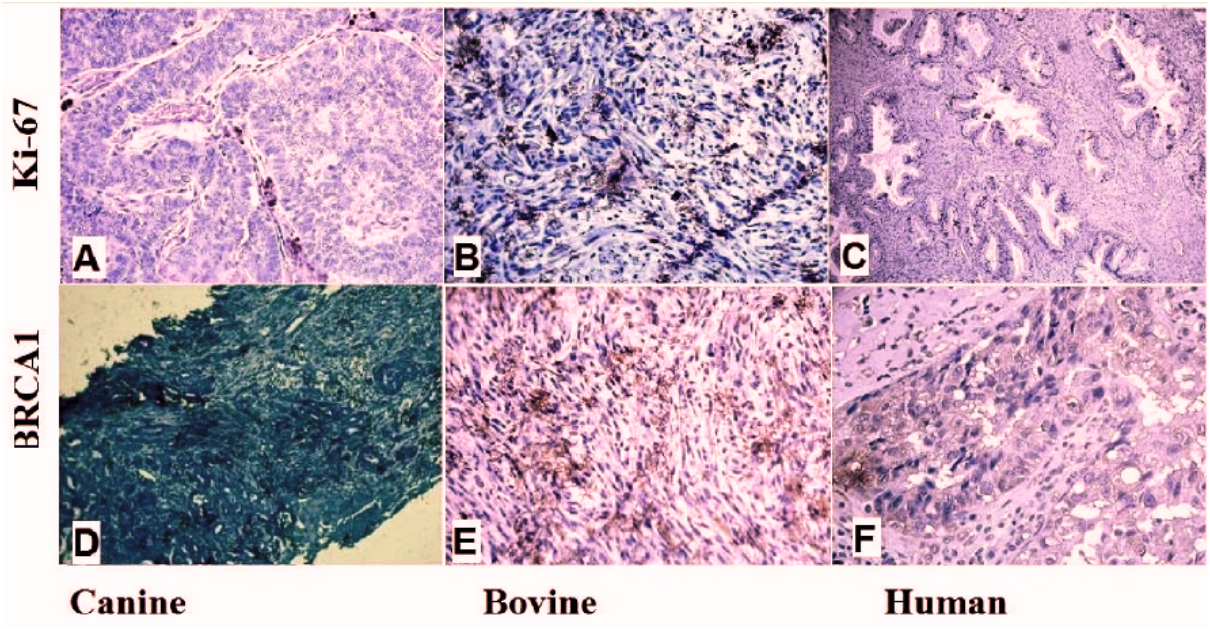

Figure 2: Multiple fields of Immuno-histochemical staining using Ki-67 and BRCA1 antibodies from archived cases of the author's work and research

A, B, C: Ki-67 in the malignant mammary gland of dog, cow, and woman, respectively. A; negative grade, B: moderate grade 2, C: poor grade.

D, E and F: BRCAI staining in malignant mammary gland of female dog, cow and woman

respectively. D: Grade 0, E: Grade 1 (+) and F: Grade 1 (+) Mostly the cytoplasm of the cells was stained but not the nucleus.

Canine mammary tumors (CMTs)

The main physical examination sign of mammary tumors in female dogs is the presence of a mass or lump (usually painless). The mass is easily detected by gently palpating the dog's mammary glands. Previous studies showed the ages of the dogs, with a mean of 7.5 years. Military female dogs were more frequent and then pet dogs or guard dogs. Tumor density on palpation almost solid or fibrosis. The appearance of the lesions depended on the aggressiveness of the tumor. The most common glands, which were usually close to the thigh (4th and5th). Sometimes, edema occurs in the proximal part causing lameness. In general, the benign masses are small, soft, distinct, and slow-growing. They are usually movable under the skin. On the other hand, malignant tumors are fast-growing, involve multiple glands, are immobile, and are attached to the overlying skin or underlying muscle. Sometimes, malignant tumors cause skin ulceration and bleeding. (2, 4)

The animals survive by surgical treatment, especially those of grade I and II. Usually in other grades there is a metastatic cancer to other organs such as the lung, which is often diagnosed by X-ray examination. In dogs, mammary tumors are frequent and tend to be sporadic as in humans. Mammary tumors represent approximately 50% of all tumors in female dogs, and about 50% of them are malignant (16), which have been shown to be caused by genetic mutations or promoted by hormones. Cancers in women and female dogs have similar expression profiles. Furthermore, CMTs have epidemiological and clinical features, the morphology and prognosis are similar to those of human mammary cancer (17). The high incidence of CMTs may be due to the prolonged exposure to estrogens during estrus without mating, which can expose the mammary gland to a significant risk factor. Normally, the estrus cycle lasts for days in a female dog. The incidence of CMTs has been found to be low 0.05% in female dogs spayed before the first estrus cycle, while it increases to 8% or 26% if spayed after the first or second cycle, respectively. If the female dog is spayed after the second estrus cycle, the risk of malignancy is the same as in intact dogs (18). Usually dogs have different sizes and numbers of lumps, previous studies have found the tumor size is beneficial for staging and is closely related to prognosis (chance of survival). In general, smaller tumors tend to have a better prognosis. In terms of breeds, some breeds are more prone to mammary tumors than others, particularly the German shepherd and Belgian Malinois, while Pointer, Terrier, Pomeranian, and Rottweiler are less exposed. Some breeds have been observed to develop CMTs at a younger age, for example the English springer spaniel which was found to have a mean age at onset of 6.9 years (19).

Women breast cancer

Malignant lesions are painless, dense or firm to palpation, hypoechoic on ultrasound with ill-defined borders, X-ray appearance, irregular edges, and sometimes tender, smooth, or round lesions. Swelling of all or part of the breast, skin irritation or darkening sometimes like an orange peel, nipple retraction, redness, crusting, or thickening of the nipple or breast skin, nipple discharge, and sometimes lumps spread to the lymph nodes under the armpit or around the collarbone. Tumor size, tissue texture, and description of the breast and surrounding area are estimated by a pathologist or radiologist based on the largest diameter of the resected specimen or on ultrasound examination. Histopathological evaluation reveals almost the ductal carcinoma in situ, lobular carcinoma in situ, or fibroadenoma. However, pathologists tend to round the tumor size to the nearest centimeter (20).

Breast cancer is often familiar; however, several genes are known to confer an increased risk of hereditary mammary cancer in humans, including BRCA1 (21). A similar genetic pattern has not been described for mammary tumors in dogs, and it has been suggested that the origin of CMTs and human mammary cancer is multifactorial and depends on the interaction of several major and minor genes and environmental factors. Female dog with a history of inbreeding, which may

lead to slow levels of genetic variation and accumulation of the worst genetic traits. Mammary tumors in dogs have been found to be more homogeneous within a single breed. (22)

Cow mammary tumor

On the other hand, in our three decades of practice as a veterinarian in a veterinary clinic, we reported the first case of a mammary gland mass in a cow. The masses rose in the teat of the left front quarter of the mammary gland and close to the mammary gland, with enlargement in supra-mammary and prescapular lymph nodes. Other clinical signs appeared were loss of appetite, fever, lameness and depression. Because mammary cancer in cattle is rare and uncommon, the case is of clinical interest. This case represents an opportunity to understand the processes occurring in mammary gland cells in cows that will provide clinical benefits for the treatment of other types of mammary tumors in mammals. (23) It is worth mentioning that the enzootic bovine leukosis (EBL) has been diagnosed by the presence of tumors and/or general lymph node enlargement. Approximately 5% of animals infected with EBL grow B-cell lymphoma or lymphosarcoma in various lymph nodes and organs after a long latent period when cancer cells penetrate many organs including udder and its skin as secondary metastatic tumors (24). The cow of this study may be infected with EBL especially the lymph nodes were also enlarged. The EBL was recorded in Iraq in 1994 (25,26) and other studies were conducted in Baghdad and other governorates. Yousif in 1997 reported that the serum positive rate was 8.4% in imported (Friesian) cattle but was non-existent in local animals using ELISA (2, 3, 27). Differential diagnoses for mammarymors in cow several issues include mastitis, abscess, hematoma and other conditions that may lead to misdiagnosis when the animal removed from the herd without proper examination (28). However, the primary tumor may have originated within the interstitial tissue of the mammary gland, or in a subcutaneous location near the gland, where it can invade the mammary tissue. Still, the incidence of mammary gland tumors in ruminants is still almost non-existent (29). Ford and colleagues had reported only 41 cases of mammary gland neoplasia in cattle from 1902 until 1989. Only one spontaneous case has been reported of secretory mammary carcinoma in a cow, the tumor was highly aggressive and malignant (30).

The most convincing opinion of low levels of circulating estrogen in the body of a dairy cow and the high lactation requirements also provide protection against mammary cancer (2, 31). In humans, early pregnancy reduces a woman's lifetime risk of breast cancer by up to 50%. Although female breast cancer is a complex disease, the pathology and risk factors are only partially understood. In the normal state the mammary gland develops to perform its function and influence by growth factors and hormones. During the tumorigenic process, signals are released, allowing the mammary epithelium to expand, proliferate, and invade neighboring tissues (hyperplasia). In women, several factors are associated with an increased risk of breast cancer, including early puberty, late first child, late menopause, poor diet, lack of exercise, obesity, alcohol consumption and the presence of benign breast disease, radiation exposure and family history (1, 32, and 33).

Conclusions

The nature of dogs' food as a carnivore may become a major factor in the development of mammary tumors in addition to hormonal factors. Also in humans reduces the risk factors when intake low-fat- high-fiber diet, fruit and vegetable may protect against breast cancer. Comparative research may help find new information about the specific susceptibility to mammary tumors, reduce risk and discover new preventive approaches and therapeutic targets for the treatment of breast cancer. Through this review, there is an opportunity to understand the processes that occur in mammary cells of cattle and dogs that will ultimately provide clinical benefits for the prevention, diagnosis, and treatment of human breast cancer. Comparing the pathogenesis of mammary tumors in domestic animals and humans, including the hormonal, nutritional, and environmental factors in which they evolved, may help distinguish between critical and incidental risk factors.

References

1. Alabbody HHK, Al- Nasiry BS, Kadhim KH Applying food frequency questionnaire to evaluate the dietary pattern and lifestyle on women with breast cancer, Journal of the Faculty of Medicine Baghdad, 2018; (60) 2:119-125
2. Alabbody HHK., Mammary tumor in mammals and the risk factors: comparative clinical pathological study, Journal of Biodiversity and Environmental Sciences, 2019;14(5)83-92
3. Alabbody HHK, Bovine leukosis and the possibility to cause cancer in humans: A scientific review, The Iraqi Journal of Veterinary Medicine, 2018; 42 (1), 52-60
4. Alabbody HH, Lafta IJ, , Clinical pathology and immuno-histochemistry of mammary tumors from military/pet dogs in Iraq. Online Journal of Veterinary Research, 2018 22 (7), 547-560
5. Alabbody HHK, Assessment the owners awareness towards livestock diseases at rural of Iraq, CAHIERS MAGELLANES-NS,2024; 6 (2), 749-757
6. Alwan NAS Hobi BM , Bilateral Breast Cancer: Clinical Presentation and Pathological Characteristics in Iraqi Patients, J. Cardiovasc Disease Res 11 (3), 111-116
7. Alwan NAS, commentaries Breast Cancer Among Iraqi Women: Preliminary Findings From a Regional Comparative Breast Cancer Research Project, , Journal of Global Oncology, 2016; 2 (5), 255-258
8. Alabbody HH, Alwan MJ, Zenad MM, Wali AA., Clinical and Histopathological Study on Dog's Tumors in Iraq, Iraqi Journal of Science, e, 2017, 58(3C): 1617-1630, DOI: 10.24996/ ijs.2017.58.3C.6
9. Lafta IJ, Alabbody HH Incidence of cutaneous and subcutaneous tumors of dogs from Baghdad city: clinical, cytological and histopathological features, Iraqi Journal of Veterinary Sciences, 2020 34 (1), 129-137
10. Sorenmo KU, Kristiansen VM, Cofone MA. Canine Mammary gland tumours; a, histological continuum from benign to malignant, clinical and histopathological evidence. Vet Comp, Oncol, 2009 7, t6z-t72.
11. Queiroga FL, Raposo T, Carvalho MI, Prada J, Pires I. Canine mammary tumours as a model to study human breast cancer: most recent findings. In Vivo 2011; 25,455-65.
12. Patricio R, Malin M, Tara B,. Mammary Tumor Development in Dogs is associated with BRCA1 and BRCA2, Cancer Res, 2009 69(22), 8770-4
13. Rismanchi S, Yadegar O, Muhammad Nejad S, Arnanpour.. Expression of vimentin filaments in canine malignant mammary gland tumours: A simulation of clinicopathological features of human breast cancer. Biomed Rep e, 2014; 725- 28.
14. Raposo TP, Arias-Pulido H, Chaher N,.Comparative aspects of canine and human inflammatory breast cancer. Seminars in Oncology, 2017 44(4), 288-300.
15. Guoxin R, Xuhui M, Yunteng W. Ki67 Proliferation Index as a Histopathological Predictive and Prognostic Parameter of Oral Mucosal Melanoma in Patients without Distant Metastases, Journal of Cancer 2017; 8(18), 3828-3837. DOI: ro.7r5o /jca.zoggs Research Paper Ki67.
16. Megalhaes GM, Silveira ACT, Maunari DP, Alessi AC. Behavior of CD44 receptors in mammary tumors of dogs. Open Journal of Veterinary Medicine 2012; 2, 48-51.
17. Sharma N Gupta, A K. BhaR A. and Shah O S. Epidemiological Studies on Canine Tumours in Jammu, 2017;8(5), 246-254. doi:10.5455/ijlr.20170905050513

18. Sostaric-Zuckermann, I.C., Severin, K., Hohsteter, M., Artukovic, B., Beck, A., Gudan Kurilj, A. and Grabarevic, Z. Incidence and types of canine tumours in Croatia. Veterinarski Arhive, 2013; 83(1): 31-45.
19. Munson L, Moresco A. 2007. Comparative pathology of mammary gland cancers in domestic and wild animals. Breast Disease 28, 7-21.
20. Alwan N, Tawfeeq F, Muallah M, Sattar S The Stage of Breast Cancer at the Time of Diagnosis: Correlation with the Clinicopathological Findings among Iraqi Patient, Journal of Neoplasm, 2017; 2 (3:22), 1-10
21. Wang W, Xu ZZ, Costanzo M, Boone C, Lange CA, Myers CL., Pathway-based discovery of genetic interactions in breast cancer. PLoS Genet, 2017; 13(9): e1006973. https://doi.org/10.1371/journal.pgen.1006973
22. Keum Im -, Kim II H , Kim Na-H , Youn Ha-g L , Kim JHb , Jungg Sur, Breed-related differences in altered BRCA1 expression, phenotype and subtype in malignant canine mammary tumors, The Veterinary Journal 2013;195(3 366-372
23. Hughes K., Comparative mammary gland postnatal development and tumourigenesis in the sheep, cow, cat and rabbit: Exploring the menagerie, Seminars in Cell & Developmental Biology 2021;114,June: 186-195, https://doi.org/10.1016/j.semcdb.2020.09.010
24. Povey RC, Osborne AD. 1969. Mammary gland neoplasia in the cow. Path. Vet. , 6,502-512.
25. Hasso SA, Zenad MM, Abdulla M.,.Preliminary diagnosis of bovine viral leukosis in Iraq, Bovine Pract 1969; 28, 164.
26. Khrudhair YI, Hasso SA, Yaseen NY, Al-Shammari AM. , . Serological and molecular detection of bovine leukemia virus in cattle in lraq, Emerging Microbes Infect. , 2016 56(5), 1-6.
27. Yousif AA. 1997. Serological study of bovine leukosis in Iraq local and imported cow. Iraqi J. Vet. Med 21(1), 137-142.
28. Singh R, Kour H, Kumar P and Bhadwal MS. , Role of awareness on animal welfare measures and health care management of dairy animals, Ruminant Science, 2021;10(2):433-438.
29. Rainard P, Gilbert F B., Germon P., Immune defenses of the mammary gland epithelium of dairy ruminants, Frontiers in Immunology, 2022; 13:1-26 https://doi.org/10.3389/fimmu.2022.1031785
30. Ford TS, Ross MW, Acland HM, Madison JB. 1989. Primary teat neoplasia in two yearling heifers. J. Am. Vet. Med. Assoc., 195,238-239.
31. Alabbody HHK, Lafta IJ, Incidence of canine digestive system tumours in Baghdad Province, The Iraqi Journal of Veterinary Medicine, 2019; 43 (2), 67-76
32. Lafta, R.; Saeed, E. and Isa, S. Risk factor of breast cancer among women. Iraqi Journal. Comm. Med., 2013: 26 (1):1-6.
33. Alabbody HHK The Control and Preventative Measures for the Health Problems of Pets, Journal of Animal Health and Production, 2024 12 ((s1)), 139-144