*IOSR Journal of Agriculture and Veterinary Science (IOSR-JAVS)*
*e-ISSN: 2319-2380, p-ISSN: 2319-2372. Volume 10, Issue 8 Ver. II (August 2017), PP 64-69*
*www.iosrjournals.org*

# Recent Overview of Mammary Cancer in Dogs and Cats: Classification, Risk Factors and Future Perspectives for Treatment

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***Abstract:*** *Mammary cancer remains as the common cancer in intact female dogs and cats. Its share similarities with human breast cancer as the cancer initially arise from the mammary gland. Therefore, the treatment protocols for the mammary cancer in animal mostly were extrapolated from human breast cancer treatment. In this review, we highlight various key aspects of mammary cancer information in dogs and cats with special emphasis on classification, epidemiology, diagnosis, prognosis, and treatment options. This review also highlights the recommendation for future study as information given could be extrapolated to human breast cancer.*

***Keywords****:Mammary cancer, breast cancer, treatment, dog, cat*

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Date of Submission: 08-08-2017 Date of acceptance: 29-08-2017

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## I. Introduction

Mammary cancer is very well known non-communicable disease and become a serious illness worldwide, occurs in human and animal. In humans, it is commonly known as breast cancer due to the anatomical location which is at breast [27]. In animals, female intact dogs and cats have high prevalence of mammary cancer which account to 52% and 17%, respectively [23, 25, 22]. Mammary cancer that occurs in animal shares similarities in clinical, histopathological and molecular features with human breast cancer [11, 35]. For that reason, study on animal model of mammary cancer is very relevant especially to correlate prognostic and therapeutic values before entering to clinical trials.

Surgery remains the main approach for intervention of mammary cancer followed with treatment of adjuvant therapies such as chemotherapy, hormonal therapy and radiation therapy. The selection of adjuvant therapy depends on the individual status such as age, current health condition and stage of the cancer. Despite many modern therapeutic approaches, unfortunately, the side-effects and prognosis of the treatment still consistently remain the major topic of discussion among practitioners. Fifty-eight (58%) and sixty six percent (66%) recurrence of cancer occurs after surgeryin feline and canine cases, respectively [1, 39]. Currently, the ability of cancer cells to undergo mutagenesis during treatment leads to a relapse, thus making the treatment more complicated. Therefore, this review is made with intention to updated information about mammary cancer disease in dogs and cats. This review also gives correlations between animal mammary cancer and human breast cancer vice versa, thus can contribute for the further investigation especially for treatment and prevention.

## II. Methodology

Science Direct, ProQuest, Pubmed and Google databased were used for articles collection. The articles from 10 years backward between 2007 to 2017 were mostly used. The article were find from databased using terms ‘mammary cancer’, ‘breast cancer’, ‘canine mammary gland tumour’, ‘feline mammary gland tumor, and ‘cancer’. Details pertaining to mammary cancer in animals and humans were recorded.

## III. Cancer

Cancer is a very complex and life threatening disease. According to American Cancer Society 2016, cancer that occurs in humans and other organisms arise from a single cell which has undergone genetic change due to interaction from external factors and genetic susceptibility of the host. External factors such as stress, radiation, and infection may act together with the host and developed the state of redox imbalance, which is an alteration in the homeostasis between oxidants and antioxidants, resulting in overwhelming oxidants within the cell. Studies have shown that redox balance plays an important role in the maintenance of stem cell self-renewal and differentiation [48]. Oxidative stress leads to damage of lipids (lipid peroxidation), proteins (protein denature) and DNA by reactive oxygen species (ROS). In particular, ROS activation of AP-1 (activator protein) and NF-kappaB (nuclear factor kappa B) signal transduction pathways, which in turn leads to the transcription of genes involved in cell growth regulatory pathways, inclusive in the carcinogenesis process. It appears that the DNA damage is predominantly linked with the initiation process. DNA mutation is a critical step in carcinogenesis and elevated levels of oxidative DNA lesions (8-OH-G) have been noted in various tumours, strongly implicating such damage in the initiation of cancer development [46]. Antioxidant defences such as superoxide dismutase, catalase, glutathione peroxidase as well as other non-enzymatic antioxidants normally protect against such damage. The reducing levels of antioxidants would result in increasing the cancer risk [3]. These theories thus give a role for antioxidants as one of a possible cancer preventions and treatments although have not yet been successful.

## IV. MAMMARY CANCER

The terminology for mammary cancer is implying for both animal and human since the cancer is from the mammary gland. However, for human it is well known as breast cancer. Breast cancer is the most frequent cancer amongst women throughout the world, and account high mortality rates especially in non-developing country due to late diagnosis and increasing population [14]. It also can develop in males, however it is relatively very rare (less than 1%), and the pathophysiology remains uncertain [2, 38]. For animals, it is one of the commonest tumours in intact dogs [35]. [4] stated that dogs are most susceptible to develop mammary cancer and 50% of the mammary tumour in bitch is malignant [24]. Dogs and cats have an equal chance of getting mammary cancer [7, 35]. The aetiological agent of mammary cancer in animals is unknown, but many studies showed the similarities with human breast cancer in term of classification, risk factor, treatment and prognosis [32, 35].

## V. Diagnosis

Physical examination, fine needle aspiration of mammary gland and lymph node followed with cytology evaluation are often been the standard technique for diagnosing mammary cancer [28]. Radiograph evaluation also has been used to assess whether the cancer metastasize to other organs but the confirmation of diagnosis is still through biopsy. The two types of abnormal mass that may arise can be either a benign tumour or malignant tumour. As the name implies, benign tumour is localized and not life threatening;however this is not a guarantee of safeness because the risk of the benign tumour to become malignant still there under some circumstances (interaction between external factor and genetic alteration).

## VI. Prognosis

The prognosis of an animal that having mammary cancer depends on many factors such as the age and stage of mammary cancer. The early the detection, the higher the chance of survival but however, event there is a prevention and control measure but still no guaranteed cure for mammary cancer and other cancer diseases due to mutation.

Thus, survival rates need to be evaluated within 5-year intervals.

## VII. Classification of Mammary Cancer

The classification of mammary cancer in animals was being adapted from breast cancer classification systems [39]. Since 2003, there have been several new updates of mammary cancer classifications. However, until now, the fundamentals of mammary cancer classification is still based on pathology and molecular biology [18, 47]. Pathological classification based on characteristic seen under light microscopy of biopsy specimens. In 2003, the report by World Health Organization stated that there are 20 major tumour types [46]. It is still in debate mode about how many classes of mammary cancers there are [46]. The majority accepted that mostly mammary cancers are derived from epithelium lining ducts and lobules [47]. Besides as part of pathological classification, presence of pathological grade such as presence of acinar, glandular and pleomorphic in mammary cancers morphology also would be able to determine the prognosis of the patient [30, 16]. Actually until now, there is no clearly well achieved classification of mammary cancer in a molecular biological aspect.

Mostly the biological classification is based on endocrinology gene expression, which are oestrogen receptor (ER) positive/negative, progesterone receptor
(PR)-positive/negative, type of mammary cancer [46, 47]. There is still space to study the molecular biology classification of mammary cancer due to some overlapping amongst immunohistochemistry surrogate and many molecular classes and subtypes [18].

## VIII. Epidemiology

For dogs, the prevalence of mammary cancer is 52% and mammary cancer has become the most common cancer amongst bitch globally [4, 23] meanwhile for cats, mammary cancer is the third most frequent type of cancer and it contributes for 17% of total cancer cases after lymphoma and skin cancer [25]. The incidence rates of bitch worldwide is sharply associated with age, which shows increasing prevalence in female dogs is more than 9 years old [33, 35].

## IX. Risk Factors

The aetiology of mammary cancer is still not clear [49, 10]. However, it believed that both interaction between the external factor and host susceptibility play a significant role in mammary cancer development. The chance of getting mammary cancer also has been influence by several risk factors that may probably be predisposed to the disease. Many studies have been conducted in order to find the risk factor of the mammary cancer with the intention to provide knowledge to the owner about preventive measures.

## X. Reproductive History of Patient

Women who have had relative with breast cancer or ovarian cancer usually have a high risk of having mammary cancer, two to three times that of the general population. The risk factor is even higher if the relative was affected with mammary cancer at early age [12]. However, for animals, the breed of dog such as Rottweilers, Boxers, Cocker Spaniels and Golden Retrievers are at high risk of developing mammary cancer [43] while for cats, is the Siamese breed [13].

[40] revealed that canine mammary cancer is a hormone- dependent disease similar to human breast cancer. About 60% canine mammary cancer is estrogen receptor (ER) positive. Like humans and dogs, feline mammary cancer also depends on hormone. However, which hormone (oestrogen or progesteron) that contributes to the development of mammary cancer is still unclear [43]. Dogs and cats that have history of taking hormonal drugs for the purpose to stop oestrus cycle are at high risk of getting mammary cancer [43]. Unspayed animals (dogs and cats) have 7 times higher risk than that of spayed because the source of hormone that contribute to the development of mammary cancer is still presence [43].

## XI. Genome Alterations

Alteration in BRCA 1 and BRCA 2 germline would increase the risk of mammary cancer in both human and animal [33]. BRCA 1 and BRCA 2 are genes that responsible in repairing DNA damage or alteration. It is hereditary genes that can pass from one generation to another and account for about 40-85% risk of breast cancer, if these genes are mutated [16]. BRCA 1 is located on chromosome 17q while BRCA 2 is located on chromosome 13q12-13. Currently, no available technique can provide a guarantee of identification of all cancer-predisposing allelic variants in BRCA 1 or BRCA 2 [29]. Furthermore, data from history is very crucial in order to reduce the risk. Beside as a treatment option, health care providers sometimes may suggest tamoxifen as a preventive drug to reduce the incidence of mammary cancer at 50% but this method has not been evaluated by case-control studies in high-risk women [16, 29]. Besides that, patients who have p53 tumour suppression gene mutation also at high risk of developing breast cancer. The gold standard method of treating patient with known genetic alterations is still being intensively studied and investigated [16].

## XII. Oxidative Stress

Oxidative stress refers an imbalance population between oxidants and antioxidant substance in the body thus leading to cellular destruction of lipid, DNA and protein [2]. Mammary cell contains many cells including a group of connective tissue cell named stromal cell. Fibroblasts are one of the types of stromal cells responsible in support animal's tissue framework. During oxidative stress, fibroblasts cell undergo differentiation into myofibroblasts which result in increasing amount of oxidants particularly hydrogen peroxide, thus creates favour environment for mammary cancer development [44, 6, 41]. Over activation of stromal cell would induce the carcinoma associate fibroblasts (CAFs) and promote tumour growth within the mammary cells. Additionally, the differentiation fibroblasts into myofibroblasts would also increase the type I collagen secretion by myofibroblasts, which contributes to mammary cancer formation and metastasis [31]. Studies have revealed that excessive secretion of type I collagen contributes to decreased chemotherapeutic susceptibility, subsequently altering the genome and finally drug resistance against chemotherapies [15].

## XIII. Mammary Cancer Treatment

Mastectomy is often becoming a mainstay choice of local therapy but it is dependent on multiple factors including the status of tumour margin, age, patient status and the metastasize condition. Adjuvant therapy is really necessary to follow up in order to eliminate the entire cancer cell systemically. The major issue regarding mastectomy is a cosmetic outcome but the prognosis is relatively good when it is performed at the early stage of mammary cancer [26, 17].

## XIV Adjuvant Chemotherapy

Chemotherapy has been used for a long time for mammary cancer patients. In the early stage of mammary cancer, the usage of chemotherapy as adjuvant therapy has shown remarkable improvement in the overall survival rate [16]. Chemotherapy is well known as very painful treatment. In human, patient tolerability has often been a consideration before planned with chemotherapy cycle but this is not happened for animal. Radiation has often been an alternative option of adjuvant therapy, replacing chemotherapy. It can also control the relapse by 50-66% if used in the correct dose in human mammary cancer [5].

## XV Adjuvant Hormonal Therapy

The decision to advocate adjuvant hormonal therapy is based on the histopathology assessment when there is an evidence presence of hormone receptor. Tamoxifen (Nolvade) is an example of oestrogen receptor (ER) antagonism drug which interferes with oestrogensignalling by binding with oestrogen receptor in mammary cancer cell. Apart from that, tamoxifen also demonstrated chemopreventive medicine for a high risk breast cancer patient especially a patient with heredity issues [16, 8].

Studies by [9] showed that tamoxifen also can exhibit an anticancer effect to ER negative breast cancer by inducing apoptosis mechanisms. This is in agreement with [20] that proved tamoxifen can control the ER negative breast cancer through inactivation of protein phosphatase 2A (PP 2A) and phopho-Akt (p-Akt) inhibition in the oestrogen receptor, eventually will stimulate apoptotic activity of tamoxifen and sensitizes susceptibility of ER-negative breast cancer cells to tamoxifen.

In animal, even though the mammary cancer in dogs and cats share similar clinical, histopathological and molecular features with human mammary cancer, however, the study pertaining therapeutic treatment especially using hormonal therapy approach is very limited. Study by [42] on healthy dog reveal prolonged exposure of tamoxifen would cause pyometra. Nevertheless, ovariohysterectomy is recommended to overcome the problem. Therefore, many studies need to be conducted using adjuvant hormonal therapy such as tamoxifen for animal especially dogs and cats. Since canine mammary cancer mostly is a type of oestrogen receptor (ER) positive breast cancer. Therefore, theoretically, tamoxifen should be effective to mammary cancer. The advantage of using tamoxifen compared to chemo drug is convenience to the owner. This is because tamoxifen can give orally but chemo drug need to be administer intravenously. In addition, tamoxifen more selectively cytotoxic to cancer not but not to normal cells compared to chemo drug.Tamoxifen may become therapeutic approach for mammary cancer cases considering its benefit in human mammary cancer cases if its side effects are correctly assessed and controlled.

## XVI Prevention

Performing ovariohysterectomy as early as 6 months of age before the first oetrus cycle started significantly reduce the risk of mammary cancer by 95%. Spayed female dogs before the second oestrus have reducing the risk up to 92% [37]. In humans, late age at first birth are related to increased risk of breast cancer. This is because when there is no pregnancy, the mammary cells been exposure to oestrogen and progesterone hormones that are produced by ovaries. In dogs, there is no association was found between gestation, giving birth at young age and the occurrence of canine mammary cancer [36, 34].

## Acknowledgements

This article is self-funding.

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Muhammad LuqmanNordin. "Recent Overview of Mammary Cancer in Dogs and Cats: Classification, Risk Factors and Future Perspectives for Treatment." IOSR Journal of Agriculture and Veterinary Science (IOSR-JAVS), vol. 10, no. 8, 2017, pp. 64–69.