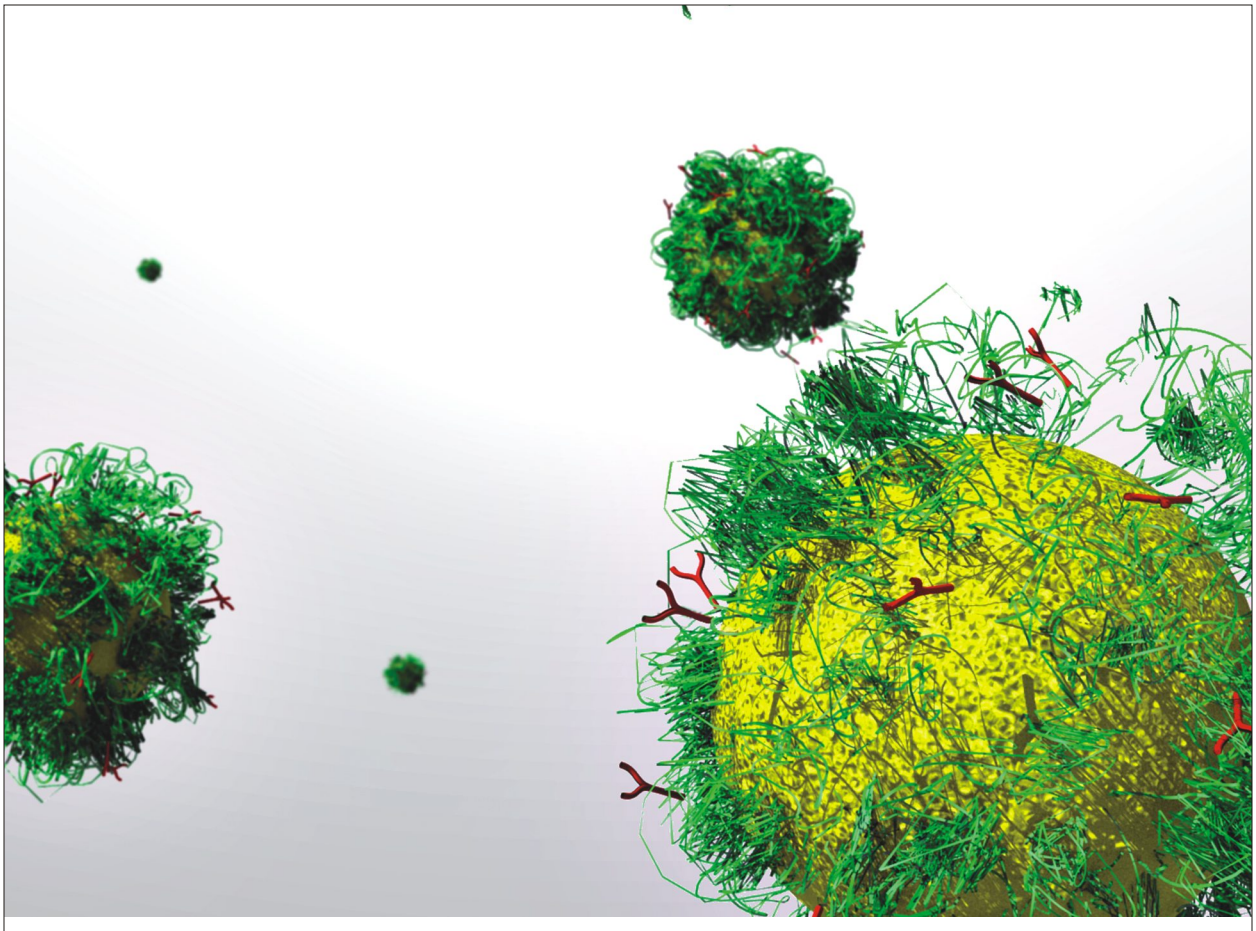

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# Canine Prostate Cancer: Would the Dog be an Important Model for the Study of New Drugs?

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## ABSTRACT

Prostate cancer is ranked as the second leading cause of cancer-related death in men aged above 50 years and the long-term survival of patients with metastatic disease has not changed significantly. This fact is related mainly to the limited therapeutic options available. Despite numerous studies on PCa in humans, success was not obtained in clinical trials of targeted therapies because of the difficulty in standardizing an ideal animal model for application in clinical trials. The use of dogs as a model for the clinical trials of new drugs can bring in higher accuracy in assessing the response of tumors to the drugs tested, with the assumption that the dog is a natural model of the disease and shares the same environment as humans. Due of the importance of prostate carcinoma in man the goal of the review is to identify the strengths of the dog as a model for the development of new therapy for prostatic carcinoma.

**Key words:** Animal model, clinical trial, men, prostatic carcinoma

## INTRODUCTION

According to the National Cancer Institute (INCA) for the year 2012 are expected 60,180 new cases of prostate carcinoma in Brazil, ranked as the second leading cause of cancer related death in men over 50 years old. The latest global estimate of prostate cancer incidence showed an increase rate, what me be due to the use of Prostate Specific Antigen (PSA) exam as a routine procedure. Prostate cancer is the most common tumor in men and is a rapidly growing cause of morbidity and mortality in the Western world (LeRoy and Northrup, 2009).

The study of sporadic prostate cancer in animal models are critically important of our understanding of the development of cancer, defining the molecular basis of the disease and are also required to accelerate the development of new therapies. Currently, few animal models for the study of prostate cancer are described, this fact could be due to the complexity of the disease or whether in this models the carcinogenesis is induced not mimicking that occurs in man (Fonseca-Alves *et al*., 2010).

The canine prostate cancer show many characteristics with humans, such as morphology, concomitant presence of Prostatic Intraepithelial Neoplasia (PIN), Proliferative Inflammatory Atrophy (PIA), bone and regional lymph node metastasis (Bell *et al*., 1991; Bostwick and Qian,

2004). Other important aspect is that the prostate cancer in dogs is androgen independent. In this context, the dog can be considered an important model for the study of advanced disease (Lamb and Zhang, 2005).

For the study of prostate cancer in men there are few animal models used in experimental practice, considering that the dog is the only non-human specie which prostate carcinoma that occurs spontaneously (Bell *et al*., 1991; Bostwick and Qian, 2004). Genetic manipulation of rats and mice provided a number of animal models for studying cancer progression from the study of PIN and the prostate cancer, however, it is genetically modified with carcinogenesis models induced, thus not showing changes that occur spontaneously in humans (Fonseca-Alves *et al*., 2012).

The purpose of this review was current understanding of prostate cancer in dogs, with significant comparative aspects of human disease.

**Incidence and risk factors of prostate cancer in humans and animals:** Dogs and humans have the highest prevalence of prostate carcinoma among all species. With the exception of aging (Fonseca-Alves *et al*., 2010), the factors that contribute to the increase of dogs or men to prostate carcinoma are poorly defined. In humans the risk for prostate cancer increases progressively with age. There is a higher prevalence in men between 65 and 75 years old.

In men, both endogenous and exogenous factors have been identified which increase the risk of PCa. These include family history, advanced age and nutritional factors (Bostwick and Qian, 2004). Some authors consider that this effect is related to income and access to basic health and nutrition of the population studied. Genetic factors may be involved in the etiology of prostate cancer. There is a risk of 5 to 11 times greater for the development of prostate cancer in those with two or more relatives with the disease.

The development of sporadic tumors is closely related to environmental factors. Among these they stand out the dietary factors. Many studies have linked the consumption of fat and animal products with the development of prostate cancer in humans. Exposure to cadmium mineral that is found in minute quantities in cigarette smoke and in alkaline batteries, is also cited as a possible risk factor for prostate cancer (Ellwood-Yen *et al*., 2003).

It is also evident that androgens play an important role, because its metabolite, dihydrotestosterone (DHT), works by activating genes linked to prostate cell division. Several androgen receptor gene polymorphisms have been studied. In dogs a few risk factors are related to the development of prostate cancer in dogs. But prostatic tumors in dogs are closely related with the loss of androgen receptor.

An important difference between human and canine prostate cancer is the role of androgen. The majority of human prostate cancers at an early stage are highly dependent on androgens as growth factor and therefore, androgen deprivation therapy is critical for men with prostate cancer, it provides rapid and marked clinical improvement.

The reason for reducing the incidence of prostate cancer in intact male dogs is unknown, but possible explanations may include a potential protective role of androgens mediated through the anti-proliferative effects in prostatic ductal epithelial cells or transient. The castration of dogs has been shown to alter the stromal component of the prostate mainly from the actin-positive smooth muscle cells of mesenchymal cells vimentin-positive which could play a role in the development of prostate cancer in castrated male dogs (Bostwick and Qian, 2004). Furthermore, neutered dogs live longer than intact dogs and being predisposed to developing age-associated neoplasms such as PCa.

**Prostatic Cancer in dogs and humans:** In humans and dogs, prostatic carcinoma is clinically aggressive, often presenting metastases in regional lymph nodes, lung and bone (Bell *et al*., 1991). Prostatic carcinoma in dogs shares many features with that of humans, such as morphology, presence of concomitant PIN and foci of bone and lung metastasis (Teske *et al*., 2002).

Some authors suggest that the vast majority of cases occur in dogs from 8 years old on average 8.9 years (Karr *et al*., 1995). In the human species the prostatic neoplasia is also considered a disease of the elderly, accounting for over 50% of deaths in men over 70 years (Armbruster, 1993). The similarity in the pathogenesis of prostate cancer between dogs and humans have become the natural canine model to study this disease, although prostatic neoplasms are not as common in dogs as they are in man, but an injury is extremely rare in any other animal species (Lowseth *et al*., 1990; Karr *et al*., 1995).

The clinical signs are often found tenesmus and dysuria, hematuria, anorexia and weight loss (Cornell *et al*., 2000). The prognosis of patients affected by prostatic carcinoma is unfavorable, since not using biochemical markers such as PSA for early detection, as well as in man. The World Health Organization (WHO) divides the prostatic neoplasms in dogs in two classifications: Carcinoma and undifferentiated carcinoma (Owen, 1980). Carcinomas are classified into intra-alveolar and acinar. Histologically canine PCa show standard intra-alveolar morphology (Fig. 1) with foci of well-differentiated cells to poorly differentiated cell layer (LeRoy and Northrup, 2009). In man PCa is classified according to the Gleason score which assigns scores to various caps according to cell differentiation, the dog that classification is not used (Cornell *et al*., 2000).

**Models for development of new drugs:** Animal models are essential for basic and applied research in the life sciences. Experimental models have a central place in medical and pharmaceutical research and biotechnology, including drug discovery, preclinical and toxicology. Although pharmaceutical companies have long employed animal models based on mammalian species such as mice, rats, dogs, cats, pigs and primates. Models using mice and rats are widely used in the literature.

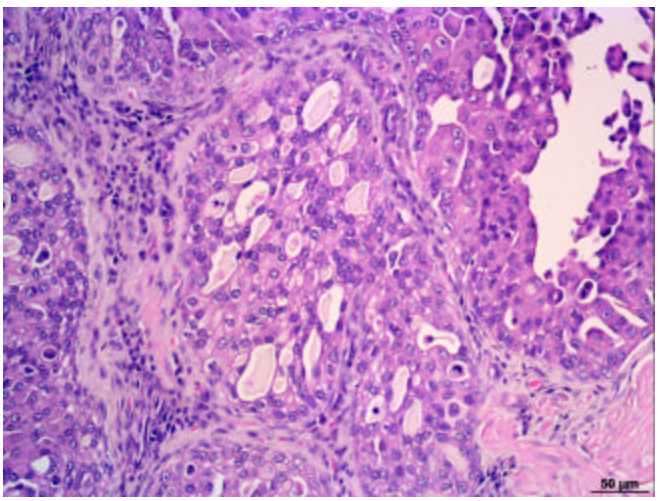

Fig. 1: Hematoxylin and eosin stain. Note the proliferation of neoplastic cells of canine prostatic epithelium. Note the similarity to the human prostatic carcinoma. 200x. Scale bar: 50 μ

The use of these models greatly helped in understanding the development, progression and metastatic mechanisms of prostate cancer in men. These models are developed from induced carcinogenesis, not mimicking what occurs naturally in man. Due to these conditions the drugs tested in these models have not been successfully used in humans. Nowadays many human cancers exhibit specific drugs in treatment (tyrosine kinase inhibitors and monoclonal antibodies), however, for prostate cancer no medication was successful in treating.

Another interesting model for the study of prostate cancer is a cell culture. In cell culture it is possible to directly test the effect of a drug on prostatic cells. It can even be carried out a primary cell cultures from the patient and test individual sensitivity to different chemotherapeutic. The limitation of this model is the evaluation of isolated cells without of tumor microenvironment and interference of cytokines and growth factors produced endogenously by the patient.

**Spontaneous canine model for prostate cancer:** The dog develops naturally many tumors and can be considered a sentinel for environmental carcinogenic factors by being exposed to the same factors like men and presented a shorter life cycle. However, in practice canine model it is not widely used. The dog is rarely used due to the small number of published studies that demonstrate the genomic similarities of prostate cancer in man and dog. The prostate cancer in men is closely involved with the loss of expression of NKX3.1 and increased expression of C-MYC (Zhang *et al*., 2008). Recently the loss of NKX3.1 and increased C-MYC stain was associated with prostate cancer in dogs, demonstrating the similarity of the disease in both species (Fonseca-Alves *et al*., 2013).

The advantage of the dog as a model for the study of spontaneous prostate cancer is that animals can be used in routine of veterinary hospitals avoiding the use of experimental animals besides having a more reliable response to different drugs. The canine model is widely used to test for response to chemotherapy of osteosarcoma. Many drugs are tested in this spontaneous neoplasm in dogs and represent an excellent model (Vail *et al*., 2002).

## CONCLUSION

The canine prostate cancer develops spontaneously and can be an excellent option for clinical trials of new drugs for prostate cancer in men. Molecular studies involving prostate cancer in dogs would be required to elucidate the genic changes that occur in the development of this tumor and identification of therapeutic targets.

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