Pathogenesis of prostatic neoplasia in castrated dogs: why the increased risk?
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Introduction
Prostatic neoplasia in dogs is most often malignant carcinoma. Incidence is increased after castration.1-4 The disease mimics advanced prostatic neoplasia in men. Parallels will be drawn between the disease in humans and in dogs, possible causes for increased risk after castration in dogs discussed, and potential research avenues described.

Keywords: Prostate, neoplasia, dog

In men, prostatic cancer is the most common neoplasm diagnosed and is the second most common cause of cancer-related death.5,6 The disease most commonly is diagnosed in men greater than 65 years of age. Autopsy studies have demonstrated that about one-third of men over the age of 50 have some neoplastic change in their prostate and that this increases to about 90% incidence in men aged 90 years or more.5

Despite the high incidence of prostatic neoplasia, most men do not die of their disease.6 Early in the progression of the disease in men, prostatic neoplasia is androgen-dependent.7 Over time, as androgen-dependent cells die off spontaneously or as a consequence of therapy, a heterogeneous small population of androgen-independent cells undergoes clonal replication.7 It is unclear whether androgen receptors play into this activation of androgen-independent cells and, if they are involved, if it is due to onset of androgen insensitivity or hypersensitivity.8,9 This heterogeneous cell population invades locally and metastasizes to distant sites including lymph nodes, lung, bone, and liver.10 The metastatic cells have a low rate of proliferation and so are relatively resistant to chemotherapy.11

Risk factors identified in men for development of prostatic neoplasia include genetics, race, and intact status. Up to 10% of tumors have a hereditary component and incidence is increased in men with an affected father or brother.12,13 African American men are at greater risk than men of other races.13,14 Finally, men who never have significant androgen exposure, either because of prepuberal castration or congenital hypogonadism, are at less risk of developing prostatic neoplasia than men who go through puberty and have normal serum concentrations of testosterone and dihydrotestosterone.14

In dogs, prostatic neoplasia is an uncommon tumor, with reported incidence ranging from 0.1 to 0.7%.15,16 The lower incidence in dogs may be due to inability to diagnose the disease until it is advanced enough to cause clinical signs or may be due to different etiology than the disease in men.17 Diagnosis of prostatic neoplasia is most common in aged dogs, with reported mean age at diagnosis ranging from 8.5 to 9.9 years.2,16,18 Age at time of diagnosis has not been shown to vary between intact and castrated dogs.2,4

Androgen-responsive prostatic neoplasia, as described in men, has not been reported in dogs. The most common cell type and location described are basal cells of ductal or urothelial origin.1,19 Metastases are most common locally and in lung, liver, spleen, colon and rectum, urethra and urinary bladder, heart, kidney, and bone.4,20,21 Morbidity and mortality are high; in studies, 76 to 80% of dogs with prostatic carcinoma were euthanized at the time of diagnosis and mean survival of those who lived for more than one week after diagnosis was 30 days with only one dog reported to live for more than four months.3,22

Prostatic intraepithelial neoplasia (PIN) is a histologic change in the prostate that some consider to be a pre-neoplastic change in men.23 In dogs, PIN has been identified that is identical to that in humans.24 Prostatic intraepithelial neoplasia may be seen in intact or castrated dogs and may or may not be a significant precursor of prostatic neoplasia or a cause of prostatic neoplasia significantly associated with castration in dogs.24,25

Age is a risk factor for disease, as described above. Breed has not been demonstrated as a consistent risk factor in dogs; this may be due to difficulty in identifying familial trends with such a low-incidence disorder. A well-recognized risk factor is intact status, usually described as an odds ratio. Odds ratios are calculated by dividing the odds in one group by the odds in another, in this instance by dividing the odds of developing prostatic neoplasia in castrated dogs by the odds of developing prostatic neoplasia in intact dogs. If the odds ratio is greater than one and if the confidence interval for the odds ratio does not include one, a significant risk exists. In dogs, the reported odds ratio for development of prostatic neoplasia after castration varies from 2.1 to 4.3.1,4 For disorders with low incidence, the odds ratio is virtually identical to the relative risk, suggesting that castrated dogs have a two to four times greater risk of developing prostatic neoplasia than do intact dogs.

Castration is associated with loss of significant secretion of testosterone and its main metabolite, dihydrotestosterone. Lack of androgen feedback to the pituitary is associated with persistent high serum
concentrations of interstitial cell stimulating (luteinizing) hormone. Prostatic atrophy occurs with loss of secretory epithelium and relative increase in the population of proliferative basal cells. The epithelium present after castration is less well-differentiated. In dogs castrated after development of prostatic neoplasia, neoplastic cells do not atrophy, further suggesting that it is this highly proliferative basal cell population that is the affected cell type in dogs. Prostatic tumors in castrated dogs are less well-differentiated with a more heterogeneous growth pattern than that seen in affected intact dogs.

What might be the factors associated with castration that increase neoplastic transformation of prostatic epithelial cells? If decreased circulating androgen is assumed to be causative, one must consider that the great variability between time of castration and onset of tumor suggests castration favors tumor progression, not initiation. One could argue that there may be sources of non-testicular androgen present in circulation but that does not explain the increased incidence in castrated dogs. Androgen deprivation makes cells more resistant to apoptosis, and the loss of androgen and relative increase in serum estrogen may be associated with squamous metaplasia and other pre-neoplastic changes. The expression of androgen receptors is variable in dogs with prostatic carcinoma, with those receptors capable of binding testosterone, dihydrotestosterone, progesterone, androstane, androstanediol, 17-beta estradiol, and cortisol. The androgen receptor pathway also is associated with expression of polypeptide regulatory proteins, membrane-bound receptors, and metabolic enzymes that may be altered, with subsequent changes in other processes along the androgen signaling pathway.

If androgen deprivation is not the link between castration and neoplastic change in the prostate, could it be simply that castration is associated with a larger population of rapidly dividing basal cells? Other factors also may be implicated; castration is associated with an increased number of endothelin receptors on the prostate, which is associated with uncontrolled cell growth and increased osteoblast function, promoting metastasis.

One could turn the question around and ask why is prostatic neoplasia less common in dogs left intact? Possibilities include a protective effect of androgens by maintenance of a slowly growing secretory epithelial cell population, or perhaps to the negative association of intact status with longevity.

Can we use humans as a model of animal disease and extrapolate information about prevention and treatment from the human literature? A comparison of human and canine prostatic neoplasia suggests not (Table 1). Future research should be focused on better identifying the apparent link between the decline in androgen secretion and increased incidence of prostatic neoplasia. Possible studies include characterization of circulating and intraprostatic concentrations of steroid hormones, their binding to prostatic steroid receptors, and identification of processes signaled by that binding, and treatment response to androgens in dogs with prostatic neoplasia. Measurement of luteinizing hormone receptors on the basal cell population and effect, if any, of their stimulation should be investigated. Use of gonadotropin releasing hormone analogs to downregulate luteinizing hormone secretion as a therapy may be useful. The author hopes to undertake a study better characterizing metabolic change within the prostate as a marker of pre-neoplastic change in castrated and intact dogs. Another illuminating study would be prostatic biopsy of castrated and intact dogs with and without prostatic neoplasia, again to try to better identify pre-neoplastic change. If pre-neoplastic disease or early onset disease could be identified, associated risk factors may be more evident and disease prevented.

Table 1. Comparison of prostatic neoplasia in humans and dogs

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<thead>
<tr>
<th>AGE AT DISEASE ONSET</th>
<th>HUMAN</th>
<th>CANINE</th>
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<tbody>
<tr>
<td>Present in about 1/3 of men aged 50 years or more</td>
<td>Greater than 9 years (equivalent of 50 to 52 human years)</td>
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<table>
<thead>
<tr>
<th>HEREDITARY PREDISPOSITION</th>
<th>Genetics, race</th>
<th>None reported</th>
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<tr>
<th>EFFECT OF ANDROGEN DEPRIVATION</th>
<th>Incidence decreased with castration, congenital hypogonadism</th>
<th>Incidence increased with castration</th>
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<table>
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<tr>
<th>ANDROGEN Influence</th>
<th>Significant early, not significant late in disease course</th>
<th>Not significant at any point</th>
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<tr>
<th>DISEASE PROGRESSION</th>
<th>Neoplasia aggressive and metastatic only late in disease course</th>
<th>Neoplasia aggressive and metastatic from diagnosis</th>
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References