The Role of Neutering in Cancer Development

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KEYWORDS

• Neuter • Cancer • Sex hormone • Spay • Castration

KEY POINTS

- Sex hormone receptors have been found in some canine and feline tumors and implied in others through sex predilection or response to neutering.
- A few studies indicate that some tumor types may be increased in surgically altered dogs; other tumor types may be decreased in neutered animals.
- Neutering has other effects on certain behaviors, noncancerous diseases, and lifespan that may outweigh cancer risks.
- Recommendations may be different for owned animals and those in a shelter or rescue setting.
- Veterinarians and pet owners should discuss the risks and benefits of neutering for each individual.

INTRODUCTION

Sex hormones normally influence many tissues in the body, and hormone receptors are present in some canine and feline neoplasms: mammary tumors,[1–6] meningiomas,[7,8] perianal gland tumors,[9] and likely others. The administration of exogenous hormones has been associated with the development of some tumors, such as progestins in the development of canine and feline mammary tumors.[10,11] Signalment of dogs that present with certain tumor types have been associated with variable sex predilection, implying hormonal influence. Other tumors may regress or have decreased recurrence after surgical alteration.[12–14] Recently, increased scrutiny of the role of neutering in dogs on disease incidence has resulted in some interesting findings, and questions, on the potential role of sex hormones in cancer development in this species (**Table 1**).

Steroid hormones interact with cells in several ways: (1) diffusion through the cellular membrane and binding to cytoplasmic (androgen) or nuclear (estrogen) receptor proteins. The activated receptor then interacts with coregulator proteins and binds to

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Table 1
Tumor types that may be influenced by gonadectomy

	Concerning Breeds
Tumors with increased risk post-castration	
Cardiac tumors	All
Osteosarcoma	All, purebred dogs, Rottweilers (<1 y of age at castration)
Prostatic tumors (carcinoma, adenocarcinoma, transitional cell carcinoma)	All
Transitional cell carcinoma of the urinary bladder	All
Lymphoma	All, Golden retrievers (<1 y of age at castration)
Tumors with decreased risk post-castration	
Testicular	All
Tumors with increased risk post-spay	
Cardiac tumors	All
Cardiac hemangiosarcoma	All
Osteosarcoma	Purebred dogs, Rottweilers (<1 y of age at spay)
Splenic hemangiosarcoma	All, Vizslas, Golden retrievers (>1 y of age at spay)
Mast cell tumor	All, Vizslas, Golden retrievers
Lymphoma	All
Tumors with decreased risk post-spay	
Ovarian tumors	All
Uterine tumors	All
Mammary tumors (canine, with spay before 3rd estrus)	All
Mammary tumors (feline, with spay before 3rd estrus)	All

hormone-responsive elements in the promoter regions of the DNA, which causes transcription of hormone-regulated proteins.[15] (2) Hormones may bind to receptors that interact with other transcription factors that bind to the DNA, causing indirect activation of proteins.[16] (3) Receptors may not require binding of the hormone to induce DNA transcription, rather may be activated through other growth factor pathways.[16] In humans, estrogen and testosterone affect breast and prostatic cancer growth and viability in a large percentage of patients, leading to treatments that modulate hormone levels or block their receptors.[16]

MAMMARY TUMORS

Historically, the influence of spaying on mammary tumor development has been the most well-studied veterinary sex hormone–tumor link. In sexually intact female dogs, mammary neoplasia is the most common form of cancer, based on many current large European cancer registries' databases.[17–20] Because early neutering is rare in these countries, these data help us to understand the risk in intact female dogs. Incidence of mammary tumors increases over time, which also correlates with increased exposure to female sex hormones.[17,21,22] Exogenous hormone exposure also increases the risk of tumor development.[10] Significant tumor risk occurs around 7 to

8 years of age, and increases until 11 to 13 years of age, with malignant tumors having a mean age of development around 9 to 11 years. In altered female dogs, in which female sex hormones are almost eliminated, the incidence of mammary cancer is almost eradicated by spaying before the first estrus cycle, with a 0.5% lifetime risk.[23] For a dog spayed between the first and second estrus cycle, the lifetime risk increases to 8%, and for a dog spayed after the second estrus cycle, the risk is 26%.[23] Surgical alteration between the third estrus cycle and approximately 4 years of age provides only modest protection, if any, against the development of mammary tumors.[22–25]

In cats, there are fewer data available regarding hormone-associated cancer development. A few studies have looked at the incidence of mammary tumors in intact versus spayed female cats.[26–28] In unaltered cats, mammary tumors are reported to be the third most frequent tumor type in the United States, and the most common type in European countries, although the overall incidence (25/100,000 in the United States) is less than that is reported in dogs (198/100,000 in the United States).[26–28] Increasing age increases the risk of cancer development, with significant increases occurring between 7 and 14 years.[10,26,29,30] With increasing age comes increased hormonal exposure, with intact female cats having up to a 7 times greater risk of developing mammary tumors than spayed cats.[10,26,31] Neutering before the first estrus provides a 91% risk reduction, before the second estrus an 86% risk reduction, and before the third estrus an 11% risk reduction.[31] After the age of 2 years, no benefit to surgical alteration is reported.[31] As with dogs, exogenous progestin exposure increases the incidence of mammary tumor development, more frequently benign than malignant.[10,11]

To complicate matters, an analysis of the literature on the subject of the association of neutering and canine mammary tumor development found that the evidence for the recommendation of early spay is “weak”.[32] However, this is likely a reflection of the veterinary literature in general, rather than an indictment of the conclusions drawn by the multiple studies looking at the relationship between surgical alteration and mammary cancer development.

REPRODUCTIVE ORGAN TUMORS AND TUMORS TREATED BY NEUTERING

Obviously, removal of an organ does eliminate the potential for tumor development within that organ: (1) ovariohysterectomy for uterine and ovarian neoplasia and (2) castration for testicular tumors. Removal of testosterone through castration also cures greater than 90% of dogs with perianal gland tumors,[12] and testosterone production by adrenal tumors has been shown to influence the development of perianal gland tumors in female dogs.[33] Vaginal leiomyomas occur almost exclusively in intact female dogs, and ovariectomy significantly decreases the incidence of recurrence even with incomplete surgical removal of the tumor.[13,14]

Several studies have shown an increase in various prostatic carcinomas in neutered male dogs, ranging from a twice to eight times risk compared with intact male dogs.[34,35] This increase is in contrast to the androgen dependence seen in most early human prostate tumors, but may be consistent with the development of androgen-independence with disease progression.[36] However, remaining intact does not eliminate the possibility of developing prostatic carcinomas,[37] and the overall prevalence of prostatic cancer in dogs is estimated to be very low (0.2%–0.6%).[37–40]

OSTEOSARCOMA

Many studies investigating the influence of sex on appendicular osteosarcoma incidence seemed to indicate an increased risk in male dogs, although some breeds appeared to have female predilection.[41–45] A larger review of all patients with

osteosarcoma (n = 1775) presenting to the Colorado State University over a 27-year period (1978–2005) did not confirm these findings, with an equal male-to-female ratio.[46] However, castration appears to have some influence, with one study reporting an increased risk of 1.3 in altered dogs compared with intact males.[47] Another study characterizing risks in purebred dogs found that neutering increased risk by approximately 1.9 times in females and 1.4 times in males when controlled for age of onset.[48] Further studies in Rottweilers (n = 683) found an increased risk of osteosarcoma development in both males and females when dogs were gonadectomized at an early age (<12 months).[49]

HEMANGIOSARCOMA

A large review of Golden Retrievers presenting to the University of California at Davis (n = 759) found that females neutered after 12 months of age (late) had a risk of being diagnosed with hemangiosarcoma 4 times greater than that of intact or females spayed early (<12 months of age).[50] No differences were found in hemangiosarcoma diagnosis based on neuter status or time of alteration in male dogs.[50] Another review assessing the role of gonadectomy on the risk of cancer development, this time in Vizslas, found that spayed females were 9 times more likely to develop hemangiosarcoma compared with intact females.[51] Females spayed early had an odds ratio (OR) of 6.0 and late-spayed females had an OR ratio of 11.5 compared with intact females.[51] Late-castrated males were 5 times more likely to develop hemangiosarcoma compared with intact males.[51] A broader study examining splenic hemangiosarcoma in multiple breeds found that spayed females were twice as likely to develop hemangiosarcoma than intact females.[52] Previous studies have also found that spayed females have a 4 times greater relative risk for the diagnosis of heart tumors compared with intact females, with the risk of cardiac hemangiosarcoma diagnosis more than 5 times greater in spayed versus intact females.[53] Neutered males also had a slightly increased risk (1.6) for developing heart tumors compared with sexually intact dogs.[53]

LYMPHOMA

A study of 15,000 canine lymphoma patients from the VMDB (Veterinary Medical Database, which collates information from multiple veterinary colleges) compared with a population of 1.2 million dogs found that intact female dogs were approximately half as likely to develop lymphoma compared with spayed females or males that were sexually altered or intact.[54] This finding is similar to findings in people, in which men are more likely to develop non-Hodgkin lymphoma (the canine counterpart) than women.[55] Other breed-specific studies have also found that spaying increases the risk of lymphoma.[50,51] However, castration was also found to be a risk factor, with alteration of both males and females increasing the risk approximately 3 to 4 times in Golden Retrievers and Vizslas.[50,51] In Golden Retrievers, specifically, early castration (before 1 year of age) increased the risk for lymphoma 3-fold, which was statistically significant.[50]

TRANSITIONAL CELL CARCINOMA

Transitional cell carcinoma of the bladder has a distinctly higher risk in females compared with males, with a 1.71 to 1.91:1 ratio of females to males.[56–58] Additionally, neutering increases risk up to 3-fold in both sexes.[58] Transitional cell carcinoma of the prostate is also more likely in castrated males, with an OR of 8.35.[35]

MAST CELL TUMORS

No consistent gender predilection has been reported for mast cell tumors in dogs,[59] but the recent study evaluating Golden Retrievers found a disparity (although not statistically significant) between the number of mast cell tumors diagnosed in altered females (2.3% in those spayed prior to one year and 5.7% spayed later) compared with intact (0%).[50] Males did not show such a disparity in mast cell tumor development between castrated and unaltered dogs.[50] When evaluating vizslas, however, investigators did find that gonadectomy in both males and females increased the risk of mast cell tumor development by twice to over fourfold, and that the tumors developed at an earlier age.[51] Another study looking at various breeds found that spayed females were at increased risk, with an OR of 4.11.[60] Interestingly, estrogen hormone receptors were not found in mast cell tumors in one study, which makes determining the role of the sex hormonal influence even less clear.[61]

THE INFLUENCE OF STERILIZATION ON LIFESPAN

Several large studies have been performed evaluating the impact of gonadectomy on overall lifespan and cause of death in dogs. Two thousand dogs submitted for necropsy revealed increasing incidence of cancer death with age (20% at 5 years, increasing to 40%–50% at ages 10–16). Neutered dogs of both sexes were older than intact dogs, although the difference was not statistically significant.[62] A 1999 study[63] evaluating 3126 general population British dogs found that the average lifespan for all dogs was approximately 11 years. Overall, cancer was the most common cause of death, with unneutered dogs dying of cancer more frequently than neutered dogs: 44.9% of intact male dogs, 34.7% of castrated males, 50.2% of intact female dogs, and 39.6% of spayed female dogs. Specific cancers were not examined. Spayed females lived longest (statistically significant) when all causes of death were considered, with an average age of 12 years, but for dogs dying of natural causes (only 8% of the population studied), intact females lived longest, with an average age of slightly over 13 years (not statistically significant). Males, both neutered and intact, lived approximately 11 years when considering all causes of death, whereas those dying of natural causes lived approximately 12 years. In both groups, intact males lived on average 3 months longer than their castrated counterparts (no statistical difference).

In American dogs, one investigator found that in more than 40,000 subjects, an average of 7.9 versus 9.4-year lifespan was found in intact versus gonadectomized dogs. Females benefitted from sterilization more than males, with a 26% increase in life expectancy and 14% increase, respectively. However, neutered dogs were more likely to die of cancer (and immune-mediated disease), whereas they were less likely to die of causes such as degenerative disease, vascular disease, infections, or trauma. Although overall risk of cancer appeared to be increased in sterilized dogs, specific cancer types were more likely to occur: transitional cell carcinoma, osteosarcoma, lymphoma, and mast cell tumors. Mammary tumors were less likely, and melanoma, squamous cell carcinoma, and prostate cancer did not appear to be affected by neutering.[64]

The previous patients were from a veterinary teaching hospital database (Veterinary Medical Database), but the results appear to be consistent when looking at a more general American population. In the 2013 Banfield report (2.2 million dogs; 460,000 cats),[65] the average lifespan of dogs was 11 years, with spayed dogs living 11.6 years compared with unspayed dogs living 9.5 years, a 23% difference. Castrated males lived 18% longer with an average lifespan of 11.1 years compared with uncastrated

with a lifespan of 9.5 years. Similarly, altered cats lived longer. Overall average survival was 12.1 years, with spayed females living an average of 13.1 years, and unspayed 9.5 years, a 39% increase. Castrated cats lived 62% longer, an average of 11.8 years compared with an average of 7.5 years for intact male cats. Unaltered dogs and cats were 2 to 4 times more likely to present for trauma by being hit by a car or bitten by another animal.

In contrast, the study examining Vizslas did not find an increase in lifespan in neutered versus intact dogs.[51]

CRITIQUES OF THE DATA PRESENTED

Determining a specific cause-effect relationship is difficult, at best, given confounding factors that must be considered in any epidemiologic study. In humans, factors related to cancer development include age, gender, ethnicity, diet, occupation (often related to carcinogen exposure), environment (such as urban vs rural), and smoking, to name a few. Genetics, epigenetics, proteomics, and metabolomics are now also factored into studies of cancer etiogenesis. Rarely are these factors taken into account in veterinary studies, although research continues to expand in these areas. Selection bias is prevalent in the veterinary literature, because so many studies are conducted through teaching hospital databases. The pet population that is seen at a specialty hospital may not be representative of the general pet population: these patients are often preselected for geography, finances, and willingness to treat before referral. Pet owners who cannot afford sterilization surgery may not be able to afford treatment when a serious disease condition occurs, resulting in a perception that those animals that are intact live a shorter time. Intact animals are also likely to be referred to a specialty hospital for reproductive issues more frequently than neutered animals, resulting in a skewed population in the diagnosis database. Additionally, much of the data presented here are derived from breed-specific studies. Although these may be quite useful for recommendations for certain breeds, extrapolating to the general canine population may not be valid. These studies are also using breed clubs as their primary contacts for gleaning information. Breeders may be a different population than the general pet owner. They are more likely to be aware of diseases within certain lines and adjust their intact versus neutered animals accordingly. The response rate to questionnaires for many of these studies is also low, selecting for only those willing to respond, which may over- or underrepresent certain populations. As we learn more about the genetics and breed-specific heritability of certain cancers, we will better be able to advise our clients about the influence of many factors on the development of cancer. Finally, these studies are retrospective, which again, introduces bias and incomplete data points based on the record keeping and memories of the patients and clinicians involved. Case-control cohorts attempt to address many of the concerns mentioned earlier. Ideally, large prospective studies will be conducted (eg, the Morris Animal Foundation Lifetime Golden Retriever study; www.caninelifetimehealth.org/) that have rigorous data collection and monitoring over a long period of time to help clarify these issues.

THE PRACTITIONER'S DILEMMA

The veterinary practitioner must now weigh this information to make recommendations on the spaying and castration of dogs: both whether and when. Certainly surgical alteration can carry risks related to anesthesia and surgery, as well as sequelae such as hormone-responsive incontinence, perivulvar dermatitis, atrophic vaginitis, and endocrine alopecias.[66] Other potential problems suggested to be related to neutering,

at least in the Golden Retriever, include cranial cruciate ligament rupture and hip dysplasia.[50] Several studies have linked sterilization to certain behavioral problems, as well.[51,67–69] Nonneoplastic complications with an intact reproductive system, especially in females, are also a factor. Pyometra is common in bitches over 6 years of age; vaginal prolapse may occur in young, intact, large-breed dogs during estrus; unintended pregnancy or whelping complications may ensue; pseudopregnancy and estral bleeding can often be inconvenient for owners; and finally, some behavior associated with intact females, both canine and feline, can be problematic.[66] For male dogs and cats, sexual behavior associated with roaming, fighting, urine marking, and mounting are more concerning in uncastrated animals. Benign prostatic hypertrophy occurs in more than 60% of intact dogs older than 5 years; sequelae such as prostatitis, abscessation, and urinary and defecation problems can necessitate surgical correction with associated morbidities later in life.[66]

Regarding the influence of neutering on cancer development, pros and cons for the potential increase in certain cancer types when sterilization is recommended versus the potential for overall increases in survival and decreases in certain cancer types for neutered animals should be considered. The overall incidence of the cancer type when discussing this increased risk must also be taken into account. Although lymphoma and mast cell tumor are very common, other tumor types are less; prostatic and cardiac tumors are very rare. Markedly increasing risk for a cancer type that occurs in less than 1% of dogs may remain acceptable for some clients. Breeds with high risks of certain cancers may require special consideration when discussing the risks and benefits of sterilization.

The ethics of discontinuing the recommendation for early gonadectomy, given the persistent pet overpopulation problem in the United States, is disturbing. As with other areas of medicine, the concept of personalization applies to this situation. In unowned, shelter or rescue populations, the population benefits of neutering likely outweigh any potential for increasing cancer risk. For owned animals, veterinarians will need to discuss the pros and cons for each individual and determine the best strategy for that pet based on breed, lifestyle, longevity expectations, concurrent diseases, cancer risks, other considerations for intact and sterilized dogs, and owner preferences.

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