

## **CONTROVERSIES IN SPAYING AND NEUTERING: EFFECTS ON CANCER AND OTHER CONDITIONS**

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### **Medical Justification of Gonadectomy**

Although population control is the most common reason for gonadectomy in small animals, there are several medical justifications for the procedure. For both male cats and dogs, castration eliminates the risk of diseases of the testes, including orchitis and neoplasia. In male dogs, there are several conditions mediated at least in part by testosterone, including prostatic abscesses, perineal hernia, and perianal adenomas. These conditions occur predominantly in intact male dogs, and castration is considered an important aspect of treatment. Lastly, there are several undesirable behaviors that may be mitigated by castration, including roaming, mounting, urine marking, and aggression.

Among female cats and dogs, diseases of the ovary, including cysts and neoplasia, are prevented by ovariectomy (OVE) or ovariectomy (OVH). There are several diseases of the uterus (pyometra) and vagina (edema/hyperplasia, prolapse) that are the result of hormones released by the ovaries, and therefore are prevented by OVE or OVH. In both cats and dogs, it has been widely accepted that OVE/OVH reduces the risk of mammary neoplasia (see below for further information on this topic).

Unrelated to diseases of the reproductive organs, hormone fluctuation in intact animals can interfere with regulation of certain endocrine diseases, such as diabetes mellitus.

### **Complications of Gonadectomy**

Complications of gonadectomy are uncommon. A 1996 study examining elective surgery in over 1,000 dogs and 1,400 cats showed complication rates of 6.1% and 2.6%, respectively, with complications more common in dogs older than 2 years of age. Most complications were minor, including incisional site inflammation and gastrointestinal tract upset. More significant complications are often the result of technical error, including ureteral ligation, ovarian remnant syndrome, and stump pyometra.

Gonadectomy is the most commonly reported risk factor for obesity. Metabolic rate decreases after gonadectomy in cats. The exact cause for obesity following gonadectomy in dogs is less clear, although estrogen may function as a satiety factor, which would explain the tendency for weight gain in female dogs after gonadectomy. However, obesity after gonadectomy can be avoided with an appropriate diet and exercise regimen.

Urethral sphincter mechanism incompetence (USMI) is a common problem in female dogs with reported incidence ranging between 5% and 20%.

### **Timing of Gonadectomy**

Traditionally, veterinarians recommend elective gonadectomy for dogs and cats between 6 and 9 months of age. In 1993, the AVMA supported early-age gonadectomy for dogs and cats between 8 and 16 weeks of age, primarily to reduce pet overpopulation. Studies

show that early-age gonadectomy is safe from a procedural perspective; complication rates in dogs and cats spayed at 3 months of age were similar to those spayed at 6 months of age or older. Although early-age gonadectomy is critical for population control, determining the optimal age for gonadectomy of individual, owned animals has become more controversial as new research becomes available about the risks of various diseases based on age at gonadectomy.

### **Effect of (Early) Gonadectomy on Non-Neoplastic Conditions**

#### 1. Spain et al. *J Am Vet Med Assoc* 2004

A large retrospective study examined almost 2,000 dogs adopted from an animal shelter before 1 year of age. Based on owner questionnaire and review of medical records, the investigators examined possible associations between age at gonadectomy (before 5.5 months old versus after 5.5 months old) and the development of fifty-six medical and behavioral conditions. Median follow-up time was 4.5 years (up to 11.3 years), and median age at end of follow-up was 5.0 years (up to 12.2 years).

For the vast majority of the conditions examined, disease incidence was not associated with age at gonadectomy. For female dogs, early-age gonadectomy was associated with increased risk of cystitis, although most dogs had only one self-limiting episode. More clinically significant was the association of early-age gonadectomy with increased incidence of urinary incontinence. Female dogs spayed prior to 3 months of age were at the highest risk for developing urinary incontinence. Among both male and female dogs, the diagnosis of hip dysplasia was increased in the early-age gonadectomy group (6.7%) compared to the traditional-age gonadectomy group (4.7%). Of all dogs diagnosed with hip dysplasia, 54% required veterinary care for the problem. Importantly, relinquishment for any reason was decreased among the early-age gonadectomy group.

The same study was conducted in more than 1,500 cats adopted from the same animal shelter before 1 year of age. Investigators compared the frequency of forty-seven medical and behavioral conditions in early-age and traditional-age gonadectomy groups. Median follow-up time was 3.9 years (up to 11.7 years), and median age at end of follow-up was 4.4 years (up to 12.3 years).

Among male cats, early-age gonadectomy was associated with reduced occurrence of abscesses (early in life), sexual behaviors, and urine spraying. Among both male and female cats, occurrence of asthma and gingivitis were decreased. Early-age gonadectomy was not associated with a change in the incidence of most of the medical conditions examined, including feline lower urinary tract disease and urethral obstruction. There was no difference in the rate of relinquishment between the two groups of cats.

#### 2. Torres de la Riva et al. *PLOS ONE* 2013

A large study conducted at the teaching hospital at UC Davis examined the effects of neutering on joint diseases and cancers (see below) in Golden Retrievers. The study included 759 client-owned male and female Golden Retrievers between 1-8 years of age. Dogs were classified as intact, neutered before 1 year, or neutered after 1 year.

Among males neutered before 1 year of age, the incidence of hip dysplasia was 10%, which was higher than the occurrence in intact males (5%) and males neutered after 1

year (3%). OVH (either age group) had no effect on the incidence of hip dysplasia in females.

There were no cases of cranial cruciate ligament (CrCL) rupture in intact males, intact females, or in females spayed after 1 year. The incidence of CrCL rupture in dogs neutered prior to 1 year of age was 5% for males and 8% for females, which was higher than both the intact dogs and dogs neutered after 1 year.

### 3. Hart et al. *PLOS ONE* 2014

The same research group at UC Davis performed a follow-up study similar in design to the study reported by Torres de la Riva et al. The follow-up study also examined the effects of neutering on joint diseases and cancers in dogs between 1-8 years of age, but it included both Golden Retrievers (over 1,000 dogs) and Labrador Retrievers (1,500 dogs) and further stratified the groups by neuter status as follows: before 6 months old, 6-11 months old, year 1, and years 2-8.

The results among Golden Retrievers were similar to the original study, but there were important differences among Labradors, especially with respect to cancer (see below). Among male Labradors, early neutering (before 6 months of age) was associated with increased incidences of CrCL rupture (8%) and elbow dysplasia (4%) compared to intact dogs (2% and <1%, respectively). Among female Labradors, early neutering (all groups  $\leq$  1 year of age) was associated with an increased incidence of hip dysplasia (5%) compared to intact dogs (2%).

### 4. Sundburg et al. *BMC Veterinary Research* 2016

The goal of this study was to determine the risk of immune-mediated disease relative to neuter status in dogs. Neutered dogs had a significantly greater risk of developing atopic dermatitis, autoimmune hemolytic anemia, hypoadrenocorticism, hypothyroidism, immune mediated thrombocytopenia, and inflammatory bowel disease than intact dogs. Neutered females were at the greatest risk for developing these conditions (except hemolytic anemia and hypoadrenocorticism) as compared to neutered males, and also had a significantly greater risk of developing Lupus as compared to intact females.

## **Effect of Gonadectomy on Neoplastic Conditions**

The development of a cancerous cell within an animal is an intricate and elaborate process, and is influenced by a variety of different endogenous and exogenous factors. Secretion of sex hormones is one such factor that has been shown to affect a number of different tissues in the body, and the balance of hormone levels can contribute to the development of cancer by driving cell growth and proliferation, increasing the number of cell divisions and the opportunity for random genetic errors, and promoting tumor progression. (Henderson, March 2000)

A number of recent studies have attempted to elucidate the effect of neutering animals on the incidence of various neoplastic diseases, which has raised some important and controversial questions regarding the potential role of sex hormones in cancer development and whether or not gonadectomy should be recommended (and if so, at what age). Given that the presence of certain sex hormones can contribute to cancer

development while simultaneously having a protective effect in the body (with the potential to reduce the risk of other cancers), the pros and cons of gonadectomy must be carefully considered. Various factors should be taken into account when discussing the risks and benefits of neutering on the development of cancer in client-owned animals, including breed, gender, the age of the pet, overall incidence of cancer type, effects on the development of non-neoplastic disease processes or other conditions, and client preferences.

Several recent studies have evaluated the effects of gonadectomy on the development of cancers in one breed or in pooling data from several breeds. One such study utilizing the Veterinary Medical Database of over 40,000 dogs revealed that gonadectomized males and females were more likely to die of cancer than intact dogs, especially of osteosarcoma, lymphoma, and mast cell tumor. (Hoffman, 2013) Many of the recent studies evaluating this issue (particularly those looking at all breeds together) do not address timing of alteration (i.e. early versus late gonadectomy) or breed specific cancer risk, although there are a few reports that attempt to shed more light on these topics of interest (and are discussed separately below).

#### Treatment of Tumors by Gonadectomy

The development of perianal (hepatoid) gland tumors is largely influenced by testosterone levels, and tends to develop most commonly in intact male dogs, female dogs with testosterone-secreting adrenal tumors, and in dogs exposed to exogenous forms of testosterone. Removal of this hormone through castration leads to resolution in the majority (>90%) of dogs with perianal gland tumors, and is considered the treatment of choice. (Wilson, 1979)

Vaginal leiomyomas are benign tumors that are also hormone dependent. Ovariectomy is an integral part of managing this tumor, given that it is effective in preventing recurrence and the development of new lesions. (Thacher, 1983)

#### Mammary Tumors

Mammary neoplasia is the most common form of cancer in intact female dogs, based on information obtained from large European cancer databases. (Dobson, 2002; Bronden, 2010) Compared with the incidence in sexually intact dogs, dogs spayed before the first estrus have a 0.5% risk of mammary neoplasia. Dogs spayed after the first or second estrus have an 8% and 26% risk, respectively, compared to sexually intact dogs. (Schneider, 1969) In cats, risk reductions of 91%, 86%, and 11% are seen when OVE/OVH is performed prior to 6 months, between 7-12 months, and between 13-24 months respectively. No benefit was found after 24 months. (Overley, 2005)

A systemic review discussing the effect of neutering on the risk of mammary tumors in dogs was recently published in 2012, which found that the evidence for recommending early spaying in this species is weak. (Beauvais, 2012) However, it is important to note that these results may be a reflection of the poor level of evidence available for such formal analyses, and additional studies are necessary to confirm this finding.

#### Other Reproductive Organ and Urogenital Tumors

Clearly, removal of various reproductive organs (accomplished by OHE for females and castration for males) will reduce the risk of cancer at these sites (including ovarian, uterine, and testicular cancer). On the other hand, several studies have documented an increased risk of other neoplastic conditions involving the urogenital tract in gonadectomized dogs

compared to intact dogs. Castrated dogs have an increased risk of developing prostatic carcinoma, ranging from 2 to 4 times compared to sexually intact male dogs. It has been suggested that androgen deprivation does not initiate tumorigenesis, but that it allows tumor progression. (Teske, 2002; Bryan, 2007) Gonadectomized dogs (male and female) also have an increased risk (up to 3x) of developing transitional cell carcinoma of the bladder. Interestingly, females have a higher risk of developing this cancer compared with males (1.7 to 1.9:1 ratio), supporting a hormonal influence. (Mutsaers, 2003)

#### Non-urogenital Solid Tumors

The incidence of osteosarcoma has been shown to increase by a factor of 1.3x in males and 1.9x in females with gonadectomy. (Ru, 1998) A more recent study revealed a similarly increased risk in spayed females (OR 2.5) and neutered males (OR 1.6) as compared to intact females and males respectively. (Belanger, 2017)

In a study evaluating hemangiosarcoma in dogs, spayed females were twice as likely to develop the splenic form of this cancer and had a 5x greater risk of being diagnosed with the cardiac form of this cancer as compared to intact dogs, while neutered males had a slightly increased risk (1.6x) of developing heart tumors compared to intact dogs. (Ware, 1999; Prymak, 1988) A newer study corroborated the findings that spayed females had an increased risk of developing hemangiosarcoma (OR 3.18) as compared to intact females, although males exhibited less of a risk associated with neutering than females (OR 1.39). (Belanger, 2017)

In a study evaluating cutaneous mast cell tumors and association with spay/neuter status, spayed females were >4x more likely to develop this cancer than intact females, although this degree of risk was not seen with neutered males as compared to intact males. Among intact dogs, females were found to have a lower odds of developing mast cell neoplasia as compared to males, whereas among altered dogs, females were more likely to develop mast cell neoplasia than males. (White, 2011) In another study, neutering status was also correlated with histopathological grade. Mast cell tumors in neutered dogs were less likely to be high grade tumors when compared with tumors in intact dogs, and mast cell tumors in intact males were shown to be at the greatest risk of being high grade. (Mochizuki, 2016) These results suggest the potential protective role of estrogen or the tumor-promoting role of androgens in mast cell tumor development. In one study receptors for estrogen and progesterone were found in cutaneous mast cell tumors, although a second study failed to document estrogen receptors in this form of cancer. (Elling, 1982; Larsen, 1989) These conflicting reports make it difficult to determine the true role of sex hormones in the development of canine mast cell tumors, and additional studies are necessary to further elucidate this association.

#### Lymphoma

A recent study evaluating the correlation of neuter status and expression of heritable disorders in 90,000 dogs, spayed females were at an increased risk of developing lymphoma as compared to intact females (OR 2.25). This increase in risk was not as strong for neutered males (OR 1.2). In another very large study examining >14,000 dogs, intact females had a significantly lower risk of developing lymphoma (OR 0.69). (Villamil, 2009) A similar effect of hormonal influence on the development of non-Hodgkin lymphoma is also seen in people; the risk of developing this cancer is lower for women as compared to men, although the incidence rises after 50 years age (at which time menopause is regularly reached), suggesting that female hormones may be protective for this form of lymphoma. (NCI, 2003)

## **Breed Specific Neoplastic Conditions**

### Rottweilers

In a study of 683 Rottweilers, there was a 3-4x increase in the occurrence of osteosarcoma (OSA) in male and female dogs that had undergone gonadectomy prior to 1 year of age. In addition, the overall incidence of OSA in this population was higher than the general population, which suggests a hereditary component. (Cooley, 2002)

### Vizslas

A recent study examined the incidence of various neoplastic conditions among more than 2,500 Vizslas through an on-line survey. Dogs were stratified based on age at gonadectomy for analysis as follows:  $\leq 6$  months of age, 7-12 months of age, or after 12 months of age. All gonadectomized groups had increased odds of developing mast cell tumor (3.5x) and lymphoma (4.3x) compared to intact dogs. Mast cell cancer was also diagnosed at a significantly younger age in gonadectomized dogs (as compared to intact dogs). The odds of gonadectomized females having hemangiosarcoma were 9x as high as the odds for intact females, although this was not seen in males. The odds of a gonadectomized Vizsla having cancers other than mast cell, hemangiosarcoma, or lymphoma were significantly higher (5x) than those for intact dogs. (Zink, 2014)

### German Shepherds

A study evaluating age of neutering (<6 months, 6-11 months, 12- <24 months, and 2-8) and effects on the development of cancer in German Shepherd Dogs revealed that whether the dog was intact or neutered, there was a low level of occurrence of the particular cancers followed (lymphoma, mast cell tumor, hemangiosarcoma, osteosarcoma). It is important to note that these cancers were only tracked through the first 8 years of the dog's life (given that beyond 9 years, the authors argue that the influence of neutering is fading and other age-related factors play a stronger role in cancer development). Mammary cancer (MC) was also evaluated in this study (through 11 years, given that most cases are diagnosed after 8 years of age); none of the females neutered at <6 months were diagnosed with MC, although only 4% of intact females followed through 11 years were diagnosed with MC. Neutering at 1 year and beyond resulted in an incidence level about the same as intact females, suggesting that this may not be a major cancer for this breed (at least through 11 years of age). (Hart, 2016)

### Golden Retrievers and Labrador Retrievers

In one study, the effects of early (<12 months) versus late ( $\geq 12$  months) neutering on the development of various cancers in Golden Retrievers were evaluated. Almost 10% of early-neutered males were diagnosed with lymphoma, and early neutered males had nearly 3x the occurrence of lymphoma as intact males (no cases of lymphoma were observed in the late-neutered males). Although the rate of occurrence of this cancer was lower in female intact dogs as compared to early-neutered females, the difference was not statistically significant. Late neutered females were diagnosed with hemangiosarcoma (HSA) >4x more frequently than intact females and early-neutered females. The mean ages of HSA onset for intact, early-neutered, and late-neutered female dogs were 6.4, 7.6, and 3.2 years, respectively. No differences were apparent in males with regard to neutering and the occurrence of HSA. For mast cell tumors (MCT), there was wide difference in tumor occurrence between intact and late-neutered females. Mast cell tumors did not occur in intact females, but was diagnosed in 2.3 percent of early-neutered females and 5.7 percent of late-neutered females. No differences were found in the occurrence of MCT in male Golden Retrievers. The occurrence of mammary carcinoma was very low

overall, and was only seen in a few late-neutered females. It is important to note that only dogs between 1-8 years of age were included for analysis in this study. (Torres de la Riva, 2013)

The authors postulate that the timing of estrogen removal may influence the development of MCT and HSA in females spayed later in life. This may be related to the fact that in early spayed females potentially neoplastic cells are not sensitized to estrogen, so removal of this hormone by spaying does not influence cancer development. Once the cells have been exposed through several estrous cycles, the cells become sensitized, although the estrogen is protective. Once removed, these cells could become neoplastic. The others note that this though is supported by the fact that estrogen secretion has been shown to sensitize the pathways involved in microsatellite instability in women that develop colon cancer - while in the system, it has protective effects, although once removed, may cause microsatellite instability-positive cancer-cell activation. (Slattery ML, 2001)

In a separate study comparing long-term health effects of neutering dogs in Labrador Retrievers with Golden Retrievers, intact male Golden Retrievers had a relatively high incidence of all cancers combined (11%) compared to intact female Golden Retrievers, intact male Labradors, and intact female Labradors (3-5% each group). Among male Golden Retrievers, neutering had little effect on the incidence of the cancers examined (mast cell tumors and hemangiosarcoma) except for an increased incidence of lymphoma in dogs neutered between 6 and 11 months of age (11%) compared to intact dogs. The same pattern was observed for female Golden Retrievers with respect to the incidence of lymphoma (11% in dogs neutered 6-11 months old versus 2% in intact dogs). Neutering females at any period beyond 6 months elevated the risk of one or more cancers to 3-4x the level of intact females. In the study by Torres de la Riva et al. (described above), an increased risk of HSA was observed among female Golden Retrievers spayed after 1 year (7%) compared to intact dogs and dogs spayed prior to 1 year (2% each group). This finding was not corroborated by the follow-up study by Hart et al. Interestingly, among male and female Labrador Retrievers, neutering at any time had little to no effect on the incidence of any cancer investigated (LSA, MCT, HSA). (Hart, 2014)

## Conclusions

Animals housed at humane societies should be treated as a population. **Societal benefit resulting from gonadectomy of unowned dogs and cats in the United States outweighs all other concerns.** Male and female dogs and cats should be spayed or castrated before being offered for adoption (Root Kustritz 2007).

Owned pets should be considered individually, with the understanding that population control is less important than the health of each animal. Veterinarians and owners must consider the benefits and detriments of timing of gonadectomy for each individual (Root Kustritz 2007). Factors to consider in making this decision include the incidence and morbidity of various neoplastic and non-neoplastic conditions that may affect that animal, based on its age, sex, breed, heredity, and other risk factors.

There appears to be little evidence that gonadectomy is detrimental to the health of male cats, whereas the behavior of most sexually intact male cats makes them undesirable as pets. Because castration substantially reduces these sexually dimorphic behaviors, male cats intended for pets should be castrated prior to puberty.

For female cats and dogs, mammary neoplasia and pyometra represent significant health concerns in terms of frequency, morbidity, and owner financial burden, and thus remain compelling factors in recommending routine OVH/OVE for most animals. Evidence suggests that female dogs should be spayed after 3 months of age when possible to reduce the risk of urinary incontinence.

Finally, there is new evidence to consider regarding the timing of gonadectomy and the risk of certain orthopedic and neoplastic conditions in specific breeds of dogs. Although statistically significant, the increases in disease incidence with gonadectomy reported in some of the studies described above were numerically small. It is important to remember that these studies show associations between disease incidence and age at gonadectomy but not a cause and effect relationship or a mechanism of causality.

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