Determining optimal age for gonadectomy in the dog: a critical review of the literature to guide decision making

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Abstract

Gonadectomy is the most common elective surgery performed on dogs in the United States. Concerns have been expressed by veterinarians, dog breeders, and pet owners or guardians about the need to better understand effects of gonadectomy on individual animal health. Many studies to date on this topic have been performed on small or unique populations of dogs and data from those studies may or may not readily be extrapolated to dogs seen by veterinarians in private practice. Veterinarians should be careful to read manuscripts in their entirely whenever possible rather than to rely on brief summaries that do not permit the reader to make their own decisions regarding value of the data as presented to their clinical practice.

Keywords: Gonadectomy, ovariohysterectomy, castration, lifespan, neoplasia, orthopedics

Introduction

Proposed benefits and detriments of spay and castration surgeries in dogs have been reported in a growing body of literature over the last 20 years. Some of the data are contradictory or are difficult to reconcile with known pathophysiology. Some of the papers have received a great deal of coverage in the popular press, leading to inappropriate attention to limited data points. This manuscript is a review of the current literature on this topic, an argument for better attention to detail about published studies by veterinarians before extrapolating small data sets to all populations, and a discussion of some options about how best to present information from the literature to clients.

Gonadectomy is the most common elective surgery performed on dogs in the United States, with reported prevalence of 67% in female dogs and 61% in male dogs.[1] It is recommended that all animals surrendered to humane organizations should undergo gonadectomy prior to adoption for purposes of population control.[2] Large review articles on the topic of determining optimal age of spay / castration surgery in dogs have been published over the last ten years.[3-6] Concerns have been expressed by veterinarians, dog breeders, and pet owners or guardians about the need to better understand effects of gonadectomy on individual animal health. A review of pet owners' needs for information regarding the decision whether or not to neuter their animal demonstrated that clients desire information regarding positive and negative pet health and welfare outcomes.[7] To best meet needs of dog owners, veterinarians must maintain an awareness of studies published and, most critically, the value they bring to the question of suitable age for gonadectomy in dogs.

The question about impact of gonadectomy on health is one of causation: does gonadectomy at certain ages cause or prevent specific health issues? Answering this type of question requires a large body of high quality data of varying types ranging from laboratory studies to clinical trials and observational studies of populations. No single study can prove causation. Many studies to date on this topic have been performed on small or unique populations of dogs and data from those studies may or may not readily be extrapolated to dogs seen by veterinarians in private practice. Conclusions about causation are less likely to be true when there are few studies in a given field, when samples sizes are very small, when differences between groups are small, when the study subjects are not similar to animals seen in private veterinary practice, when not enough attention is paid to confounding effects, and when measurement error is present (Table 1).[8,9] Researchers, manuscript reviewers, and readers of publications must be aware of possible biases in measurement and must pay attention to whether or not findings that are statistically significant have any practical implications in veterinary practice. Peer-reviewed publications should include an in-depth assessment of the study limitations and generalizability; studies which do not provide this should be assessed with extra caution. Veterinarians should be careful to read manuscripts in their entirely whenever possible rather than to rely on brief summaries that do not permit the reader to make their own decisions regarding value of the data as presented to their clinical practice.

Current information from the literature

The association between intact status and behavior in dogs is complex. This review will focus on medical concerns and will not address effect of gonadectomy on behavior.

Data from the studies below may be described as relative risk, hazard ratios or odds ratios (OR). A relative risk is the likelihood that an event will occur after a specific exposure. Interpretation is the following: a relative risk of 2.0 means that a dog that has been gonadectomized is twice as likely to develop the condition as is an intact dog. Specifically, a relative risk is the ratio of the risk of developing the condition in gonadectomized dogs to the risk of developing the condition in intact dogs. The odds ratio is typically interpreted similarly to the relative risk; specifically the odds ratio is the odds of the condition in the gonadectomized dogs divided by the odds in intact dogs. Hazard ratios are similar but compare the hazard of an event or death and assume that risk is constant over time. Put another way, we can say that if the relative risk or the odds ratio is 1.0, the risk (odds) in the exposed animals equals the risk (odds) in the non-exposed animals. If the RR (OR) is greater than 1.0, the risk (odds) in exposed animals is greater than the risk (odds) in non-exposed animals. If the RR (OR) is less than 1.0, the risk (odds) in exposed animals is less than the risk (odds) in non-exposed animals. All of these values have 1 as the "no difference" value and should be accompanied by a confidence interval, which is the range of values defined with a specific probability that the "real" value lies within that range.

Mammary neoplasia

Reported incidence of mammary gland tumors in dogs is 3.4% with some select populations reporting incidence as high as 13% by ten years of age.[10,11] Mammary neoplasia is the most common form of cancer in female dogs based on data from several large European cancer registries.[12-15] Increasing age and breed are risk factors for development of mammary neoplasia.[10,16-19] Age at time of diagnosis does not vary between spayed and intact dogs.[20] Being thin as a young dog is reported to be protective.[20] High fat diet and obesity have not been demonstrated to increase risk of development of mammary neoplasia in dogs.[20]

There are six studies in the literature reporting an association between gonadectomy and mammary neoplasia in dogs, with five of those studies documenting decreased incidence (Table 2). These studies report that bitches that are spayed are one-third to one-half less likely to develop tumors than are bitches that are left intact, and that bitches that remain intact are seven times more likely to develop tumors than are spayed bitches.[17,19] Benefit of spaying is increased with younger age or decreasing number of heat cycles prior to spay, with a classic paper describing female dogs as having 0.5% the risk of intact dogs if spayed before their first heat, 8% the risk if spayed between their first and second heat, and 26% if spayed after their second heat.[20,21] In general, greatest benefit is described for any bitch spayed before 2.5 years of age with a decreasing benefit up to nine years of age.[20,22] No difference was shown between intact and spayed dogs in one study, which evaluated dogs of one breed presented to a specialty hospital.[23] A systematic review of effect of gonadectomy on incidence of mammary neoplasia concluded that there was insufficient evidence to support any connection.[24] Systematic reviews are analyses of all of the published literature on a given topic performed in a repeatable and objective fashion and strive to identify bias that would nullify results of published studies.[25] Of the 13 studies they chose to include in their initial analysis, nine were deemed to have a high risk of bias and four to have a moderate risk of bias. The inability to identify a connection in that systematic review was more a reflection of the lack of depth in the veterinary literature on this topic than a true evaluation of the association between gonadectomy and mammary neoplasia.

Hormonal stimulation is assumed to be the cause of mammary neoplasia in dogs. Eighty percent of mammary tumors and 95% of normal mammary tissues have estrogen receptors, progesterone receptors, or both.[26] Studies differ regarding correlation of estrogen and progesterone receptors with type of tissue, with some studies suggesting that there are fewer receptors as tumors become less differentiated.[26,27] An association has been reported between treatment with exogenous progestins and increased incidence of mammary tumors.[18] Mammary neoplasia may be more common in bitches that had multiple episodes of overt pseudopregnancy with lactation, suggesting either a hormonal effect or the possibility of malignant transformation of mammary tissue that is metabolically active and undergoes the physical changes associated with lactation.[22]

Prostatic neoplasia

Reported incidence of prostatic carcinoma is 0.2-0.6%.[28,29] It is difficult for pathologists to differentiate prostatic adenocarcinoma, which arises directly from glandular tissue, from invasion of transitional cell carcinoma from the prostatic urethra into the prostatic parenchyma. Data presented encompasses both forms of prostatic carcinoma, a limitation in understanding the disease process. Incidence is reported to be increased in some breeds.[28,30] Evaluation of other factors for association with incidence of prostatic carcinoma, including diet, activity level, housing, and exposure to tobacco smoke, failed to demonstrate any significant associations.[31]

There are five studies in the literature evaluating association between gonadectomy and prostatic neoplasia, with four showing increased incidence with gonadectomy (Table 3). Mean and median age at the time of diagnosis may vary between castrated and intact dogs, with one study demonstrating disease in castrated dogs at an older age compared to intact dogs.[30] No study to date has demonstrated any sparing effect dependent on age at the time of gonadectomy.[28-33]

The cause-and-effect relationship between gonadectomy and prostatic carcinoma has not been defined. Prostatic tumors in dogs arise from ductal / urothelial tissues, which are androgen-independent.[28] It may be that testosterone exerts a carcinogenic effect earlier in life.[29] Because of the great variability reported in time from castration to diagnosis of prostatic neoplasia, it has been suggested that castration does not promote tumor formation but instead promotes tumor progression.[28] It may be that lack of testosterone after castration is associated with atrophy of androgen-dependent tissues in the prostate and less inhibition of growth of androgen-independent tissues.[34] Epigenetic effects associated with silencing of genes associated with function of androgen receptors have been demonstrated in humans with prostatic neoplasia.[30] Finally, superoxide dismutase activity declines in prostatic tissue by six months after castration, suggesting a lack of response to the toxic effects of reactive oxygen species, which could be associated with oncogenesis.[35] The authors are unaware of any published research documenting these phenomena in dogs.

Transitional cell carcinoma (non-prostatic)

Incidence of transitional cell carcinoma is at most 1%.[36] Predisposing factors previously reported include increasing age, breed, and exposure to environmental herbicides and insecticides.[37,38] There are two studies documenting increased incidence of transitional cell carcinoma related to neutering in dogs (Table 4).[30,37,39] One study evaluated dogs of only one breed and that breed has a hereditary predisposition to transitional cell carcinoma, making extrapolation to other populations of dogs difficult.[37] The cause-and-effect relationship between gonadectomy and transitional cell carcinoma has not been defined.

Osteosarcoma

Incidence of canine osteosarcoma is $<0.1\%$.[19] Factors reported to be associated with incidence of osteosarcoma include increasing age, breed and increasing size.[40-42] There are four studies in the veterinary literature specifically addressing effect of gonadectomy on incidence of osteosarcoma with three showing increased incidence and one showing no effect (Table 5).[23,40,42,140] Two studies evaluated dogs of only one breed, and one evaluated Rottweilers a breed that has a hereditary predisposition to osteosarcoma, making extrapolation to other populations of dogs difficult.[42] The cause-and-effect relationship between gonadectomy and osteosarcoma has not been defined.

Hemangiosarcoma

Reported incidence of hemangiosarcoma is 0.2%[43]. Predisposing factors previously reported include increasing age and breed; there is no variation in prevalence between female and male dogs.[43-46]

There are seven studies describing relationship between gonadectomy and hemangiosarcoma (Table 6). Splenic and cardiac hemangioma and hemangiosarcoma were reported to be more common in spayed females than in intact females.[43,45,140] Castrated males had a slightly increased risk of developing a heart based tumor compared to intact males.[43] Hemangiosarcoma was reported to occur more commonly in females spayed after 12 months of age than in females spayed early or left intact in one study and to be more common in females spayed at less than six months or more than 12 months in another study; there was no reported effect of castration in male dogs in either study.[47,48] Several studies have reported raw data showing numbers of affected spayed females, intact females, castrated males, and intact males with hemangiosarcoma in specific breeds using data drawn from records of a referral hospital, with varying amounts of statistical analysis.[23,47,49] It can be difficult to assess the value of raw data without more complete information about the population of dogs presented to that hospital. Referral hospitals see a unique population of dogs, generally those with non-standard or complicated disorders, often owned by individuals who have disposable income available for advanced care for their dog, and perhaps more likely to be related as they tend to be drawn from a specific geographic region.[50]

The cause-and-effect relationship between gonadectomy and hemangiosarcoma has not been defined in dogs. One hypothesized association is alteration in immune function with gonadectomy including decreased immune surveillance for cancer cells due to lack of sex steroids.[48] The authors are unaware of any published research documenting this phenomenon in dogs.

Lymphoma

Reported incidence of lymphoma in dogs is 1.1%.[15] There is a hereditary component, increasing age is a risk factor, and environmental factors also may play a role in tumor development.[15,51]

There are six reports evaluating the effect of gonadectomy on incidence of lymphoma with conflicting results (Table 7). Five studies showed increased risk with two studies showing increased risk in females only and two reports showing a difference in males only.[47-49,51] Several studies have reported raw data showing numbers of affected spayed females, intact females, castrated males, and intact males with lymphoma in specific breeds using data drawn from records of a referral hospital, with varying amounts of statistical analysis.[23,47,49] Concerns are as described for hemangiosarcoma.

The cause-and-effect relationship between gonadectomy and lymphoma has not been defined in dogs. Hypothesized associations include a possible protective effect of estrogens, and alterations in immune function with gonadectomy including decreased immune surveillance for cancer cells due to lack of sex steroids.[48,51] The authors are unaware of any published research documenting these phenomena.

Cutaneous mast cell tumor

Prevalence of mast cell tumors in a study evaluating information submitted to an electronic database by a large number of private practices was 0.27%.[52] Some breeds are reported to be at increased risk.[52,53]

There are seven reports evaluating association between gonadectomy and mast cell tumors, with conflicting conclusions. Five reported increased incidence with gonadectomy (Table 8). Two studies demonstrated increased incidence with gonadectomy only in females.[49,53] Several studies have reported raw data showing numbers of affected spayed females, intact females, castrated males, and intact males with mast cell tumor in specific breeds using data drawn from records of a referral hospital, with varying amounts of statistical analysis.[23,47,49] Concerns are as described for hemangiosarcoma.

The cause-and-effect relationship between gonadectomy and mast cell tumor has not been defined in dogs. Hypothesized associations include alterations in immune function with gonadectomy including decreased immune surveillance for cancer cells due to lack of sex steroids, and increased attention from owners who have already had their dogs spayed or castrated.[48,53] The authors are unaware of any published research documenting these phenomena.

Testicular neoplasia

Reported incidence of testicular neoplasia in dogs is 0.9%, with increasing age a reported risk factor.[54] Castration early in life obviously is protective in all cases and castration at the time of diagnosis is reported to be curative in the majority of cases.[25]

Obesity

Reported incidence of obesity varies from 21.4-44.4%.[55-58] Some studies report higher incidence in females than in males and a breed predisposition is described.[55-57] Other factors reported to be associated with obesity in dogs include housing, increasing age, and ownership by an overweight person or a person ≥ 40 years old.[56,57,59-61]

Although many studies report percent of a population of dogs that is reported to be obese, either by veterinarians or by pet owners, only three studies with veterinarian determined body condition have been published specifically addressing the association between gonadectomy and obesity, with all three studies showing increased incidence with gonadectomy (Table 9). Risk for development of obesity after neutering was reported to be greatest for the first two years after surgery, with no difference in likelihood of becoming obese when comparing neutered to intact dogs over ten0 years.[62]

The cause-and-effect relationship between gonadectomy and obesity has not been defined in dogs. In cats, decline in metabolic rate after gonadectomy has been demonstrated.[63,64] Estrogen has been reported to effect satiety in women, perhaps through modulation of cholecystokinin.[65] Studies disagree regarding effect of estrogen on satiety in dogs. In a study comparing dogs gonadectomized at seven weeks of age or seven months of age, or left intact, the dogs showed no difference in food intake or depth of back fat at 15 months of age.[66] In other studies, spayed female dogs have been demonstrated to have an increase in food intake and increase in indiscriminate appetite after spaying compared with sham-operated or age-matched control dogs.[67,68] Testosterone may effect satiety in men through secretion of gastric ghrelin.[69] Castration was associated with increased appetite and subsequent weight gain in one study in dogs.[70]

Cranial cruciate ligament injury

The incidence of cranial cruciate ligament injury was reported to be 0.6-3.5%.[71-74] The disorder may or may not be more common in females than in males and is more prevalent in some breeds.[71-77] Other factors reported to be positively associated with incidence of cranial cruciate ligament injury are age and weight, as well as obesity.[73,74,76,78] Association of cranial cruciate ligament with conformation of the pelvic limb and with exercise are controversial, with conflicting reports in the literature.[79]

There are ten studies evaluating the effect of gonadectomy on incidence of cranial cruciate ligament injury, with nine showing increased incidence with gonadectomy (Table 10). Some factors may be confounded; in one study, intact dogs that developed cranial cruciate ligament injury did so at a younger age than did neutered dogs.[77] Several studies have reported raw data showing numbers of affected spayed females, intact females, castrated males, and intact males with cranial cruciate ligament injury in specific breeds using data drawn from records of a referral hospital, with varying amounts of statistical analysis.[23,47-49] Concerns are as described for hemangiosarcoma. In another study, it was suggested that incidence in neutered dogs was artificially elevated because owners who had paid to have their dog spayed or castrated were perhaps more attentive or more willing to bring their dog in for orthopedic treatment.[72]

The cause-and-effect relationship between gonadectomy and cranial cruciate ligament injury has not been defined. Because cranial cruciate ligament injury occurs more commonly in women than in men with incidence associated with phases of the menstrual cycle, it may be that hormonal changes alter the properties or function of the ligament.[71,80] Closure of the growth plate in long bones may or may not be delayed if dogs undergo gonadectomy prior to puberty. A study evaluating long bone length up to six months of age after ovariohysterectomy failed to show statistical significance between groups, while a study evaluating long bone length at 15 months of age did demonstrate such a difference.[66,81] It has been hypothesized that delayed closure of growth plates may be associated with variation in length of long bones and subsequent misalignment of joints. Specific attention has been paid to possible delay in closure of femoral physes compared to tibial physes, such that there is relative overgrowth of the femur and accentuation of the tibial plateau angle. Several studies have refuted the connection of degree of the tibial plateau angle and incidence of cranial cruciate ligament injury.[82-84] The authors are unaware of any published research documenting development of cranial cruciate ligament injury due to asynchrony of long bone growth and subsequent anatomic abnormalities of the stifle.

Patellar luxation

Reported incidence of patellar luxation was 1.3% in one study.[85] Patellar luxation is a hereditary disorder that is equally prevalent in males and females and is reported to be more prevalent in some breeds.[85,86] Incidence is reported to be positively correlated with age and body weight.[85,86]

There are three studies describing a possible link between gonadectomy and patellar luxation; two showed an increased incidence with spay or castration (Table 11). One study sampled dogs from 119 clinics across England, which minimizes the bias that may be present in studies performed at single locations.[85] However, there may be differences in the breed genetics of dogs from different countries that could influence the generalizability of results.

The cause-and-effect relationship between gonadectomy and patellar luxation has not been defined. Age may be a confounding factor, as increased age, which also was shown to be correlated with increased incidence of patellar luxation, may be associated with increasing laxity of the stifle joint.[86] The association with increased body weight in these studies was not a reflection of increased incidence in obese dogs but rather an increased incidence in dogs with higher than average adult bodyweight for their breed and sex.[85] The authors of one of these studies concluded that the available data was insufficient to permit any deductions about effect of removal of sex hormones on development of patellar luxation.[86]

Hip dysplasia

Reported incidence of hip dysplasia is 1.7-3.5%.[72,87] This is a hereditary condition that is equally prevalent in males and females and is more prevalent in some breeds.[72,87] Environmental influences, including diet, exercise, and housing, also play a role in clinical manifestations of the disorder.[88-92]

Effect of gonadectomy on incidence of hip dysplasia is well described in six studies. Incidence was increased with gonadectomy in five of those studies; no change in incidence in at least one sex was noted in three studies (Table 12). Several published studies described incidence relative to gonadectomy in specific breeds, automatically making the data less valuable for wide extrapolation due to the hereditary component of this disorder.[23,47,49,93] In addition, these studies did not include any genetic analysis of dogs in the study so the influence on genetics even within the breed could not be evaluated. In one study, incidence of hip dysplasia was reported to be higher in dogs neutered before 5.5 months of age but dogs neutered early that developed hip dysplasia were less likely to be euthanized for it than dogs neutered between six and 12 months, suggesting variation in clinical manifestation of the disorder as well as possible owner preferences for various treatment options.[58] It was not clear in that study whether or not all dogs defined as having hip dysplasia had been diagnosed with the disorder by a veterinarian.[58] Similarly, it is not clear in all studies at what age hip dysplasia was diagnosed, if dogs were presented for routine screening or were clinical for hip dysplasia, and if the diagnosis was made by a private practitioner or a specialist, or verified by the Orthopedic Foundation for Animals or other external reviewer. Several studies have reported raw data showing numbers of affected spayed females, intact females, castrated males, and intact males with canine hip dysplasia in specific breeds using data drawn from records of a referral hospital, with varying amounts of statistical analysis.[23,47,49] Concerns are as described for hemangiosarcoma.

The cause-and-effect relationship between gonadectomy and canine hip dysplasia has not been defined. As with cranial cruciate ligament injury, it has been hypothesized that delayed closure of growth plates may be associated with variation in length of long bones and subsequent misalignment of joints. The authors are unaware of any published research documenting misalignment of joints.

Benign prostatic hypertrophy/hyperplasia

Benign prostatic hypertrophy/hyperplasia (BPH) is very common in middle-aged to older dogs, with reported incidence of 50% by 2.4 years of age and 75-80% by six years of age.[94-96] Development is androgen-dependent so castration early in life is protective in all cases. Surgical castration at the time of diagnosis is curative.[97] Castration also is reported to increase effectiveness of treatment and long-term resolution of bacterial prostatitis in dogs, most likely through resolution of underlying BPH.[98]

Pyometra

Incidence of pyometra in bitches increases with age, with reported incidence of 24-25% by ten years of age.[99] Ovariohysterectomy early in life obviously is protective in all cases. Reported mortality associated with ovariohysterectomy at the time of diagnosis is 0-17%.[100,141]

Urinary incontinence

Urethral sphincter mechanism incompetence, formerly known as estrogen-responsive urinary incontinence, is reported to occur in 4.9-20.0% of spayed dogs.[58,101-105] The disorder has been reported to be more common in some breeds.[103,106] Other factors reported to be associated with increasing incidence include increasing age and body weight, and tail docking.[103,105-107]

There are ten studies specifically documenting the association between gonadectomy and urethral sphincter mechanism incompetence, with all four showing increased incidence with spaying (Table 13). Incidence may vary with age or physiologic status; studies have demonstrated increased incidence when bitches were spayed at fewer than three to five months, greater than six months, or before their first estrus.[23,58,104,108, 142-144] Others have refuted any connection between incidence and age at time of spaying.[105] A systematic review was performed to evaluate this topic. As with mammary neoplasia, the veterinary literature is not deep enough to permit this type of analysis and the authors were forced to conclude that currently available data is insufficient for determination of the effect of neutering on the risk of urinary incontinence.[109]

The cause-and-effect relationship between urethral sphincter mechanism incompetence and gonadectomy has not been defined. It has been demonstrated that maximum urethral closure pressure and functional urethral length are decreased after spaying.[110] Serum concentrations of follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary are persistently elevated after spaying, most likely due to lack of negative feedback to the hypothalamus and pituitary from the ovaries.[111] Elevated concentration of serum FSH has been associated with incontinence but effect to changes in gonadotropin concentration on changes in urethral closure pressure and subsequent incontinence are not clear.[111,112, 144]

Urolithiasis – calcium oxalate and struvite

Prevalence of first time calcium oxalate urolithiasis in one study was reported to be 0.01%.[113] Incidence of struvite urolithiasis was reported to be 0.004%.[114] Calcium oxalate urolithiasis is reported to be more common in males than in females and to be more common in smaller breeds of dog.[113,115,116] Struvite urolithiasis is reported to be more common in females than in males and to be more common in small breeds.[114,116] In one study, calcium oxalate urolithiasis was reported to be more common than struvite urolithiasis in males, older dogs, and smaller breed dogs.[117]

Association between urolithiasis and gonadectomy has been reported in four studies, three of which showed increased incidence in gonadectomized dogs (Table 14). Incidence of calcium oxalate urolithiasis is reported to be increased after castration in males and incidence of struvite urolithiasis is reported to be increased after spaying in females.[114,117] Again, it is possible that owners who have had their dogs gonadectomized are more observant and/or more willing to seek veterinary care and treatment. The cause-and-effect relationship between urolithiasis and gonadectomy has not been defined.

Diabetes mellitus

Reported incidence of diabetes mellitus in dogs is 0.5-0.6%.[118,119] It has been reported to occur more commonly in females than in males and a higher prevalence is reported in some breeds.[119,120] Other factors associated with increased incidence of diabetes mellitus are increasing age and obesity.[119,121,122] There are four studies evaluating the possible connection between gonadectomy and incidence of diabetes mellitus (Table 15). Two studies showed no change for females but an increased risk for diabetes mellitus in castrated males.[119,121] One study showed no change in either gender.[58] The most likely cause-and-effect relationships between gonadectomy and diabetes mellitus are through effect of progestogens in insulin resistance and increased likelihood of spayed or castrated dogs being obese.[119,121,122,146]

Chronic kidney disease

Prevalence of chronic kidney disease in the single study evaluating association with gonadectomy was 0.37%.[123] Incidence is increased with increasing age and some breeds are at increased risk. Gonadectomy was associated with increased incidence in one of two studies (Table 16). This study sampled 107,214 dogs from 89 clinics across England, which minimizes the bias that may be present in studies performed at single locations.[123] The cause-and-effect relationship between chronic kidney disease and gonadectomy has not been defined.

Atopic dermatitis

Incidence of atopic dermatitis is 1.7%.[124] Factors associated with incidence include age, breed, sex, and geographical location.[124] There are only three studies documenting the association between gonadectomy and atopic dermatitis, with two showing increased incidence and one showing no association (Table 17).[58,124,125] All studies evaluated large populations of dogs, with one describing 90,090 dogs seen at a referral hospital, one describing 22,280 dogs seen at a corporate practice, and the third describing 1842 dogs adopted from a humane organization. The first and largest of these studies also demonstrated that gonadectomized dogs were more likely to be diagnosed with other autoimmune disorders, including autoimmune hemolytic anemia (OR 1.67±0.28 in females, 1.76±0.31 in males), hypoadrenocorticism (OR 1.49±0.32 in females, 2.07±0.54 in males), hypothyroidism (OR 3.03±0.39 in females, 1.29±0.11 in males), immune-mediated thrombocytopenia (OR 3.14±0.73 in females, 2.05±0.42 in males), inflammatory bowel disease (OR 2.2±0.54 in females, 1.43±0.23 in males) and lupus erythematosus (systemic and discoid, OR 2.64±1.24 in females, not significant in males).[125] The cause-and-effect relationship between autoimmune disorders, including atopic dermatitis, and gonadectomy has not been defined.

Idiopathic epilepsy/cluster seizures

Incidence of idiopathic epilepsy is reported to be 0.6%.[126] One study reported increased incidence in male dogs and some breeds are at increased risk.[126,127] There are three studies evaluating association between gonadectomy and idiopathic epilepsy (Table 18). Two studies showed increased incidence in spayed or castrated dogs and one study showed no change in incidence with gonadectomy.[126-128] Regarding cluster seizures, intact males were reported to be more likely to have cluster seizures than neutered males and intact females had cluster seizures with greater frequency than did spayed females.[128] The cause-and-effect relationship between idiopathic epilepsy and gonadectomy has not been defined. One study suggested that hormones may play a role, perhaps by having an excitatory effect, but the infrequent cycling of female dogs would argue against an effect of such a stimulus throughout the normal prolonged anestrus.[128] One author suggested that any association between gonadectomy and idiopathic epilepsy may be artefactual if owners of dogs with epilepsy present their dogs for gonadectomy as a way of managing their seizures or to prevent them from reproducing.[127]

Lifespan

Gonadectomy has been associated with increased lifespan in most studies where this was evaluated (Table 19). Spayed dogs have been reported to live 23.0-26.3% longer than intact bitches and castrated males have been reported to live 13.8-18.0% longer than intact males.[129-133] Therefore, any health problem that tends to occur in older dogs could be more common in gonadectomized animals than in intact animals, simply because gonadectomized animals may live long enough to develop the health problem. Suggested reasons for this increased longevity include increased attention from owners of dogs they have had neutered, and changes in behavior, for example decreased roaming for breeding purposes, which minimize risks to the animal. The latter hypothesis is supported by data demonstrating that neutered dogs were less likely to die of infectious disease or trauma and were more likely to die of cancer and immune-mediated disease.[130] One study evaluating a group of exceptionally long-live bitches of one breed demonstrated increased lifespan associated with increased ovary exposure over their lifetime, suggesting benefit of exposure to compounds secreted directly from the ovary or compounds for which synthesis or secretion is modulated by the ovary.[134] An example of one such compound is LH, for which concentrations are persistently elevated after ovariectomy and for which many tissues have receptors.[135]

Interpretation and explanation of data

When reading any scientific study, the reader is recommended to ask questions to help them interpret the data. Suggested concerns include:

What kind of study was performed? Ideally, to study causation, the animals should be newly diagnosed with the disease of interest (incident cases). Studies that identify animals for inclusion based on the outcome (the health problem rather than on gonadectomy) are more prone to bias than those studies which sample based on gonadectomy status or age. Studies sampling on the outcome may include errors from missing records and the need for dog owners and veterinarians to rely on memory.[50] For these reasons, studies that do not rely on historical data or memory (prospective studies) generally are considered to generate more accurate information. A study where the dogs were randomly assigned to age of gonadectomy (clinical trial) would be the best design to decrease bias. However, such studies are rare and expensive. Other studies that do not sample based on outcome and are prospective are the next best option (cohort designs). For all studies, the choice of controls is crucial for an unbiased study. A control for studies which select dogs based on the outcome (case control study) is an individual selected in an unbiased manner from those individuals who would have been included in the case series had they developed the disorder under study.[136] Sampling for controls within a referral hospital is plagued with the problems described above but sampling for controls in the general population outside of the referral hospital also may introduce error. Those dogs never would have been in the case series precisely because they would not have been presented to the referral hospital. For these reasons and others, studies including dogs evaluated at a large number of private veterinary hospitals across a geographic region may be of great value and be less prone to bias.

From what population was the sample drawn? Very small samples may not be representative of the population.[8] Very small sample size may also not permit the investigator to demonstrate an effect statistically even if an effect is truly present.[8] Very large studies may show statistical significance of a very small difference between groups that is not large enough to be relevant scientifically or biologically. As previously mentioned, samples drawn from referral hospitals, including veterinary teaching hospitals, may not be an accurate reflection of the larger population. Samples collected by evaluation of dog breeders also may not be reflective of the large dog-owning public as dog breeders often have a different level of knowledge and different goals for their animals compared to pet owners.[50]

How do we know what the statistics are telling us? Statistically significant results can be due to errors in the study design or in the interpretation of the results. In addition, statistical significance is only one criterion for determining a cause-and-effect sequence. The lack of a defined cause-and-effect for gonadectomy and many of the disorders described is troubling for this reason. When looking at odds or hazard ratios or relative risks which provide an estimate of the magnitude of the risk, always consider whether the range includes unity; if so, the author is stating that there is a statistical chance that incidence in neutered animals is equivalent to incidence in intact animals. For that reason, the range of an odds ratio or similar statistical construct is more valid to assess than is any single value, including a p value. In addition, when applying these results to a clinical situation, consider the actual incidence of the problem. If the problem is very rare, even a large relative risk from a good study does not mean that the problem is a major concern. Another consideration with statistical analysis and publications, especially when performing systematic analyses is the "file drawer problem", or lack of publication of negative data. A few of the studies described above did include negative data, which helps create a more balanced overall picture. Finally, when looking at the statistical analysis, readers should be cautious not to draw conclusions solely on the apparent complexity of the analysis. Simple statistics may be superior to very complex statistics, which sometimes reveal mathematically valid evidence for statistical significance that is not supported scientifically. Conversely, more complex statistics may be necessary to evaluate confounding factors within a study, for example the association between gonadectomy and any disorder to which animals are predisposed by increasing age, sex, heredity, or other factors.[8]

Statistical significance demonstrating associations is only one small piece of evidence for causation. Sir Austin Bradford Hill established in 1965 what have become known as Hill's Criteria of Causation (Table 20). These provide a framework to help the reader understand the complexities of determining causation. They also put into context data that is statistically significant but may not make an obvious contribution to demonstrating causation. Veterinarians are strongly encouraged to read manuscripts completely, not just to read the abstract or short summaries of studies, and to consider criteria such as these when evaluating information.

One of the authors (MVRK) used data from a veterinary teaching hospital to try to illustrate the above points. For one calendar year, information was gathered regarding how many unique spayed female, intact female, castrated male, and intact male dogs were seen overall and how many dogs in each category were diagnosed with a variety of disorders, as coded in the electronic medical record, a cross-sectional study (Table 21). Two-way contingency table analysis was performed. As is obvious from the table, very few of the disorders described in this paper were supported by data from this unique population. Specific errors that arose in this small study were lack of data due to inadequate completion of medical records by clinicians and subsequent lack of coded data; low number of animals admitted to the referral hospital for common conditions such as mammary neoplasia; and lack of consideration for confounding factors where appropriate. Some examples demonstrate finding of p values that are misleading when looking at the single odds ratio estimate. For example, the odds ratio for transitional cell carcinoma is 4.1; this is a rather large odds ratio (far from unity). However, the p value is not significant and the range for the odds ratio includes unity, due in part to a small sample size. If only the single value for the odds ratio had been provided, a high risk if gonadectomized would appear to be present using these data. Without the p value or confidence interval, statistical significance cannot be determined. For osteosarcoma, the p value is just significant (near the cutoff of 0.05) but the range for the odds ratio just includes unity. If only the single p value or the single value for the odds ratio had been provided, a significant risk would appear to exist that is not clearly supported if all the data are presented. These data demonstrate the value of confidence intervals and how they can be used to identify significant risk when single values are near the cutoff point.

It is not uncommon for practicing veterinarians to contact one of the authors and ask for a one-sentence response to their question of the best age at which to spay or castrate dogs. There is no appropriate simple response as there is a great amount of information available, all of which will be assessed slightly differently by each person reading those studies, and non-medical considerations must be taken into account, including population control, effects of gonadectomy on behavior, and the wishes of and ability to provide care by the owner or guardian of the dog.

General recommendations are the following:

For populations of unowned dogs, for example at humane organizations, population control concerns outweigh concerns about individual animals. Animals that leave the humane organization intact may repopulate that shelter with their offspring, and may well be returned to the shelter themselves, as it has been demonstrated that being intact is a risk factor for surrender.[137]

For animals with a responsible owner or guardian, veterinarians need to develop a means of communicating this large amount of contradictory data. One way to help clients think through the information is to provide them with an idea of the varying impacts of the disorders the veterinarian believes to be associated with gonadectomy. In one example of this method, veterinarians generated a morbidity score for various disorders that was multiplied by incidence of those disorders to create an impact score (Table 22).[138] Positive impact scores were associated with better health after gonadectomy and negative impact scores with worse health after gonadectomy. For female dogs, benefits of ovariohysterectomy outweighed detriments and prepubertal spay was recommended; for male dogs, benefits of castration did not outweigh detriments until the animal was likely to develop age-related, benign diseases of the reproductive tract, or about 2.5 years of age.[138] Use of this kind of tool also gives veterinarians an opportunity to talk with clients about other topics in preventive medicine. For example, this provided a very real way to demonstrate to clients the concerns associated with obesity, which had a high impact score in both females and males.[138]

Another technique would be to provide clients with some idea of positives and negatives for their specific animal. This requires specific knowledge of predispositions due to age, breed, and other factors for all of the disorders described. An example previously described is the following:[4] You are a veterinarian speaking to the owner of an eight-week-old female Labrador Retriever that is not intended for breeding. This dog would benefit greatly from spaying before her first estrus as a means of preventing mammary gland tumors, which are extremely common relative to other diseases of concern and cause substantial morbidity. Because of her breed, reported detriments of spaying include an increased predisposition to cranial cruciate ligament injury, hemangiosarcoma, and obesity. However, there is a low incidence of hemangiosarcoma, and obesity can be readily controlled with diet and exercise, which leaves cranial cruciate ligament injury as the most important possible detriment. Because the incidence of cranial cruciate ligament rupture is lower than that of mammary gland neoplasia, you choose to recommend spaying and educate the owner about maintenance of optimal body condition and other management techniques that will minimize potential for cranial cruciate ligament injury. The best age at which to perform the spay must include considerations of when the dog's first estrus is likely to occur and how young one can spay a dog before greatly increasing risk of urethral sphincter mechanism incompetence. The likely recommendation for this bitch would be ovariohysterectomy at about five to six months of age.

All of these methods rely on the veterinarian having taken the time to assess the information available and to use their knowledge of the subject to educate clients as they collaborate on the best decision for a specific individual animal. Research on this topic surely will continue and hopefully will include more information about effect of neuter at various ages on these disorders and a greater elucidation of cause-and-effect.

Acknowledgements

The authors wish to think Laurel Schedin and Tina Roeser for data collection.

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Table 1. Key criteria to consider when reviewing studies about gonadectomy and disease causation or prevention

Best study design for evidence for causation, when done well: randomized clinical trials provide the strongest link between potential cause and potential effect. Cohort studies are next, followed by case-control and then case series. Expert opinion and non-systematic reviews provide the weakest evidence for causation.
Unbiased subject selection (how were the dogs selected and from where): One source of potential bias is if there are many missing data points or large losses to follow-up. In addition, whether the dogs were recruited from private practice, referral or specialty hospitals, breed clubs or pathology services can also influence the disease diagnosis frequency, severity and age. Dogs seen at referral hospitals are not likely to be representative of dogs seen in private practices. Factors such as cost, distance to travel, severity of the disease or complexity of the treatment, interest of faculty and availability of funding to pay for treatment all influence which dogs are referred and at what stage of disease.
Adequate sample size: A large enough sample helps to ensure that the animals in the study represent the animals to whom we would like to extrapolate the results. Also, a large enough sample is needed to be sure that the study had enough animals to be able to find a difference statistically if one really existed (power calculations can ensure this). Conversely, an extremely large sample may identify statistical significance that is mathematical in nature and not reflective of underlying science.
Accurate and precise measurement of the characteristics of interest: in this case, accurate assessment of the age of gonadectomy is critical. Data from the veterinarian performing the surgery is likely most accurate. Owner recollection of the date is prone to difficulty in recall, particularly for older dogs. Dogs who were acquired as adults and were already gonadectomized may not have a known date of surgery and therefore will be systematically excluded from the data set.
Adequate control of confounding factors: a listing the confounders, why each was included and how each was addressed is critical. In this case, age, sex, breed, genetics, body condition score, diet and exercise may be important for the diseases of interest.
Cautious and critical assessment of results by the authors: there should be a section in the discussion about the limitations of the study as well as the interpretation of the results in light of the objectives, limitations, analysis, other published work and other relevant evidence that highlights the strengths and weaknesses of the current study.

Table 2. Literature review – mammary neoplasia

REFERENCE NUMBER	VARIATION WITH GONADECTOMY	SIGNIFICANT RESULTS	STUDY TYPE	SUBJECT SELECTION	SAMPLE SIZE	DETERMINATION OF AGE AT GONADECTOMY	CONTROLS / ANALYSIS FOR CONFOUNDING FACTORS
17	Decreased	Neutered bitches 1/3 as likely as intact bitches to develop condition	Case-control study	Diagnostic laboratory submissions	2075 tumors	Not available in all medical records accessed	Age-matched controls, breed variation identified in study but not incorporated into statistical analysis
20	Decreased	OR 0.01 if spayed before 1 year of age, 0.11 if spayed 1-2.5 years of age	Case-control study	Diagnostic laboratory submissions	150 affected dogs	Owner questionnaire	Controls matched for age (n=147) and size (n=131); obesity and high fat diet were included in statistical analysis
18	Decreased	$p<0.0001$	Case- control study	Patients admitted to private practices and shared with a cancer registry	576 affected dogs	Review of hospital records	Controls (n=1455) and history of progestin treatment, age were evaluated separately
19	Decreased	2X greater incidence in intact females, $p<0.0001$	Case-control study	Cancer registry submissions	---	Not considered	Controls from private practices, age, sex and breed included in statistical analysis
58	Unchanged	---	Retrospective cohort study	Animals adopted from humane organization	1842 dogs	Owner questionnaire, review of hospital records	Purebred or not, owner surrender or stray intake type, time in shelter and other dogs in household were included in statistical analysis, low number of affected animals may have

							decreased statistical power
23	Unchanged	---	Retrospective cohort study	German shepherd dogs admitted to specialty/referral hospital	705 female dogs	Review of hospital records including referring veterinarians	Small sample size, breed-specific study (German shepherd dogs), sex included in statistical analysis
140	Decreased	OR 0.4 (ex vivo or post-mortem samples) or 0.6 (post-mortem samples) compared to OR=1 for intact females	Retrospective study	Cancer registry submissions	Exact number of tumors in female dogs not provided	Not considered	Sex and age included in statistical analysis. Tumor types not always separated by anatomic location.

Table 3. Literature review – prostatic neoplasia

REFERENCE NUMBER	VARIATION WITH GONADECTOMY	SIGNIFICANT RESULTS	STUDY TYPE	SUBJECT SELECTION	SAMPLE SIZE	DETERMINATION OF AGE AT GONADECTOMY	CONTROLS / ANALYSIS FOR CONFOUNDING FACTORS
33	Increased	OR 3.9 (2.3-6.8)	Case-control study	Diagnostic laboratory submissions	70 affected dogs	Review of hospital records, necropsy reports, owner / DVM questionnaire/interview, just gonadectomized yes or no	Age-matched controls
28	Increased	OR 4.3 (2.5-7.6)	Case control study	Patients admitted to specialty/referral hospital	56 affected dogs	Review of hospital records, owner interview, just gonadectomized yes or no	Breed variation identified in study but not incorporated into statistical analysis
29	Increased	OR 2.4 (1.0-9.6)	Case series	Patients admitted to specialty/referral hospital	31 affected dogs	Review of hospital records, just gonadectomized yes or no	No controls
30	Increased	OR 2.8 (2.6-3.1)	Case-control study	Patients admitted to specialty/referral hospital (VMDB registry)	681 affected dogs	Not available through registry; just gonadectomized yes or no	Age-matched controls, breed included in separate analysis
32	Unchanged	----	Case series	Patients admitted to specialty/referral hospital	43 affected dogs	Review of hospital records	No controls, small sample size

OR = odds ratio

Table 4. Literature review – transitional cell carcinoma

REFERENCE NUMBER	VARIATION WITH GONADECTOMY	SIGNIFICANT RESULTS	STUDY TYPE	SUBJECT SELECTION	SAMPLE SIZE	DETERMINATION OF AGE AT GONADECTOMY	CONTROLS / ANALYSIS FOR CONFOUNDING FACTORS
37	Increased	OR 4.4 (1.4-13.8)	Case-control study	Scottish terriers recruited through specialty/referral hospital, breed club	83 affected dogs	Owner questionnaire	Age-matched controls, breed-specific study
39	Increased	OR 2.0 (no CI reported), p=0.03	Case-control study	Diagnostic laboratory submissions	115 tumors	Review of hospital records	Control population from specialty/referral hospital, age, breed, gender, weight were analyzed separately

OR = odds ratio

Table 5. Literature review – osteosarcoma

REFERENCE NUMBER	VARIATION WITH GONADECTOMY	SIGNIFICANT RESULTS	STUDY TYPE	SUBJECT SELECTION	SAMPLE SIZE	DETERMINATION OF AGE AT GONADECTOMY	CONTROLS / ANALYSIS FOR CONFOUNDING FACTORS
42	Increased	RR 3.8 (1.5-9.2) females; RR 3.1 (1.1-8.3) males	Retrospective cohort study	Recruited through breed clubs	86 affected dogs, 597controls without condition,	Owner questionnaire/interview for age at gonadectomy	597controls without condition, breed-specific study (Rottweiler), height, weight included in statistical analysis
23	Unchanged	---	Retrospective cohort study	German shepherd dogs admitted to specialty/referral hospital	465 male dogs, 705 female dogs	Review of hospital records including referring veterinarians	Small sample size, breed-specific study (German shepherd dogs), sex included in statistical analysis
140	Increased	OR 1.6 (ex vivo or necropsy samples) or 2.0 (necropsy samples) compared to OR=1 for intact males, no significant effect in females	Retrospective study	Cancer registry submissions	Exact number of tumors in male dogs not provided	Not considered	Sex and age included in statistical analysis.

RR = relative risk

Table 6. Literature review – hemangiosarcoma

REFERENCE NUMBER	VARIATION WITH GONADECTOMY	SIGNIFICANT RESULTS	STUDY TYPE	SUBJECT SELECTION	SAMPLE SIZE	DETERMINATION OF AGE AT GONADECTOMY	CONTROLS / ANALYSIS FOR CONFOUNDING FACTORS
45	Increased (females)	OR 2.2 (1.2-4.1)	Case-control study	Diagnostic laboratory submissions	59 affected dogs	DVM questionnaire, just gonadectomized yes or no	Random sample of biopsy submissions , age included in statistical analysis
43	Increased	RR 5.3 (4.0-7.2) females; 1.6 times more likely if castrated	Case control study	Patients admitted to specialty/referral hospital (VMDB registry)	633 affected dogs	Review of registry records, just gonadectomized yes or no	Sex, breed and year of diagnosis were evaluated separately
47	Increased (females); Unchanged (males)	RR 6.1 (1.2-31.4) for females spayed after 1 year of age	Retrospective cohort study	Golden retrievers admitted to specialty/referral hospital	364 female dogs, 395 male dogs	Review of hospital records	Breed-specific study (golden retrievers), sex was included in statistical analysis, age was analyzed separately
23	Unchanged	---	Retrospective cohort study	German shepherd dogs admitted to specialty/referral hospital	465 male dogs, 705 female dogs	Review of hospital records including referring veterinarians	Small sample size, breed-specific study (German shepherd dogs), sex included in statistical analysis
49	Unchanged	----	Retrospective cohort study	Labrador and Golden retrievers admitted to specialty/referral hospital	1147 female dogs, 1435 male dogs	Review of hospital records	Breed-specific study (golden and Labrador retrievers), sex was included in statistical analysis

48	Increased (females); Unchanged (males)	OR 9.0 (2.8-29.4)	Retrospective cohort study	Vizslas recruited through breed clubs	2505 dogs	Owner questionnaire	Breed-specific study (vizslas), sex was included in statistical analysis
140	Increased	OR 1.6 (ex vivo or post-mortem samples) or 2.4 (post-mortem samples) compared to OR=1 for intact females	Retrospective study	Cancer registry submissions	Exact number of tumors in female dogs not provided	Not considered	Sex and age included in statistical analysis. Tumor types not always separated by anatomic location.

OR = odds ratio, RR = relative risk

Table 7. Literature review – lymphosarcoma

REFERENCE NUMBER	VARIATION WITH GONADECTOMY	SIGNIFICANT RESULTS	STUDY TYPE	SUBJECT SELECTION	SAMPLE SIZE	DETERMINATION OF AGE AT GONADECTOMY	CONTROLS / ANALYSIS FOR CONFOUNDING FACTORS
51	Increased (females)	OR 1.5 (1.4-1.6) Golden and Labrador retrievers, German shepherds and boxers were at increased risk	Case-control study	Patients admitted to specialty/referral hospital (VMDB registry)	14,573 dogs	Review of registry records, gonadectomized yes or no	Age- and breed-matched controls from registry, also sex, breed and age were included in statistical analysis
47	Unchanged (females); Increased (males)	$p<0.05$ for males castrated early	Retrospective cohort study	Golden retrievers admitted to specialty/referral hospital	364 female dogs, 395 male dogs	Review of hospital records	Breed-specific study (golden retrievers), sex was included in statistical analysis, age was analyzed separately
23	Unchanged	---	Retrospective cohort study	German shepherd dogs admitted to specialty/referral hospital	465 male dogs, 705 female dogs	Review of hospital records including referring veterinarians	Small sample size, breed-specific study (German shepherd dogs), sex included in statistical analysis
49	Increased (female Goldens); Increased (male Goldens); Unchanged (Labs)	$p=0.01$ for females spayed from 6-11 months of age; $p=0.007$ for males castrated from 6-11	Retrospective cohort study	Labrador and Golden retrievers admitted to specialty/referral hospital	1147 female dogs, 1435 male dogs	Review of hospital records	Breed-specific study (golden and Labrador retrievers), sex was included in statistical analysis, age was analyzed separately

		months of age					
48	Increased	OR 4.3 (1.9-9.7)	Retrospective cohort study	Vizslas recruited through breed clubs	2505 dogs	Owner questionnaire	Breed-specific study (vizslas), sex was included in statistical analysis
140	Increased	OR 1.1 (ex vivo or post-mortem samples) or 1.6 (post-mortem samples) compared to OR=1 for intact females; OR 1.3 (ex vivo or post-mortem samples) or 2.3 (post-mortem samples) compared to OR=1 for intact males	Retrospective study	Cancer registry submissions	Exact number of tumors in female versus male dogs not provided	Not considered	Sex and age included in statistical analysis.

OR = odds ratio

Table 8. Literature review – mast cell tumor

REFERENCE NUMBER	VARIATION WITH GONADECTOMY	SIGNIFICANT RESULTS	STUDY TYPE	SUBJECT SELECTION	SAMPLE SIZE	DETERMINATION OF AGE AT GONADECTOMY	CONTROLS / ANALYSIS FOR CONFOUNDING FACTORS
53	Increased (females)	OR 4.1 (2.2-7.7)	Case-control study	Patients admitted to specialty/referral hospital	252 affected dogs	Review of hospital records, just gonadectomized yes or no	Controls from hospital population without condition, age, sex and breed were included in statistical analysis
52	UnchangedIncreased	OR 0.1 (0.1-0.2) all neutered compared to all intact, no influence of sex	Case-control study	Registry from private practice submissions	453 affected dogs	Review of registry records, just gonadectomized yes or no	Age, sex, insurance status, breed, weight and breed type were included in statistical analysis
47	Increased (females); Unchanged (males)	Could not complete statistical analysis	Retrospective cohort study	Golden retrievers admitted to specialty/referral hospital	364 female dogs, 395 male dogs	Review of hospital records	Breed-specific study (golden retrievers), sex was included in statistical analysis, age was analyzed separately
23	Unchanged	---	Retrospective cohort study	German shepherd dogs admitted to specialty/referral hospital	465 male dogs, 705 female dogs	Review of hospital records including referring veterinarians	Small sample size, breed-specific study (German shepherd dogs), sex included in statistical analysis
49	Increased (female Goldens); Unchanged (male	p=0.01 for females spayed at 2-8 years of	Retrospective cohort study	Labrador and Golden retrievers	1147 female dogs,	Review of hospital records	Breed-specific study (golden and Labrador retrievers),

	Goldens); Unchanged (Labs)	age		admitted to specialty/referral hospital	1435 male dogs		sex included in statistical analysis, age was analyzed separately
48	Increased	OR 3.5 (2.3-5.4)	Retrospective cohort study	Vizslas recruited through breed clubs	2505 dogs	Owner questionnaire	Breed-specific study (vizslas), sex was included in statistical analysis, age was analyzed separately
140	Increased	OR 1.2 (ex vivo or post-mortem samples) or 3.7 (post-mortem samples) compared to OR=1 for intact females; 1.2 (ex vivso or post-mortem samples) or 3.0 (post-mortem samples) compared to OR=1 for intact males	Retrospective study	Cancer registry submissions	Exact number of tumors in male dogs not provided	Not considered	Sex and age included in statistical analysis.

OR = odds ratio

Table 9. Literature review – obesity

REFERENCE NUMBER	VARIATION WITH GONADECTOMY	SIGNIFICANT RESULTS	STUDY TYPE	SUBJECT SELECTION	SAMPLE SIZE	DETERMINATION OF AGE AT GONADECTOMY	CONTROLS / ANALYSIS FOR CONFOUNDING FACTORS
55	Increased	OR 1.6 (1.2-2.1)	Case-control study	Patients admitted to private practices in China; DVMs determined body condition score (BCS)	2391 dogs	Owner questionnaire/interview, just gonadectomized yes or no	Age, breed, sex and many other variables included in statistical analysis
57	Increased	Gonadectomized dogs 2 times more likely to be obese than intact dogs	Cross sectional study	Patients admitted to specialty/referral hospitals and private practices in England; DVMs determined BCS	8268 dogs	DVM questionnaire, just gonadectomized yes or no	Breed, sex and age were include in statistical analysis
62	Increased	Gonadectomized dogs (yes/no) HR ~2 for 1 to 2 years after gonadectomy; no difference for age at gonadectomy	Retrospective cohort study	Corporate private practice; hospital staff determined BCS	2599 dogs	Review of hospital records	Age-matched controls, breed size, sex, and other variables included in statistical analysis

OR = odds ratio

Table 10. Literature review – cranial cruciate ligament injury

REFERENCE NUMBER	VARIATION WITH GONADECTOMY	SIGNIFICANT RESULTS	STUDY TYPE	SUBJECT SELECTION	SAMPLE SIZE	DETERMINATION OF AGE AT GONADECTOMY	CONTROLS / ANALYSIS FOR CONFOUNDING FACTORS
71	Increased	OR 2.2 (1.3-3.8) females; OR 1.6 (0.8-3.0) males	Case-control study	Patients admitted to specialty/referral hospital	112 affected dogs	Review of hospital records, just gonadectomized yes or no	Breed, size and sex were included in statistical analysis
72	Increased castrated males or spayed females Decreased intact males or intact females	Castrated males compared to all other dogs 1.68 (1.6-1.7) Spayed females compared to all dogs OR 2.35 (2.3-2.4) Intact males compared to all other dogs OR 0.47 (0.46-0.49) Intact females compared to all other dogs OR 0.51 (0.49-0.53)	Cross-sectional study	Patients admitted to specialty/referral hospital (VMDB registry)	1193 affected dogs	Review of registry records, just gonadectomized yes or no	Breed, sex and age were analyzed separately
139	Increased if gonadectomized before 6 months	OR 3.0 (1.2-8.0) if gonadectomized prior to 6	Case-control study	Recruited from specialists in practice	38 affected dogs	Owner questionnaire/interview	42 controls matched for body weight and tibial plateau angle, breed, weight,

		months of age					body condition and other variables analyzed separately
78	Increased	p<0.0001	Case-control study	Patients admitted to specialty/referral hospital (VMDB registry)	10,769 affected dogs	Review of registry records	Breed, age, sex and weight were analyzed separately
73	Unchanged	----	Case-control study	Patients admitted to a private practice in England	189 affected dogs	Review of hospital records, just gonadectomized yes or no	Control group from same hospital, Breed, sex, age and obesity were statistical analysis
76	Increased	Data not provided	Case-control study	Patients admitted to three specialty/referral hospital	201 affected dogs	Review of hospital records, just gonadectomized yes or no	Age-matched controls, breed, sex and weight were analyzed separately
74	Increased (females)	OR 2.1 (1.6-2.9)	Case-control study	Registry submissions from private practice in England	953 dogs	Review of registry records	Controls within registry population, breed, purebred or not, sex, insurance, age, body weight were included in statistical analysis
47	Increased	p<0.05 for dogs gonadectomized at less than 1 year of age	Retrospective cohort study	Golden retrievers admitted to specialty/referral hospital	364 female dogs, 395 male dogs	Review of hospital records	Breed-specific study (golden retrievers), sex was included in statistical analysis, body condition score analyzed

							separately
23	Increased	HR 9.5 (1.2-74.9) females; HR 26.2 (5.6-123.3) males	Retrospective cohort study	German shepherd dogs admitted to specialty/referral hospital	465 male dogs, 705 female dogs	Review of hospital records including referring veterinarians	Breed-specific study (German shepherd dogs), sex was included in statistical analysis, body condition score was analyzed separately
49	Increased (female Goldens); Increased (male Goldens); Unchanged (female Labs); Increased (male Labs)	p=0.03 (female Goldens), p<0.001 for male Goldens castrated at less than 6 months of age, p=0.004 for male Goldens castrated at 6-11 months of age; p=0.02 for male Labs castrated at less than 6 months of age	Retrospective cohort study	Labrador and Golden retrievers admitted to specialty/referral hospital	1147 female dogs, 1435 male dogs	Review of hospital records	Breed-specific study (golden and Labrador retrievers), sex was included in statistical analysis, body condition score analyzed separately

OR = odds ratio, HR = hazard ratio

Table 11. Literature review – patellar luxation

REFERENCE NUMBER	VARIATION WITH GONADECTOMY	SIGNIFICANT RESULTS	STUDY TYPE	SUBJECT SELECTION	SAMPLE SIZE	DETERMINATION OF AGE AT GONADECTOMY	CONTROLS / ANALYSIS FOR CONFOUNDING FACTORS
86	Increased	OR 3.1 (1.3-7.5), but confounded by older age associated with gonadectomy	Case-control study	Patients admitted to specialty/referral hospital, recruited through breed clubs (small and miniature breeds only in Austria)	432 affected dogs	Review of hospital records, just gonadectomized yes or no	262 unaffected dogs as controls, breed, age, sex and weight were included in statistical analysis
85	Increased	OR 2.4 (1.8-3.2), females also at increased risk OR 1.3 (1.1-1.5)	Case-control study	Registry submissions from private practices in England	751 affected dogs	Review of registry records, just gonadectomized yes or no	Breed, purebred or not, body weight, age, sex and insured or not were included in statistical analysis
58	Unchanged	----	Retrospective cohort study	Animals adopted from humane organization	1842 dogs	Owner questionnaire, review of hospital records	Purebred or not, owner surrender or stray intake type, time in shelter and other dogs in household were included in statistical analysis, low number of affected animals may have decreased statistical power

OR = odds ratio

Table 12. Literature review – hip dysplasia

REFERENCE NUMBER	VARIATION WITH GONADECTOMY	SIGNIFICANT RESULTS	STUDY TYPE	SUBJECT SELECTION	SAMPLE SIZE	DETERMINATION OF AGE AT GONADECTOMY	CONTROLS / ANALYSIS FOR CONFOUNDING FACTORS
93	Increased	Gonadectomized dogs 1.5X more likely to develop condition than are intact dogs	Nested case-control study	Dogs registered with national breed club	97 affected dogs	Owner questionnaire, just gonadectomized yes or no	Breed-specific study, age, sex, slippery floor covering or not and other variables included in statistical analysis
72	Increased castrated males Decreased intact females and spayed females	Castrated males compared to all other dogs1.2 (1.18-1.24) Intact females compared to all other dogs OR 0.93 (0.91-0.96) Spayed females compared to all dogs OR 0.97 (0.95-0.99)	Cross-sectional study	Patients admitted to specialty/referral hospital (VMDB registry)	1193 affected dogs	Review of registry records, just gonadectomized yes or no	Breed, sex and age were analyzed separately
58	Increased	HR 1.7 (1.0-2.8) >5.5 months at neuter	Retrospective cohort study	Animals adopted from humane organization	1842 dogs	Owner questionnaire, review of hospital records	Purebred or not, owner surrender or stray intake type, time in shelter and other dogs in household were included in statistical analysis,, not clear if all diagnoses made by veterinarian

47	Increased (males)	$p<0.01$	Retrospective cohort study	Golden retrievers admitted to specialty/referral hospital	364 female dogs, 395 male dogs	Review of hospital records	Breed-specific study (golden retrievers), sex was included in statistical analysis, body condition score analyzed separately
23	Unchanged	---	Retrospective cohort study	German shepherd dogs admitted to specialty/referral hospital	465 male dogs, 705 female dogs	Review of hospital records including referring veterinarians	Small sample size, breed-specific study (German shepherd dogs), sex was included in statistical analysis, body condition score analyzed separately
49	Unchanged (female Goldens); Increased (male Goldens); Unchanged (female Labs); Unchanged (male Labs)	$p<0.001$ for males castrated at less than 6 months of age, $p<0.05$ for males castrated 6-11 months of age	Retrospective cohort study	Labrador and Golden retrievers admitted to specialty/referral hospital	1147 female dogs, 1435 male dogs	Review of hospital records	Breed-specific study (golden and Labrador retrievers), sex was included in statistical analysis, body condition score analyzed separately

OR = odds ratio, HR = hazard ratio

Table 13. Literature review – urinary incontinence

REFERENCE NUMBER	VARIATION WITH GONADECTOMY	SIGNIFICANT RESULTS	STUDY TYPE	SUBJECT SELECTION	SAMPLE SIZE	DETERMINATION OF AGE AT GONADECTOMY	CONTROLS / ANALYSIS FOR CONFOUNDING FACTORS
104	Increased	RR 7.8 (2.6-31.5)	Prospective cohort study	Patients admitted to private practices	809 female dogs	Records completed by private practitioners	Controls within hospital population, age, breed, estrus influencing drugs were included in statistical analysis
108	Increased	OR 4.9 (3.1-7.8)	Retrospective cohort	Patients admitted to specialty/referral hospital	3260 female dogs	Review of hospital records	Only included intact and spayed at 6 months and older, no confounding factors included
58	Increased	HR 1.2 (1.1-1.3) overall, HR 3.5 if spayed before 3 months of age	Retrospective cohort study	Animals adopted from humane organization	983 female dogs	Owner questionnaire, review of hospital records	Purebred or not, owner surrender or stray intake type, time in shelter and other dogs in household were included in statistical analysis
23	Increased	$p<0.05$ for dogs spayed at 6-11 months of age	Retrospective cohort study	German shepherd dogs admitted to specialty/referral hospital	705 female dogs	Review of hospital records including referring veterinarians	Small sample size, breed-specific study (German shepherd dogs), age was analyzed separately
142	Interaction between age at neuter and weight with lower risk of incontinence for dogs >25 kg for	HR 0.89 (0.82-0.97)	Retrospective cohort study	Patients admitted to American Animal Hospital Association accredited US	356 female dogs	Review of hospital records	Controls within hospital population, age at presentation and body condition score were analyzed separately; weight was included in

	every month older neutering was done			veterinary clinics			statistical analysis
143	Increased for dogs >=15 kg, age of neuter was not significant	OR dogs >= 15 kg 7 (2.5-21)	Retrospective cohort study	Patients admitted to a multi-practice general and specialty veterinary clinic	566 female dogs	Review of hospital records and interviews of owners	Controls within hospital population, body weight in categories, number of litters, elective or emergency neuter were included in statistical analysis
144	Increased with decreasing FSH plasma concentrations Increased with increasing age at sampling	OR 0.5 (0.24-0.91) FSH all breeds except boxers and German shepherds OR 2.7 (1.3-5.9) age at sampling	Cross-sectional study	Individual pure bred dogs, often at dog shows	499 female dogs	Interviews with owners	Boxers and German Shepherds analyzed separately, time since neuter and before or after first estrus, age at sampling, body weight, breed, LH and FSH levels were statistically analyzed.

OR = odds ratio, HR = hazard ratio, RR = relative risk

Table 14. Literature review – urolithiasis

REFERENCE NUMBER	VARIATION WITH GONADECTOMY	SIGNIFICANT RESULTS	STUDY TYPE	SUBJECT SELECTION	SAMPLE SIZE	DETERMINATION OF AGE AT GONADECTOMY	CONTROLS / ANALYSIS FOR CONFOUNDING FACTORS
113	Increased, influenced by age and sex	OR 2.6 (1.4-4.6)	Case-control study	Patients admitted to corporate veterinary practice	452 affected dogs with struvite uroliths	Review of hospital records, just gonadectomized yes or no	Controls from same hospital population, diet, breed size, age, sex, hospital location and more included in statistical analysis
117	Unchanged	OR 1.4 (0.99-1.8), p=0.06	Case-control (oxalate vs struvite)	Urolith center submissions	3867 calcium oxalate uroliths, 3430 struvite uroliths	Review of records accompanying submissions, just gonadectomized yes or no	No controls, age, sex, breed, body condition, diet were included in statistical analysis
114	Increased, influenced by age and sex	OR 2.2 (1.6-3.0)	Case-control study	Patients admitted to corporate veterinary practice	508 affected dogs with calcium oxalate urolithiasis	Review of hospital records, just gonadectomized yes or no	Controls from same hospital population, diet, breed size, age, sex, hospital location and more included in statistical analysis
58	Unchanged	----	Retrospective cohort study	Animals adopted from humane organization	1842 dogs	Owner questionnaire, review of hospital records	Purebred or not, owner surrender or stray intake type, time in shelter and other dogs in household were included in statistical analysis,, low number of affected animals may have decreased statistical power

OR = odds ratio

Table 15. Literature review – diabetes mellitus

REFERENCE NUMBER	VARIATION WITH GONADECTOMY	SIGNIFICANT RESULTS	STUDY TYPE	SUBJECT SELECTION	SAMPLE SIZE	DETERMINATION OF AGE AT GONADECTOMY	CONTROLS / ANALYSIS FOR CONFOUNDING FACTORS
119	Unchanged (females); Increased (males)	OR 1.9 (1.7-2.2)	Case-control study	Patients admitted to specialty/referral hospital (VMDB registry)	6860 affected dogs	Review of registry records, just gonadectomized yes or no	Age- and institution-matched controls, breed, sex and weight included in statistical analysis
121	Unchanged (females); Increased (males)	OR 2.5 (1.5-4.3)	Case-control study	Registry submissions from private practices	209 dogs	Review of registry records, just gonadectomized yes or no	Age-matched controls, weight, breed and other variables were included in statistical analysis
58	Unchanged	----	Retrospective cohort study	Animals adopted from humane organization	1842 dogs	Owner questionnaire, review of hospital records	Purebred or not, owner surrender or stray intake type, time in shelter and other dogs in household were included in statistical analysis, low number of affected animals may have decreased statistical power
145	Increased (females and neutered males compared to intact male) No difference between neutered and intact females	RR 2.2 (1.5-3.0) neutered male relative to intact male RR 2.5 (2.1-2.9) neutered female compared to intact male	Case control study	Patients admitted to specialty/referral hospital (VMDB registry and Animal Medical Center)	1468 dogs	Review of hospital records	Several different control groups used, gonadectomized or not, age and breed included in statistical analysis, month of diagnosis analyzed separately.

OR = odds ratio

Table 16. Literature review – chronic kidney disease

REFERENCE NUMBER	VARIATION WITH GONADECTOMY	SIGNIFICANT RESULTS	STUDY TYPE	SUBJECT SELECTION	SAMPLE SIZE	DETERMINATION OF AGE AT GONADECTOMY	CONTROLS / ANALYSIS FOR CONFOUNDING FACTORS
123	Increased	OR 3.2 (2.1-4.7), $p<0.001$	Case-control study	Registry submissions from private practices in the UK	228 affected dogs	Review of registry records, just gonadectomy yes or no	Controls from registry population, age, breed, sex, weight, insurance and others were included in statistical analysis
58	Unchanged	----	Retrospective cohort study	Animals adopted from humane organization	1842 dogs	Owner questionnaire, review of hospital records	Purebred or not, owner surrender or stray intake type, time in shelter and other dogs in household were included in statistical analysis , low number of affected animals may have decreased statistical power

OR = odds ratio

Table 17. Literature review – atopic dermatitis

REFERENCE NUMBER	VARIATION WITH GONADECTOMY	SIGNIFICANT RESULTS	STUDY TYPE	SUBJECT SELECTION	SAMPLE SIZE	DETERMINATION OF AGE AT GONADECTOMY	CONTROLS / ANALYSIS FOR CONFOUNDING FACTORS
124	Increased	RR 3.2 (no CI reported)	Case-control study	Patients admitted to corporate veterinary practice	22,280 affected dogs	Review of hospital records	Controls from same hospital population, age, breed, sex, region, other diagnoses included in statistical analysis
58	Unchanged	----	Retrospective cohort study	Animals adopted from humane organization	1842 dogs	Owner questionnaire, review of hospital records	Purebred or not, owner surrender or stray intake type, time in shelter and other dogs in household were included in statistical analysis , low number of affected animals may have decreased statistical power
125	Increased	OR 2.2 (2.0-2.5) females; OR 1.5 (1.2-1.8) males	Retrospective cohort study	Patients admitted to a specialty / referral hospital	90,090 dogs	Review of hospital records	Large sample size and low prevalence of disorders in sample population may have promoted artificial designation of significance.

RR = relative risk, CI = confidence interval

Table 18. Literature review – epilepsy

REFERENCE NUMBER	VARIATION WITH GONADECTOMY	SIGNIFICANT RESULTS	STUDY TYPE	SUBJECT SELECTION	SAMPLE SIZE	DETERMINATION OF AGE AT GONADECTOMY	CONTROLS / ANALYSIS FOR CONFOUNDING FACTORS
126	Unchanged	---	Case-control study	Registry submissions from private practices in the UK	539 affected dogs	Review of registry records, just gonadectomy yes or no	Age, sex, breed, color and weight were included in statistical analysis
128	Decreased frequency (females), decrease in cluster seizures (males)	p=0.007 increased frequency of cluster seizures in intact females, intact males more likely to have cluster seizures OR 2.3 (1.4-3.9) cluster seizures compared to neutered	Case series	Charity veterinary practice in UK	159 affected dogs (frequency analysis), 158 affected dogs (severity analysis)	Review of hospital records, just gonadectomy yes or no	Controls unclear, just compared types of seizures; age, breed, sex were included in statistical analysis
127	Increased	OR 1.6 (1.4-1.9), males also at increased risk	Case-control study	Patient sera submitted for drug analysis	1260 dogs	Review of documents accompanying submission, DVM interview, just gonadectomy yes or no	Controls from large private practice registry, age, sex and breed were analyzed separately

OR = odds ratio

Table 19. Literature review – lifespan

REFERENCE NUMBER	VARIATION WITH GONADECTOMY	SIGNIFICANT RESULTS	STUDY TYPE	SUBJECT SELECTION	SAMPLE SIZE	DETERMINATION OF AGE AT GONADECTOMY	CONTROLS / ANALYSIS FOR CONFOUNDING FACTORS
129	Increased lifespan	23% longer (females), 18% longer (males)	Cross-sectional study	Patients admitted to corporate veterinary practice	2.2 million dogs	Review of hospital records, just gonadectomy yes or no	Descriptive statistics only
130	Increased lifespan	26.3% longer (females), 13.8% longer (males)	Retrospective cohort study	Hospitals Patients admitted to specialty/referral hospitals (VMDB registry)	---	Review of registry records	Age included in statistical analysis, breed and weight evaluated separately
134	Decreased lifespan	---	Case-control study	Specific population of exceptionally long-lived female dogs of one breed	83 long-lived dogs	Questionnaire/interview with owner/DVM	100 breed-matched controls with average lifespan, breed-specific study (rottweilers)

Table 20. Hills Criteria of Causation

Strength – The larger the association, the more likely there is a true cause-and-effect.
Consistency – Studies performed by different people looking at different populations have consistent findings.
Specificity – There is no confounding factor that is equally or more likely to have caused the effect.
Temporality – The effect always occurs after the cause.*
Biological gradient – Greater exposure leads to greater incidence of the effect.
Plausibility – The proposed cause and effect make sense with current knowledge.
Coherence – All findings (epidemiologic, laboratory testing, etc.) support the cause and effect.
Experiment – The effect can be altered through judicious experimental testing of the cause.
Analogy – All other possible causes have been taken into consideration.

* This criterion must always be present to demonstrate causation.

Table 21. Demonstration of potential in faults of data analysis by evaluation of effect of gonadectomy on a variety of disorders diagnosed at a veterinary teaching referral hospital

DISORDER	p VALUE	ODDS RATIO
MAMMARY NEOPLASIA	0.7	1.2 (0.4-5.2)
PROSTATIC NEOPLASIA	0.9	1.1 (0.1-23.4)
TRANSITIONAL CELL CARCINOMA	0.1	4.2 (0.6-82.9)
OSTEOSARCOMA	0.03	4.1 (1.0-24.4)
HEMANGIOSARCOMA	0.1	2.0 (0.8-5.7)
LYMPHOMA	< 0.001	4.0 (1.7-10.1)
CUTANEOUS MAST CELL TUMOR	0.002	5.4 (1.6-19.9)
OBESITY	0.04	3.2 (1.0-12.8)
CRANIAL CRUCIATE LIGAMENT INJURY	< 0.001	4.8 (2.1-12.0)
PATELLAR LUXATION	0.06	2.6 (0.9-8.3)
HIP DYSPLASIA	0.9	1.0 (0.4-3.0)
URINARY INCONTINENCE	0.5	1.3 (0.6-3.2)
DIABETES MELLITUS	0.3	1.5 (0.6-3.9)
CHRONIC KIDNEY DISEASE	0.6	1.3 (0.6-3.0)
ATOPIC DERMATITIS	< 0.001	3.2 (1.7-5.9)
IDIOPATHIC EPILEPSY / CLUSTER SEIZURES	0.6	1.3 (0.5-4.4)
UROLITHIASIS – CALCIUM OXALATE AND STRUVITE	0.07	2.9 (0.9-11.4)

Table 22. Impact* on health of male and female dogs after gonadectomy (used with permission; Root Kustritz MV. Use of an impact score to guide client decision-making about timing of spay-castration of dogs and cats. Clin Therio 2012;4:481-485)

DISORDER	FEMALE DOG	MALE DOG
Mammary neoplasia	+24	
Pyometra	+100	
Surgical complications	-20	-16
Osteosarcoma	-2	-2
Hemangiosarcoma	-2	-2
Transitional cell carcinoma	-7	-7
Prostate neoplasia		-3
Testicular neoplasia		+5
Urethral sphincter mechanism incompetence	-66	
Benign prostatic hypertrophy		+368
Rupture of the cranial cruciate ligament	-11	-11
Obesity	-14	-13

*Impact score is derived from incidence and severity of disease. Positive impact score = benefit from gonadectomy, negative impact score = detriment from gonadectomy