The Long-Term Health Effects of Spay and Castration for Dogs

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Abstract

Surgical sterilization of pet dogs and cats is a routine practice in the United States. An increasing research focus on the long-term effects of this management choice is emerging. Beneficial effects on behavior, increases in lifespan, and reduction of unwanted litters are major arguments in support of elective sterilization. Increased risks of obesity, urinary incontinence, neoplasia, and certain musculoskeletal diseases among sterilized dogs and cats raise concerns about this widespread practice. Current knowledge on the physiological and health effects of elective surgical sterilization in dogs and cats is summarized here.

Glossary of Abbreviations

BPH: Benign Prostatic Hypertrophy
CCLR: Cranial Cruciate Ligament Rupture
OHE: Ovariohysterectomy
OVE: Ovariectomy
TNR: Trap-Neuter-Release
USMI: Urethral Sphincter Mechanism Incompetence

Introduction

Models for life history evolution assume that investment in reproduction comes at the cost of survival.[1,2] In support of this assumption, numerous studies in both invertebrates and vertebrates have shown that reduced reproductive effort leads to longer lifespan.[3,4] Investigations that manipulate levels of reproduction in experimental animals typically evaluate survival, with fewer studies addressing other aspects of physiology or health; indeed, studies in nematodes, fruit flies and mice are poorly suited to evaluate pathology at the individual level.[5-8] Thus, the specific causes of mortality associated with reproductive capability or sterilization status have not been elucidated in these species.

Companion dogs and cats in the United States are often electively surgically sterilized by their owners,[9-11] and, thus, they represent large and accessible populations in which to assess diverse effects of reproductive effort. Additionally, these pets may be affected not only by their variable efforts toward reproduction but also by the very presence or absence of the reproductive tract and its hormones. A substantial impact on overall health could be anticipated by the removal of this endocrine axis; curiously, there has been little scientific interest in this feature of the companion animal population until recently.

Definitions

In the United States, the term "spay" nearly exclusively signifies ovariohysterectomy (OHE) of females, and the term "castration" refers to bilateral orchiectomy of males. The term "neuter" is typically primarily associated with males but can also include surgical interventions performed on females. The term "gonadectomy" can be applied to either sex. The perioperative and short-term risks associated with OHE and castration have been described and will not be addressed here.[12] When surgical complications such as retention of an ovarian remnant or cryptorchid testicle arise, the long-term consequences can include development of neoplasia in the retained gonad.[13,14] Neoplasia related to properly performed surgical sterilization is discussed in greater detail below.

Obvious direct medical benefits of surgical sterilization of female dogs and cats include avoidance of pyometra, metritis, unwanted pregnancy, and complications of pregnancy. Obvious direct medical benefits of gonadectomy of males include avoidance of unwanted siring of litters, and, in dogs, avoidance of benign prostatic hypertrophy (BPH), which is a direct consequence of chronic testosterone exposure. BPH is not reported in cats.[15]

For female dogs and cats, ongoing debate exists over the relative merits of OHE compared with ovariectomy (OVE), with some authors arguing that OVE is less-invasive and potentially less painful.[16,17] Regardless, OHE remains the technique preferentially taught in U.S. veterinary schools,[16] with limited recent advent of OVE as an option, and there are few studies that directly compare the two techniques. As most literature on long-term outcomes is retrospective, the majority of female animals studied have been sterilized by OHE. For purposes of this review, surgical sterilization, gonadectomy or the term "spay" in females will be interpreted to mean OHE, unless specifically stated otherwise.

Optimal Timing

Ongoing debate also exists over the optimal timing to perform surgical sterilization procedures. Development of mammary cancer (see later) has been convincingly linked to onset, and total number, of estrous cycles in females, and, thus, a reasonable recommendation can be made to perform OHE prior to the first heat, which occurs around 6 to 12 months of age for many dog breeds. Veterinarians have typically preferred to recommend surgical sterilization approximating the anticipated age of sexual

From the Purina Companion Animal Nutrition Summit: *Nutrition for Life*; Austin, TX; March 27-29, 2014.

maturity and have traditionally resisted suggestions to perform prepubertal surgical sterilization despite lack of evidence to justify this concern.[9,18,19] Four large studies — two in dogs and two in cats — have compared outcomes of prepubertal sterilization with traditional-age sterilization in animals adopted from humane organizations and surgically sterilized by clinics associated with the humane organizations.[20-23] It is important to note that none of these studies included a comparison group of animals left intact, so the only comparisons that can be made are related to the timing of sterilization and not sterilization as a risk factor itself.

In the first feline study,[20] owners of 38% of nearly 700 surgically sterilized cats adopted over two and half years responded to surveys a median of three years postoperatively. No differences in the number of health problems, types of health problems, number of behavior problems, or likelihood of surrender were found between cats spayed or castrated at a median of 9 weeks or 51 weeks of age. In the second feline study,[22] owners of 84% of over 1,800 adopted cats that had been surgically sterilized at 12 months of age or less responded to surveys a median of 3.9 years postoperatively. There were significant associations between age at neutering and development of human-directed aggression, urine spraying, abscesses, gingivitis, and asthma, meaning that cats neutered at younger ages had lower risks of these conditions than cats neutered later. Specifically, no association was found between age at neutering and development of obesity or feline lower urinary tract disease.

In the first canine study,[21] owners of 42% of over 600 surgically sterilized dogs adopted over two and a half years were available for surveys a median of four years postoperatively. Considering the number of health problems, types of health problems, number of behavior problems, and likelihood of surrender between dogs spayed or castrated at a median of 10 weeks or 52 weeks of age, the only identified difference was a higher risk of parvoviral gastroenteritis among the prepubertal gonadectomy cohort. This increased risk of parvovirosis in the prepubertal gonadectomy cohort may be confounded by the fact that parvovirosis is overall more prevalent in puppies than adult dogs. As the surgical sterilization event was typically the earliest age of contact with each studied dog, it is likely that medical records including the months of life where parvovirosis is most prevalent were not available for the dogs sterilized after those months of age.

In the second canine study,[23] owners of 88% of over 2,000 adopted dogs that had been surgically sterilized at 12 months of age or less responded to surveys a median of four and a half years postoperatively. There were significant *inverse* associations between age at sterilization and development of human-directed aggression, barking and growling, sexual behaviors, hip dysplasia, cystitis (in females), and urinary incontinence (in females), meaning that dogs neutered at younger ages had *higher* risks of these conditions than dogs neutered later. Behavioral effects (barking, growling and sexual behaviors) were categorized by owners as mild or serious in questionnaires. If "mild" cases were excluded, significance was lost, and no animals were reported to have been resurrendered to shelters because of these behavioral problems. Overall, 26% of studied dogs were overweight, but dogs sterilized younger had lower likelihood of overweight body condition than dogs neutered later in life. No association was found between age at the time of gonadectomy and 43 other specific medical and behavioral conditions studied.

Cumulatively, these studies suggest limited impact on the timing of surgical sterilization related to the general health of dogs and cats, with noteworthy exceptions in the categories of musculoskeletal and urinary tract problems. These specific conditions are discussed in more detail below.

Lifespan and Causes of Death

The author's recent study of canine mortality in veterinary teaching hospitals[24] revealed that sterilized dogs have a 19% increase in mean lifespan relative to intact dogs. This finding is consistent with most,[25-27] but not all,[28] prior literature. The latter study identified a beneficial effect of duration of intact status on the lifespans of a cohort of female Rottweilers. Several interesting explanations for this discrepant finding exist. In contrast to many prior studies, this cohort of female Rottweilers was able to be classified by precise age at the time of sterilization. It has been argued that the more common methodology of classifying dogs as "sterilized" or "intact" at the time of death without knowledge of when this sterilization event occurred misrepresents the beneficial effects of maintaining exposure to sex hormones for some duration of time prior to sterilization.[29]

As sterilization removes an entire organ system and its endocrine axis, clearly some information about lifetime physiologic experiences of an individual is lost when the timing of the sterilization experience is not known. As cited above, veterinarians report that they preferentially sterilize dogs and cats approximately at the age of sexual maturity, so when data on the timing of sterilization are absent, the assumption is that the majority of patients were sterilized at this reportedly preferred time. However, this is a testable hypothesis that has not yet been interrogated. Ongoing work by the author's collaborators, and other research groups, will document actual timing of surgical sterilization in large canine populations that are under prospective study for global features of health and lifespan.

Alternate explanations for the finding that this cohort of female Rottweilers derived longevity benefits from remaining intact for a period of time may result from some features of the Rottweiler breed or some features of the females in the particular lineages studied that were known to exhibit atypically long lifespans compared with the breed at large. Since cancer was a significant cause of death overall among these large-breed dogs and sterilization has repeatedly been shown to exacerbate this risk (see below), it also is possible that remaining intact helped these female Rottweilers avoid a cause of death that is particularly impactful for the breed.

Beyond lifespan itself, the domestic dog exhibits dramatic breed-based variation in terms of likely causes of death.[30] Lifespan is a composite variable of myriad causes of death and the consequences of sterilization may or may not influence all causes of death equally. The author's recent study of canine mortality in veterinary teaching hospitals revealed a striking effect of sterilization on cause of death. Sterilized dogs were dramatically less likely to die of infectious disease, trauma, vascular disease, and degenerative disease. In contrast, sterilized dogs died more commonly from neoplasia and immune-mediated disease. Effects of sterilization were seen both on common causes of death and more rare causes (e.g., vascular disease). These visible differences in causes of death for sterilized and intact dogs persisted, even among cohorts of dogs that died within limited age ranges.[24]

Impacts on Specific Areas of Development

Behavioral Effects

An excellent review article by Root Kustritz[15] provides a summary of the current literature regarding long-term effects of spay and castration on dogs and cats, including behavioral effects. Avoidance of undesirable behaviors associated with, or believed to be associated with, reproductive maturity is one of the more common reasons that owners request surgical sterilization of their pets. However, not all undesirable behaviors are associated with sexual behaviors, and not all are modified by surgical sterilization. Given the opportunity, intact male dogs are more likely than sterilized dogs to roam, fight with other male dogs and urine-mark, though the literature is conflicted about the likelihood of aggressive behaviors in intact versus spayed female dogs.[31-34] In male cats, castration reduces urine spraying, roaming, human-directed aggression, and mounting behaviors, and in female cats, sterilization reduces displays of competitive aggression.[35-37]

Growth and Musculoskeletal Development

Surgical sterilization of dogs and cats prior to sexual maturity causes delayed closure of growth plates; other than a slight increase in height, the significance on health of this delay in closure is unclear.[38-40] Development of hip dysplasia and anterior cruciate ligament injury have been compared between sterilized and intact dogs (see below), but the relationship of these conditions to bone growth and physeal closure is unclear.

Growth and development of urogenital organs also is affected by surgical sterilization. The penises of male dogs and cats sterilized prepubertally are smaller than those of intact males or males sterilized later in life.[39,41] The clinical significance, if any, of smaller penises in these patients is unclear. On the other hand, the clinical significance of small or recessed vulvas in female dogs could include increased likelihood of recurrent urinary tract infections and perivulvar dermatitis. However, the current literature is inconclusive regarding whether small or recessed vulvas are more prevalent in spayed than intact females or whether the timing of spay is associated with this anatomical finding.[39,42]

Weight Gain

Investigation into obesity in cats consistently identifies an association between sterilization and decreased metabolic rate resulting in increased body fat for both males and females.[43-47] Most, but not all, studies in dogs also identify a risk for obesity among sterilized individuals.[33,39,48-51] Interestingly, Lefebvre and others found that the timing of surgical sterilization (≤6 months of age, >6 months to ≤1 year of age, or >1 year to ≤5 years of age) did not impact the likelihood of a diagnosis of overweight or obese body condition. Furthermore, the overall risk of overweight or obese body condition in sterilized dogs compared with intact dogs was greatest in the two years following surgical sterilization, suggesting that targeted client education during that time may provide significant benefit.[51]

Activity Level and Training

The racing performances of spayed and intact female Greyhounds (excluding the period of 90 days after estrous in intact females, during which time racing performance has been shown to decline) were compared. No significant difference was found between racing performance in the two groups.[52] Meanwhile, only limited and breed-specific differences between intact and sterilized dogs were found in a separate study of owner-reported trainability.[53]

Cortisol Axis

In an interesting study of feral female cats in a trap-neuter-release (TNR) program, the effects of surgical spay on aggressive behavior and hair cortisol levels were assessed. Intact female cats displayed more instances of aggressive behavior surrounding delivered food sources and had higher levels of hair cortisol (suggesting higher cortisol concentrations over preceding weeks to months) compared with spayed females.[35] Ultimately, this study raises more questions than it answers because the cause-effect relationship, if any, between aggression and hair cortisol concentrations is not known and because chronically elevated cortisol itself is known to promote health risks such as changes in body fat composition, decreased immune function and decreased insulin activity.[54] The effect of surgical sterilization on baseline and stimulated cortisol concentrations on both dogs and cats in diverse settings warrants further investigation.

Impacts on Specific Diseases

Neoplasia

Many studies in dogs have examined the effects of neuter status on the diagnosis of neoplasia. However, in many of these studies, the relationship between sterilization and the risk of death due to a particular disease is confounded with age. Many diseases, such as cancer, in particular, increase in frequency with age.[30] If surgical sterilization increases life expectancy, then a higher occurrence of those late-acting diseases may be noted in sterilized dogs simply because they are more likely to reach the age at which such diseases become frequent. In the author's recent

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retrospective study of a large cohort of dogs presented to veterinary teaching hospitals, though sterilized dogs lived longer overall, neoplastic diagnoses remained more prevalent in sterilized versus intact dogs at the time of death, even after controlling for the effects of age at the time of death.[24]

Cancers of specific organ systems and/or specific breeds have been studied more closely in dogs, and surgically sterilized dogs have been shown to be overrepresented compared with intact dogs for anal gland carcinoma, prostate cancer, osteosarcoma, hemangiosarcoma, and mast cell tumors.[55-60] Specifically for osteosarcoma, the study of long-lived female Rottweilers identified an inverse relationship between months of age at the time of gonadectomy and risk of development of osteosarcoma, that is, the longer these dogs remained intact, the lower their risk of osteosarcoma.[56]

A large study of Golden Retrievers stratified by age at sterilization (<12 months of age or ≥12 months of age) compared with intact dogs evaluated several specific cancer diagnoses. For lymphoma, early-neutered males had greater risk than late-neutered or intact males, though sterilization did not appear to affect risk among females. Conversely, late-neutered female Golden Retrievers had the greatest risk of hemangiosarcoma compared with early-neutered or intact females, and sterilization did not affect the risk in males. Mast cell tumor also occurred more frequently in sterilized than intact females, with no difference between sterilized and intact males. Osteosarcoma did not occur frequently enough in the population to be analyzed.[61]

In cats, fewer large surveys of neoplasia among sterilized versus intact animals have been performed, and/or a predilection for sterilized versus intact animals cannot be determined for rare tumors.[62-66] In both species, mammary cancer remains a reliable exception to the pattern of increased risk of cancer among sterilized animals, as it is more prevalent among intact female dogs and cats.[67-69] Early work in dogs showed a protective effect of performing OHE prior to first the estrous, and an increasing risk of benign and malignant mammary cancer development associated with increasing number of estrous cycles experienced up to 2.5 years of age.[70] It was later shown that even among intact adult female dogs that had developed a benign mammary tumor, performing OHE at the time of tumor resection reduced the risk of subsequent tumor development by nearly 50% over the two and a half years following tumor resection compared with tumor-bearing female dogs that did not undergo OHE.[71]

Urethral Sphincter Mechanism Incompetence (USMI)

Urethral sphincter tone is mediated by sympathetic nervous innervation, and estrogen potentiates nervous action on this muscle group. Spayed female dogs are at higher risk for poor urethral tone than intact females, and the mechanism appears to involve not only decreased estrogen concentrations but also changes in follicle-stimulating hormone and luteinizing hormone concentrations.[23, 72-74] An effect of timing of spay has been suggested, with a decreased risk proposed for bitches spayed when greater than 3 months of age, but this conclusion is not uniformly accepted in the literature.[23,75,76] Additional risk factors include obesity (which may itself be related to surgical sterilization as discussed above), breed and size.[74,76-78] Interestingly, the syndrome of USMI is not described in cats.

Musculoskeletal Disease

A concern for the development of hip dysplasia in sterilized dogs has been investigated with varying results. In one study, prepubertally sterilized male and female dogs of diverse breeds were shown to have increased risk of development of hip dysplasia compared with dogs sterilized later, but no control group of intact dogs was available for comparison.[22] In a study of Boxers, sterilized male and female dogs had increased risk of hip dysplasia compared with intact dogs.[79] However, in a study of Golden Retrievers, sterilized male dogs had a greater risk of development of hip dysplasia than intact dogs with greatest risk in the early sterilized group, but no difference in risk was found between sterilized and intact female dogs.[61]

Risk of cranial cruciate ligament rupture (CCLR) between sterilized and intact dogs has also been investigated. No difference in risk was identified between prepubertally sterilized dogs of diverse breeds and dogs sterilized later, but no control group of intact dogs was available for comparison.[22] In another study of dogs of diverse breeds less than 2 years of age, the risk of CCLR was greater in sterilized than intact dogs of both sexes, but dogs with CCLR also had higher body condition scores than dogs without CCRL.[80] Another study of diverse breeds identified an increased risk in sterilized versus intact dogs, with no information about body condition.[81] A study of Golden Retrievers revealed the greatest risk of CCLR among males sterilized early, a lesser risk among those sterilized late, and the least risk among those left intact. Conversely, early-sterilized female Golden Retrievers also had the greatest risk of CCLR, and late-sterilized females were not at greater risk than females left intact.[61] It is unclear if these findings result from changes in stifle angulation due to prolonged growth, breed or sex-specific features, a tendency toward weight gain in sterilized dogs, or other factors.

Miscellaneous Diseases

No association between surgical sterilization and the diagnosis of idiopathic epilepsy could be found in a large cross-sectional study of Danish Labrador Retrievers.[82] One interesting study of spayed female cats assessed the immunologic impact of an estrogenic dose of the isoflavone, genistein. Although differences were found among genistein-treated, estradiol-treated and untreated control cats, a clear pattern of immunosuppression by either estrogenic compound was not identified. The authors highlight the variable influence on immune parameters caused by treatment with estrogen and estrogen-like compounds among diverse species.[83] Sterilized cats of both sexes have been shown to be at increased risk for development of diabetes mellitus.[84]

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Conclusions

Surgical sterilization of pet dogs and cats is commonly performed in North America for population control and for desirable effects on behavior. Increasing research interest has focused on the long-term medical effects of this common practice. It is logical to anticipate widespread impact on physiology from the removal of an endocrine organ system, and, indeed, there is growing evidence that sterilized dogs and cats have different risks of certain diseases than intact dogs and cats. These diseases for sterilized dogs include cancer overall, specific types of cancer, and hip dysplasia, though factors such as breed and the age at sterilization may play a role in these risks. For cats, sterilization increases risks of obesity and diabetes mellitus. Comparative longevity between intact and sterilized cats has not been thoroughly investigated; however, current research strongly supports the finding that sterilized dogs live longer overall than intact dogs. This finding of increased longevity against a background of specific disease risk points clearly to needed research; the lifespan-extending value of sterilization must be tailored to the risks experienced by each species, breed and sex, and the timing of sterilization may also need to be carefully selected within certain populations to minimize those risks.

References

1. Roff DA. *The Evolution of Life Histories: Theory and Analysis*. Chapman & Hall, New York, NY. 1992;535.

2. Stearns S. *The Evolution of Life Histories*. Oxford University Press, Oxford, UK. 1992.

3. Partridge L, Harvey P. Costs of Reproduction. *Nature*. 1985; 316:20.

4. Reznick D. Costs of Reproduction: An Evaluation of the Empirical Evidence. *Oikos*. 1985;44:257-267.

5. Flatt T. Survival Costs of Reproduction in Drosophila. *Exp Gerontol*. 2011(May);46(5):369-375. PubMed PMID:20970491. Epub 2010/10/26. eng.

6. Harshman LG, Zera AJ. The Cost of Reproduction: The Devil in the Details. *Trends Ecol Evol*. 2007(Feb);22(2):80-86. PubMed PMID:17056152. Epub 2006/10/24. eng.

7. Partridge L, Gems D, Withers DJ. Sex and Death: What is the Connection? *Cell*. 2005(Feb);120(4):461-472. PubMed PMID:WOS:000227271500004.

8. Penn DJ, Smith KR. Differential Fitness Costs of Reproduction Between the Sexes. Proc Natl Acad Sci (USA). 2007(Jan 9);104(2): 553-558. PubMed PMID: 17192400. Pubmed Central PMCID Pmc1766423. Epub 2006/12/29. eng.

9. Kustritz MV. Determining the Optimal Age for Gonadectomy of Dogs and Cats. *J Am Vet Med Assoc*. 2007(Dec 1);231(11): 1665-1675. PubMed PMID:18052800. Epub 2007/12/07. eng.

10. APPA National Pet Owners Survey 2011-2012. American Pet Products Association Inc. Greenwich, CT. 2011.

11. Trevejo R, Yang MY, Lund EM. Epidemiology of Surgical Castration of Dogs and Cats in the United States. *J Am Vet Med Assoc*. 2011(Apr);238(7):898-904. PubMed PMID:WOS: 000288721000018.

12. Tobias KM, Johnston SA. In: Veterinary Surgery: Small Animal. Elsevier-Saunders, St. Louis, MO. 2012;1:2332.

13. Ball RL, Birchard SJ, May LR, et al. Ovarian Remnant Syndrome in Dogs and Cats: 21 Cases (2000-2007). *J Am Vet Med Assoc*. 2010(Mar);236(5):548-553. PubMed PMID:WOS: 000274920700018.

14. Liao AT, Chu PY, Yeh LS, et al. A 12-Year Retrospective Study of Canine Testicular Tumors. *J Vet Med Sci*. 2009(Jul); 71(7):919-923. PubMed PMID:WOS:000268345100010.

15. Kustritz MVR. Effects of Surgical Sterilization on Canine and Feline Health and on Society. *Reprod Domest Anim*. 2012 (Aug);47:214-222. PubMed PMID:WOS:000306918700032.

16. DeTora M, McCarthy R. Ovariohysterectomy Versus Ovariectomy for Elective Sterilization of Female Dogs and Cats: Is Removal of the Uterus Necessary? *J Am Vet Med Assoc*. 2011(Dec);239(11):1409-1412. PubMed PMID:WOS: 000297279000008.

17. Van Goethem B, Schaefers-Okkens A, Kirpensteijn J. Making a Rational Choice Between Ovariectomy and Ovariohysterectomy in the Dog: A Discussion of the Benefits of Either Technique. *Vet Surg*. 2006(Feb);35(2):136-143. PubMed PMID:WOS: 000235220100005.

18. Diesel G, Brodbelt D, Laurence C. Survey of Veterinary Practice Policies and Opinions on Neutering Dogs. *Vet Rec*. 2010(Apr); 166(15):455-458. PubMed PMID:WOS:000277064900012.

19. Spain CV, Scarlett JM, Cully SM. When to Neuter Dogs and Cats: A Survey of New York State Veterinarians' Practices and Beliefs. *J Am An Hosp Assoc*. 2002(Sep-Oct);38(5):482-488. PubMed PMID:WOS:000177749600013.

20. Howe LM, Slater MR, Boothe HW, et al. Long-Term Outcome of Gonadectomy Performed at an Early Age or Traditional Age in Cats. *J Am Vet Med Assoc*. 2000 (Dec);217(11):1661-1665. PubMed PMID:WOS:000165459300017.

21. Howe LM, Slater MR, Boothe HW, et al. Long-Term Outcome of Gonadectomy Performed at an Early Age or Traditional Age in Dogs. *J Am Vet Med Assoc*. 2001(Jan);218(2):217-221. PubMed PMID:WOS:000166403200031.

22. Spain CV, Scarlett JM, Houpt KA. Long-Term Risks and Benefits of Early-Age Gonadectomy in Cats. *J Am Vet Med Assoc*. 2004(Feb);224(3):372-379. PubMed PMID:WOS: 000220139400019.

23. Spain CV, Scarlett JM, Houpt KA. Long-Term Risks and Benefits of Early-Age Gonadectomy in Dogs. *J Am Vet Med Assoc*. 2004(Feb);224(3):380-387. PubMed PMID:WOS: 000220139400020.

24. Hoffman JM, Creevy KE, Promislow DEL. Reproductive Capability Is Associated with Lifespan and Cause of Death in Companion Dogs. *PLoS One*. 2013(Apr);8(4). PubMed PMID: WOS:000317907200030.

25. Greer KA, Canterberry SC, Murphy KE. Statistical Analysis Regarding the Effects of Height and Weight on Life Span of the Domestic Dog. *Res Vet Sci*. 2007;82(2):208-214. PubMed PMID: WOS:000244921000011.

26. Kraft W. Geriatrics in Canine and Feline Internal Medicine. *Eur J Med Res*. 1998(Feb 21);3(1-2):31-41. PubMed PMID: 9512965. Epub 1998/03/26. eng.

27. Moore GE, Burkman KD, Carter MN, et al. Causes of Death or Reasons for Euthanasia in Military Working Dogs: 927 Cases (1993-1996). *J Am Vet Med Assoc*. 2001(Jul);219(2):209-214. PubMed PMID:WOS:000169768300018.

28. Waters DJ, Kengeri SS, Clever B, et al. Exploring Mechanisms of Sex Diferences in Longevity: Lifetime Ovary Exposure and Exceptional Longevity in Dogs. *Aging Cell*. 2009(Dec);8(6): 752-755. PubMed PMID: WOS:000271972600012.

29. Waters DJ, Kengeri SS, Maras AH, et al. Probing the Perils of Dichotomous Binning: How Categorizing Female Dogs as Spayed or Intact Can Misinform Our Assumptions about the Lifelong Health Consequences of Ovariohysterectomy. *Theriogenology*. 2011(Nov);76(8):1496-1500. PubMed PMID:WOS: 000295913900014.

30. Fleming JM, Creevy KE, Promislow DE. Mortality in North American Dogs from 1984 to 2004: An Investigation into Age-, Size- and Breed-Related Causes of Death. *J Vet Intern Med*. 2011(Mar-Apr);25(2):187-198. PubMed PMID:21352376. Epub 2011/03/01. eng.

31. Hopkins SG, Schubert TA, Hart BL. Castration of Adult Male Dogs: Effects on Roaming, Aggression, Urine Marking, and Mounting. *J Am Vet Med Assoc*. 1976(Jun)15;168(12):1108-1110. PubMed PMID:945256. Epub 1976/06/15. eng.

32. Neilson JC, Eckstein RA, Hart BL. Effects of Castration on Problem Behaviors in Male Dogs with Reference to Age and Duration of Behavior. *J Am Vet Med Assoc*. 1997(Jul);211(2):180. PubMed PMID:WOS:A1997XK06400024.

33. O'Farrell V, Peachey E. Behavioral Effects of Ovariohysterectomy on Bitches. *J Sm An Pract*. 1990(Dec);31(12):595-598. PubMed PMID:WOS:A1990EP68100002.

34. Wright JC, Nesselrote MS. Classification of Behavior Problems in Dogs — Distributions of Age, Breed, Sex and Reproductive Status. *Appl An Behav Sci*. 1987(Dec);19(1-2):169-178. PubMed PMID:WOS:A1987M591000018.

35. Finkler H, Terkel J. Cortisol Levels and Aggression in Neutered and Intact Free-Roaming Female Cats Living in Urban Social Groups. *Physiol Behav*. 2010(Mar);99(3):343-347. PubMed PMID:WOS:000274953900009.

36. Hart BL, Barrett RE. Effect of Castration on Fighting, Roaming and Urine Spraying in Adult Male Cats. *J Am Vet Med Assoc*. 1973;163(3):290-292. PubMed PMID:WOS: A1973Q339900021.

37. Hart BL, Eckstein RA. The Role of Gonadal Hormones in the Occurrence of Objectionable Behaviors in Dogs and Cats. *Appl Anim Behav Sci*. 1997(Apr);52(3-4):331-344. PubMed PMID:WOS:A1997XA61600013.

38. May C, Bennett D, Downham DY. Delayed Physeal Closure Associated with Castration in Cats. *J Sm An Pract*. 1991(Jul);32(7): 326-328. PubMed PMID:WOS:A1991FY21300002.

39. Salmeri KR, Bloomberg MS, Scruggs SL, et al. Gonadectomy in Immature Dogs — Effects on Skeletal, Physical and Behavioral Development. *J Am Vet Med Assoc*. 1991(Apr);198(7):1193-1203. PubMed PMID:WOS:A1991FD43700019.

40. Shen V, Dempster DW, Birchman R, et al. Lack of Changes in Histomorphometric, Bone Mass and Biochemical Parameters in Ovariohysterectomized Dogs. *Bone*. 1992(Jul-Aug);13(4):311-316. PubMed PMID:WOS:A1992JG23400004.

41. Root MV, Johnston SD, Johnston GR, et al. The Effect of Prepuberal and Postpuberal Gonadectomy on Penile Extrusion and Urethral Diameter in the Domestic Cat. V*et Radiol Ultrasound*. 1996(Sep-Oct);37(5):363-366. PubMed PMID:WOS: A1996VL16100008.

From the Purina Companion Animal Nutrition Summit: *Nutrition for Life*; Austin, TX; March 27-29, 2014.

42. Hammel SP, Bjorling DE. Results of Vulvoplasty for Treatment of Recessed Vulva in Dogs. *J Am An Hosp Assoc*. 2002(Jan-Feb); 38(1):79-83. PubMed PMID:11804321. Epub 2002/01/24. eng.

43. Fettman MJ, Stanton CA, Banks LL, et al. Effects of Neutering on Body Weight, Metabolic Rate and Glucose Tolerance of Domestic Cats. *Res Vet Sci*. 1997(Mar-Apr);62(2):131-136. PubMed PMID:WOS:A1997XJ54300009.

44. Kanchuk ML, Backus RC, Calvert CC, et al. Neutering Induces Changes in Food Intake, Body Weight, Plasma Insulin and Leptin Concentrations in Normal and Lipoprotein Lipase-Deficient Male Cats. *J Nutr*. 2002(Jun);132(6):1730S-1732S. PubMed PMID:WOS:000176186400044.

45. Root MV, Johnston SD, Olson PN. Effect of Prepubertal and Postpuberal Gonadectomy on Heat Production Measured by Indirect Calorimetry in Male and Female Domestic Cats. *Am J Vet Res*. 1996(Mar);57(3):371-374. PubMed PMID:WOS: A1996TX19100024.

46. Harper EJ, Stack DM, Watson TD, et al. Effects of Feeding Regimens on Body Weight, Composition and Condition Score in Cats Following Ovariohysterectomy. *J Sm An Pract*. 2001(Sept); 42(9):433-438. PubMed PMID:11570385. Epub 2001/09/26. eng.

47. Nguyen PG, Dumon HJ, Siliart BS, et al. Effects of Dietary Fat and Energy on Body Weight and Composition after Gonadectomy in Cats. *Am J Vet Res*. 2004(Dec);65(12):1708-1713. PubMed PMID:WOS:000225336600019.

48. Colliard L, Ancel J, Benet JJ, et al. Risk Factors for Obesity in Dogs in France. *J Nutr*. 2006(Jul);136(7):1951S-1954S. PubMed PMID:WOS:000238753200007.

49. Crane SW. Occurrence and Management of Obesity in Companion Animals. *J Sm An Pract*. 1991(Jun);32(6):275-282. PubMed PMID:WOS:A1991FT17200003.

50. Jeusette I, Daminet S, Nguyen P, et al. Effect of Ovariectomy and *Ad Libitum* Feeding on Body Composition, Thyroid Status, Ghrelin and Leptin Plasma Concentrations in Female Dogs. *J An Physiol An Nutr*. 2006(Feb);90(1-2):12-18. PubMed PMID:WOS: 000234671200002.

51. Lefebvre SL, Yang MY, Wang MS, et al. Effect of Age at Gonadectomy on the Probability of Dogs Becoming Overweight. *J Am Vet Med Assoc*. 2013(Jul);243(2):236-243. PubMed PMID:WOS:000321685000021.

52. Payne RM. The Effect of Spaying on the Racing Performance of Female Greyhounds. *Vet J*. 2013(Nov);198(2):37237-5. PubMed PMID:WOS:000328870200015.

53. Serpell JA, Hsu YY. Effects of Breed, Sex and Neuter Status on Trainability in Dogs. *Anthrozoos*. 2005;18(3):196-207. PubMed PMID:WOS:000235432800002.

54. Ettinger SJ, Feldman EC. Textbook of Veterinary Internal Medicine: Diseases of the Dog and Cat. Elsevier-Saunders, St. Louis, MO. 2010;7.

55. Bryan JN, Keeler MR, Henry CJ, et al. A Population Study of Neutering Status as a Risk Factor for Canine Prostate Cancer. *Prostate*. 2007(Aug 1);67(11):1174-1181. PubMed PMID:17516571. Epub 2007/05/23. eng.

56. Cooley DM, Beranek BC, Schlittler DL, et al. Endogenous Gonadal Hormone Exposure and Bone Sarcoma Risk. *Cancer Epidemiol Biomarkers Prev*. 2002(Nov);11(11):1434-1440. PubMed PMID:WOS:000179270300021.

57. Polton GA, Mowat V, Lee HC, et al. Breed, Gender and Neutering Status of British Dogs with Anal Sac Gland Carcinoma. *Vet Comp Oncol*. 2006(Sep);4(3):125-131. PubMed PMID: 19754809. Epub 2006/09/01. eng.

58. Ru G, Terracini B, Glickman LT. Host-Related Risk Factors for Canine Osteosarcoma. *Vet J*. 1998(Jul);156(1):31-39. PubMed PMID:ISI:000074890700007.

59. Teske E, Naan EC, Van Dijk EM, et al. Canine Prostate Carcinoma: Epidemiological Evidence of an Increased Risk in Castrated Dogs. *Mol Cell Endocrinol*. 2002(Nov);197(1-2): 251-255. PubMed PMID ISI:000179524400031.

60. Ware WA, Hopper DL. Cardiac Tumors in Dogs: 1982-1995. *J Vet Intern Med*. 1999(Mar-Apr);13(2):95-103. PubMed PMID: 10225598. Epub 1999/05/04. eng.

61. Torres de la Riva G, Hart BL, Farver TB, et al. Neutering Dogs: Effects on Joint Disorders and Cancers in Golden Retrievers. *PLoS One*. 2013;8(2):e55937. PubMed PMID:23418479. Pubmed Central PMCID: Pmc3572183. Epub 2013/02/19. eng.

62. Caney SMA, Holt PE, Day MJ, et al. Prostatic Carcinoma in Two Cats. *J Sm An Pract*. 1998(Mar);39(3):140-143. PubMed PMID:WOS:000072624400007.

63. LeRoy BE, Lech ME. Prostatic Carcinoma Causing Urethral Obstruction and Obstipation in a Cat. *J Feline Med Surg*. 2004(Dec); 6(6):397-400. PubMed PMID:WOS:000225410100008.

64. Rissetto K, Villamil JA, Selting KA, et al. Recent Trends in Feline Intestinal Neoplasia: An Epidemiologic Study of 1,129 Cases in the Veterinary Medical Database from 1964 to 2004. *J Am An Hosp Assoc*. 2011(Jan-Feb);47(1):28-36. PubMed PMID:WOS: 000285685800006.

From the Purina Companion Animal Nutrition Summit: *Nutrition for Life*; Austin, TX; March 27-29, 2014.

65. Sonnenschein B, Dickomeit MJ, Bali MS. Late-Onset Fracture-Associated Osteosarcoma in a Cat. *Vet Comp Orthop Traumatol*. 2012;25(5):418-420. PubMed PMID:WOS:000309252400011.

66. Yamagami T, Nomura K, Fujita M, et al. Pulmonary Intravascular Hemangiosarcoma in a Cat. *J Vet Med Sci*. 2006(Jul);68(7): 731-733. PubMed PMID:WOS:000239608000014.

67. Dorn CR, Taylor DON, Schneide.R, et al. Survey of Animal Neoplasms in Alameda and Contra Costa Counties, California. II. Cancer Morbidity in Dogs and Cats from Alameda County. *J Natl Cancer Inst*. 1968;40(2):307-318. PubMed PMID: WOS: A1968A685000011.

68. Philibert JC, Snyder PW, Glickman N, et al. Influence of Host Factors on Survival in Dogs with Malignant Mammary Gland Tumors. *J Vet Intern Med*. 2003(Jan-Feb);17(1):102-106. PubMed PMID:ISI:000180379900014.

69. Sorenmo KU, Shofer FS, Goldschmidt MH. Effect of Spaying and Timing of Spaying on Survival of Dogs with Mammary Carcinoma. *J Vet Intern Med*. 2000(May-Jun);14(3):266-270. PubMed PMID:WOS:000086984400006.

70. Schneider R, Dorn CR, Taylor DON. Factors Influencing Canine Mammary Cancer Development and Postsurgical Survival. *J Natl Cancer Inst*. 1969;43(6):1249. PubMed PMID:ISI: A1969E984300006.

71. Kristiansen VM, Nodtvedt A, Breen AM, et al. Effect of Ovariohysterectomy at the Time of Tumor Removal in Dogs with Benign Mammary Tumors and Hyperplastic Lesions: A Randomized Controlled Clinical Trial. *J Vet Intern Med*. 2013(Jul); 27(4):935-942. PubMed PMID:WOS:000321765800026.

72. Gregory SP, Holt PE, Parkinson TJ, et al. Vaginal Position and Length in the Bitch: Relationship to Spaying and Urinary Incontinence. *J Sm An Pract*. 1999(Apr);40(4):180-184. PubMed PMID:WOS:000079894000008.

73. Gregory SP, Parkinson TJ, Holt PE. Urethral Conformation and Position in Relation to Urinary-Incontinence in the Bitch. *Vet Rec*. 1992(Aug);131(8):167-170. PubMed PMID:WOS: A1992JL03900003.

74. Reichler IM, Hung E, Jochle W, et al. FSH and LH Plasma Levels in Bitches with Differences in Risk for Urinary Incontinence. *Theriogenology*. 2005(May);63(8):2164-2180. PubMed PMID:WOS:000228714300008.

75. Beauvais W, Cardwell JM, Brodbelt DC. The Effect of Neutering on the Risk of Urinary Incontinence in Bitches: A Systematic Review. *J Sm An Pract*. 2012(Apr);53(4):198-204. PubMed PMID:WOS:000302943500002.

76. Thrusfield MV, Holt PE, Muirhead RH. Acquired Urinary Incontinence in Bitches: Its Incidence and Relationship to Neutering Practices. *J Sm An Pract*. 1998(Dec);39(12):559-566. PubMed PMID:9888109. Epub 1999/01/15. eng.

77. Angioletti A, De Francesco I, Vergottini M, et al. Urinary Incontinence after Spaying in the Bitch: Incidence and Oestrogen Therapy. *Vet Res Commun*. 2004(Aug);28(Suppl 1):153-155. PubMed PMID:15372945. Epub 2004/09/18. eng.

78. Ponglowhapan S, Khalid M, Church D. Canine Urinary Incontinence Post-Neutering: A Review of Associated Factors, Pathophysiology and Treatment Options. *Thai J Vet Med*. 2012 (Sept); 42(3):259-265. PubMed PMID:WOS:000310926200002.

79. van Hagen MAE, Ducro BJ, van den Broek J, et al. Incidence, Risk Factors and Heritability Estimates of Hind Limb Lameness Caused by Hip Dysplasia in a Birth Cohort of Boxers. *Am J Vet Res*. 2005 (eb);66(2):307-312. PubMed PMID: WOS:000226922600019.

80. Duval JM, Budsberg SC, Flo GL, et al. Breed, Sex and Body Weight as Risk Factors for Rupture of the Cranial Cruciate Ligament in Young Dogs. *J Am Vet Med Assoc*. 1999(Sep);215(6): 811-814. PubMed PMID:WOS:000082471400014.

81. Slauterbeck JR, Pankratz K, Xu KT, et al. Canine Ovariohysterectomy and Orchiectomy Increases the Prevalence of ACL Injury. *Clin Orthop*. 2004(Dec)(429):301-305. PubMed PMID:WOS:000225549900045.

82. Berendt M, Gredal H, Pedersen LG, et al. A Cross-Sectional Study of Epilepsy in Danish Labrador Retrievers: Prevalence and Selected Risk Factors. *J Vet Intern Med*. 2002(May-Jun); 16(3):262-268. PubMed PMID:WOS:000175601700009.

83. Cave NJ, Backus RC, Marks SL, et al. Modulation of Innate and Acquired Immunity by an Estrogenic Dose of Genistein in Gonadectomized Cats. *Vet Immunol Immunopathol*. 2007(May); 117(1-2):42-54. PubMed PMID:WOS:000246419400005.

84. Prahl A, Guptill L, Glickman NW, et al. Time Trends and Risk Factors for Diabetes Mellitus in Cats Presented to Veterinary Teaching Hospitals. *J Feline Med Surg*. 2007(Oct);9(5):351-8. PubMed PMID:WOS:000249948500001.

From the Purina Companion Animal Nutrition Summit: *Nutrition for Life*; Austin, TX; March 27-29, 2014.