Medical FAQs

Desexing Cancer Risk FAQ

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Phil Bergman ; Kurt Verkest ; Michael Lucroy ; Julius Liptak ; Marlene Hauck ;
Louis-Philippe de Lorimier ; Craig Clifford ; Suzanne Waltman

Introduction

Desexing dogs alters risk for subsequent cancers. It decreases risk of mammary tumors. But it might increase risk of other cancers. Confused? Read on…

Clinical Use Information

What is the lifetime risk of mammary gland neoplasia in dogs that are spayed at different points in their reproductive life?

The basic numbers appear to be that if spayed before the first heat, the risk of mammary gland tumors is 0.5% (1 in 200 dogs). If spayed between the first and second heat, the risk is closer to 8%. If spayed after the second heat the risk increases to >20%.

These figures are based on various papers, which have been interpreted in various ways. The first study to look at the incidence of mammary gland tumors was published in 1969 (Schneider *et al* 1969). This case-control study observed the tumor frequencies listed above (dogs spayed after the second heat had frequencies of 26%). Furthermore, the authors observed that dogs spayed after the second heat but younger than 2.5 years of age had a lower risk than those spayed after 2.5 years of age. Subsequent investigators confirmed this observation (Sonnenschein *et al* 1991). These investigators calculated odds ratios and found that spaying before a year of age (so, mostly before a second heat) had odds ratios of 0.01 (compared to cancer controls and non-cancer controls). Spaying between 1 and 2.5 years of age had odds ratios of 0.1 (compared to the various control groups).

Spaying after 2.5 years of age was not considered protective, although one investigator observed a benefit even in older dogs (Misdorp 1988).

Priester (1979) found a 3-fold reduction in risk of developing a malignant mammary tumor in spayed dogs.

Vascellari and colleagues (2016) examined mammary tumor incidence rates in a region of Italy, where most dogs are not desexed. They found that 74% of mammary tumors occurred in intact dogs. However, they did not examine the age at spaying.

Gruntzig and colleagues (2016) also examined cancer risk with spaying. They found that spayed dogs had an odds ratio of 0.4-0.5 compared to intact female dogs, indicating a protective effect.

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At what age does this risk usually express itself?

Several studies then examined the age of onset of mammary tumors – mostly in colony Beagles (research dogs) that were left intact or spayed after 4 years of age (Taylor *et al* 1976, Moulton *et al* 1986). In these studies, malignant tumors began to increase in incidence in dogs >8 years of age (in the later study, tumors were first detected at about 10 years of age). In a more recent study, incidence increased dramatically after 8 years of age (Vascellari *et al* 2016). Egenvall and colleagues (2005) examined incidence rates in Sweden, based on insurance claims for mammary tumors, and found that claims increased from 1% at 6 years, to 6% at 8 years and 13% at 10 years (of all claims filed for all female dogs, regardless of reason). Moe (2001) examined incidence in Norway and found that mean age of diagnosis in most dogs was 9 years.

Therefore, studies that examine incidence rates in dogs substantially younger than this will likely under-report the true incidence.

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What about the series of studies from UC Davis that examined cancer risk in Golden Retrievers? Don't they argue against a protective effect of spaying?

Three studies from investigators at UC Davis gained "notoriety" in the 20-teens (Torres de la Riva *et al* 2013, Hart *et al* 2014 and Kent *et al* 2018). Many breeders and other people interpreted these studies to mean that desexing increased the risk of cancer in this breed (and maybe others). However, there are several problems with these studies. The study by Hart *et al* examined the frequencies of mammary tumor diagnosis in Golden Retrievers and Labrador Retrievers that were either spayed or intact. However, this study considered only younger dogs. Given the risk of mammary carcinoma begins to increase at 8 years of age, the authors essentially examined the wrong age group. With low incidence of mammary neoplasia prior to 8 years of age, differences between groups are much more likely to be affected by chance. Additionally, the number of dogs in each of the groups was relatively small – this could falsely exaggerate a non-existent effect (a false positive) or mask a true effect (false negative).

The study by Torres de la Riva and colleagues and the study by Hart and colleagues also examined incidence of several other cancers in Golden retrievers. They both suggested that early desexing increased the incidence of cancers such as hemangiosarcoma, lymphoma and mast cell tumors. The authors suggested that there was a "breed" effect of early desexing – something that is difficult to reconcile physiologically. Second, the tumors examined are relatively rare in Labrador Retrievers, but quite common in Golden Retrievers. This was supported by the presented data. Therefore, a desexing effect, even if present, could not have been detected in Labradors. Thirdly, cancer tends to occur in older animals. Unless all the dogs were given the same opportunity to develop cancer (i.e., were of similar age at the time of evaluation), it is impossible to determine whether desexing has an effect. Namely, if desexed animals were substantially older than intact animals, one might reasonably expect the desexed animals to have a greater incidence of various cancers.

This was borne out by a third study from the same institution (but different investigators) (Kent *et al* 2018). They found that age, but not sexual status, determined the probability of Golden Retrievers dying from cancer.

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What about other neoplasia? Does desexing change the risk for other cancers?

Several studies have examined cancer risk of various non-reproductive cancers after desexing.

Osteosarcoma

In 1998, Ru and colleagues published a case-control study of 7000 dogs (3062 with osteosarcoma) and found that desexing doubled the risk of developing osteosarcoma. Cooley and colleagues (2002) confirmed these findings. They looked at lifetime risk of osteosarcoma in 683 Rottweilers. They found that dogs (both male and female) desexed before a year of age had a 4-fold risk of developing osteosarcoma than intact dogs (27/83 vs 15/184). Overall, 12% of Rottweilers developed osteosarcomas, with risk decreasing by 1% for every month that the dog was intact. Gruntzig and colleagues (2016) also found a 50% increased risk of osteosarcoma in desexed males but not females, and, independently, in Rottweilers.

Mast Cell Tumors

Shoop and colleagues (2015) examined a database of 168,000 dogs and identified 453 mast cell tumors (prevalence of 0.3%). They found that desexed dogs had approximately 10% of the risk of intact dogs for developing mast cell tumors. Strangely enough, they also found that being insured had 5 times of the risk as uninsured dogs! Gruntzig and colleagues (2016) also found a 10-15% increased risk of osteosarcoma in desexed dogs.

Lymphoma

Villamil and colleagues (2009) examined the effect of desexing on the risk of developing lymphoma. They found that intact females had approximately 40% lower risk of developing lymphoma than spayed females. Intact males had higher risk than neutered males.

Zink and colleagues (2014) examined cancer risk in Viszlas. They found increased risk of lymphoma in desexed dogs.

Gruntzig and colleagues (2016) also found a 10-15% increased risk of lymphoma in desexed dogs.

Urogenital Tumors

Bryan and colleagues (2007) examined the risk of bladder and prostate neoplasia in male dogs. They observed that neutering increased the risk of prostatic transitional cell carcinoma, urinary bladder transitional cell carcinoma, prostatic adenocarcinoma, and all prostatic neoplasia 2-8 times above the risk in intact males. The risk for prostatic adenocarcinoma was increased in neutered dogs, but was the tumor type for which this increase in risk was smallest.

Various cancers

Gruntzig and colleagues (2016) examined the Swiss Canine Cancer Registry and concluded that desexed dogs had higher probability of developing various tumors than intact dogs, including hemangiosarcoma, and endocrine tumors. However, with most tumors, this increased risk was relatively small (less than 2x greater).

Robinson and colleagues (2020) found that desexing of male and female dogs increased the risk of developing hemangiosarcoma by 15-70% (depending on the location of the tumor and sex). The risk was increased for hemangiosarcoma of all locations, and for hemangiosarcoma of the spleen. The difference in risk was highest for spayed females compared to intact females. An increased risk was still present for neutered males compared to intact males, but the difference was smaller than for females. However, the authors did not control for breed, which they (and others) have identified as independent risk factors. In contrast to an earlier study (Ware and Hopper 1999), where desexed males and females had increased risk of cardiac hemangiosarcoma, neuter status did not affect risk of cardiac hemangiosarcoma in the 2020 study.

Study	Cases OR Risk factor present	Controls OR Risk factor absent	Study type	Breed	Results – How many of each group developed the tumor type? How did desexed vs intact animals fare?	OR	RR
Mammary gland tumor (MGT)							
Schneider 1969	93	87	Case-control	Various	24/88 (27%) spayed and 69/92 (75%) intact	0.13 (0.1-0.2)	0.37 (0.2-
Priester 1979	1045	unknown	Case-control	Various			0.3
Perez Alenza 1998	102	0	Case series	Various	91 intact, 11 spayed		

Sonnenschein	150	131	Case-control	Various	94/146 (64%) intact and 56/135 (41%) spayed	0.39 (0.2-0.6)	0.6 (0.5-
Vascellari 2016	2359 cases	0	Cross-sectional	Various	694/2359 spayed		
Gruntzig 2016	46,387	unknown		Various		0.4	
Osteosarcoma							
Cooley 2002	484	209	Retrospective Cohort	Rottweiler	13% overall lifetime risk; 10% in intact dogs; HR for neutered = 0.98. 27/83 (32%) desexed at <1 year.		
Gruntzig 2016	46,387 cases	unknown	Case-control	Various		1.5	
Ru 1998	3051	3892	Case-control	Various	1362/3835 (36%) intact vs 1689/3108 (54%) desexed	2.2 (1.9-2.4)	1.5 (1.45 1.61
Lymphoma (LSA)							

	187 desexed				14/122 (11%) males neutered at 6-12 months, but not <6		

Hart 2014	<6 mo; 204 desexed 6-12 mo; 215 desexed >1 yr	392	Retrospective Cohort	Labrador retrievers & Golden retrievers	but not <6 months (6/89; 7%); 9/82 (11%) females spayed at 6-12 months, but not <6 months (4/98; 4%)		
Torres de la Riva 2013	345	267	Retrospective Cohort	Golden retrievers	27/345 early desexing vs 7/267 intact; 95% CI between 2 proportions = 0.013 to 0.09 probably different; OR = 3.2, RR = 3.0	3.2	3.0
Villamil 2009	14573	1,157,342	Case-control	Various	8432/429253 (2%) in desexed vs 6141/742662 (0.8%) in intact		
Zink 2014	362 desexed <6 mo; 298 desexed 6-12 mo; 771 desexed >1yr	1074	Retrospective cohort	Vizslas	8/362 (2%) desexed <6mths; 7/298 (2%) desexed 6-12mths; 25/771 (3%) desexed >1yr; vs 7/1074 (0.5%) intact		
Gruntzig 2016	46,387	Unknown		Various		1.15-1.3	
Mast cell tumor (MCT)							
	362 desexed <6 mo;				25/362 (7%) desexed <6mths; 15/298 (5%) desexed 6-		

Zink 2014	298 desexed 6-12 mo; 771 desexed >1yr	1074	Retrospective cohort	Vizslas	desexed 6-12mths; 81/771 (10%) desexed >1yr; vs 27/1074 (2%) intact		
Torres de la Riva 2013	349	264	Retrospective Cohort	Golden retrievers	7/349 (2%) early desexing vs 4/264 (1.5%) intact	1.3 (0.4-4.4)	
Hart 2014	391 desexed <1 year	392	Retrospective Cohort	Labrador retrievers & Golden retrievers	No obvious effect of desexing		
Gruntzig 2016	46,387	unknown	Case-control			1.15-1.2	
Shoop 2015	130 intact; 323 desexed	102 intact; 820 desexed	Retrospective case-control	Various	No differences between sexes. Desexing had 90% reduction in odds of developing MCT	0.1 (0.1-0.2)	
Hemangiosarcoma (HSA)							

	362 desexed <6 mo;				7/362 (2%) desexed <6mths; 8/298 (2.5%) desexed 6-	1.5 (0.6-3.8)	

Zink 2014	298 desexed 6-12 mo; 771 desexed >1yr	1074	Retrospective cohort	Viszlas	desexed 6-12mths; 44/771 (5.7%) desexed >1yr; vs 14/1074 (1.3%) intact	2.0 (0.9-5.1) 4.6 (2.5-8.5)	
Torres de la Riva 2013	347	265	Retrospective Cohort	Golden retrievers	8/347 (2.3%) early desexing vs 6/265 (2.2%) intact	1.0	1.0
Hart 2014	391 desexed <1 year	392	Retrospective cohort	Labrador retrievers & Golden retrievers	No obvious effect of desexing		
Robinson 2020	426 intact females; 2190 desexed females; 1786 intact males; 1334 desexed males	756 intact females; 2258 desexed females; 1636 intact males; 1072 desexed males	Retrospective case-control	Various		1.72 for females; 1.14 for males	
Ware 1999	633 dogs	No data provided	Retrospective case-control	Various	Data not provided		5.33 fema 1.55 male
Urogenital							

							Urin TCC 3.56 Pros

Bryan 2007	832 intact; 1387 neutered;	No data provided	Retrospective case-control	Various	Data not provided	1.5 (0.6-3.8) 2.0 (0.9-5.1) 4.6 (2.5-8.5)	Pros TCC 8.00 All pros tumc 2.84 Pros CA = 3.86 Pros ACA 2.12

What about the 2020 study by Hart and others making breed-specific suggestions for spay/neuter age? Shouldn't we be relying on that as we make desexing decisions?

This study (Hart *et al* 2020) purports to recommend specific age ranges for desexing based on breed risk of different problems. Joint disorders, several cancers (lymphoma, mast cell tumor, hemangiosarcoma, and osteosarcoma), and urinary incontinence are evaluated as potential reasons to desex later, or not at all. Mammary neoplasia and pyometra are evaluated as potential reasons to desex earlier.

This article is problematic for several reasons. Let's break them down a bit for readers.

1. The authors examined each of the 35 breeds independently. Most breeds had small sample sizes, and very small numbers of events (cancers, etc). For each breed, the authors compared these proportions in a pair-wise fashion (based on the description in the Methods section) – therefore, they made at least 10 comparisons PER BREED, PER SEX for cancer-related findings alone, each at a nominal P value of 0.05. This means that **the authors made some 700 individual comparisons**! **The probability of finding differences in at least one such comparison by chance is 100%** - indeed, one would expect 10-20 "significant findings" based on chance alone! In assessing cancer risk by individual breed, sex, and desexing age categories, roughly a dozen "significant" findings were identified in this study. This fits well within the number we would expect statistically, based solely on chance.

2. The analysis proposed and used by the authors was a "**time-to-event" analysis**. However, the authors presented no "time to any event". Additionally, the type of data they acquired would not typically lend itself to a "time to event" analysis. Instead, the appropriate study design would be a retrospective case-control study, with dogs either developing a condition of interest or not, and then examining whether the "risk factor of interest" (i.e. early desexing) segregated more with the outcome (cancer, joint disease, incontinence etc). Furthermore, the authors claimed that "where the Kaplan-Meier test showed significance at the $P<0.05$ level, both the log-rank and Wilcoxon tests were used for further analysis". This raises concerns, because the Kaplan Meier graph is not a statistical test, but simply a method of representing time-to-event data that accommodates censoring. Such statements immediately raise suspicions that the authors do not actually understand the statistical testing being performed. Furthermore, "time to event"

analysis would allow investigators to examine whether cancers occurred “sooner” or “later” as a result of the intervention, but not whether they occurred at all or not (which is how the data were presented).

3. The authors state that they used a “Wilcoxon test” – but **do not state what they were comparing with this test**. Presumably, the authors are referring to a Rank Sum test, but such a test does not compare proportions. If, somehow, the authors were comparing “time to development of cancer”, and all the cases were accounted for (none lost to follow-up or censored), then a simple rank sum test could be used instead of a log rank test. The statement that “if the Wilcoxon test did not show significance, but the log rank test did for cancers, the log rank test was reported.” It is hard to understand how these would differ in their outputs if no dogs were censored.

4. There is **no biological basis for grouping the cancers they grouped**. The authors grouped 4 cancer types (lymphoma, mast cell tumor, hemangiosarcoma, and osteosarcoma) to increase the case rates. However, there would be no basis for grouping these biologically. Mammary cancer was included in the study but was not grouped with the other 4 cancers; again, any biologic basis for this distinction is not well explained. Although the study purports to find that mammary cancer is not a major concern, no statistical analysis of mammary cancer was performed.

5. Almost **none of the breeds have sufficient numbers of cases** (or sufficiently robust proportions) to be able to be analyzed, or, if done via a Fisher’s Exact test (which would be the appropriate statistical test to compare proportions), demonstrate no differences. The number (and therefore proportion) of dogs with cancers in most breeds was in the low single digits (0 to 3). If one examines the confidence intervals for such small proportions, they almost invariably overlap. The findings for all but three or four breeds (Rottweilers, Boxers, Labradors and Golden Retrievers), where the case numbers were reasonably high, can be ignored.

6. In addition to dividing the breeds into many, very-small groups for analysis, **the categories for age of desexing do not make a lot of biologic sense**. “Early desexing” could logically mean up to approximate end of development, or onset of sexual maturity, or some variation of these. For example, we can take “1 year” as the cut-off for “end of development”. If we analyze the proportions between male dogs neutered before 1 year, and those that were not neutered at all, there is no difference in cancer risk across the entire study cohort (117 cases/1802 dogs neutered <1 year vs 277 cases/4181 unneutered males, P=0.8). For females neutered under 1 year of age, there is a higher proportion of cancer cases (as long as we ignore mammary cancer) compared to intact females (117 cases/2061 dogs spayed < 1 year vs 100 cases/2968 unspayed females, P=0.0002). Or we could define groups by age of desexing as “prepubertal” (e.g., <6 months) and “immediate postpubertal” (6-12 months), and then compare the early group(s) against groups desexed later, or to an intact control group. It’s not entirely clear why we are instead comparing a dog desexed at age 8 to an intact dog, or a dog desexed at age 1 to a dog desexed at age 2. The authors also seem to combine desexing ages somewhat differently for different breeds depending on which results in a “significant” finding. This strongly suggests “P-hacking”.

7. The **recommendations make no biological sense and are not supported by the authors’ own data**. For example, the authors suggest leaving male Doberman Pinschers intact and spaying females only after 2 years. However, 0/22 Dobermans neutered before 1 year of age developed cancer, and only 2/103 intact Dobermans developed cancer; similarly, 2/41 Dobermans spayed before 1 year of age developed cancer, and 1/51 intact female Dobermans developed cancer. How the authors came to the recommendations they did based on these data is unfathomable.

8. Dogs were **not necessarily given enough time to develop cancers**. The authors noted that the mean ages and age ranges for the dogs were quite low (4.5 to 5.5 years, with the oldest dog in the study being just over 7 years old). Given that cancers are a disease of ageing in most animals, it is likely that the results missed cancers in some animals, including animals left intact or desexed later in life.

Overall

A handful of the breeds studied did have statistically significant increases in the cancers of interest (LSA, MCT, HSA, OSA) based on age of spay and/or neuter, but in most cases these were based on very small numbers within each group. Because of the generally small group sizes and the sheer number of small groups evaluated, many of these "significant" findings may have occurred by chance. The authors make a point to suggest that small numbers could have kept otherwise insignificant findings from becoming significant, but do not discuss the possibility that small numbers lent significance to chance occurrences, which is equally likely. Groups are also combined differently within different breeds depending on which combination of desexing ages gives a significant finding. The paper recommends specific ages for desexing, even when the negative outcome occurred in very low numbers of dogs (<5; for example, 2 Cocker Spaniels with mast cell tumor).

Mammary neoplasia is recorded, but is not apparently taken into account in the desexing recommendations and no comparative statistics were performed to evaluate risk of this disease across groups. It is unclear why 4 unrelated cancers should be considered together but mammary cancer is considered separately. Findings mostly did not show a significant increase in any one of the grouped 4 cancers even when the increase in the total group was considered significant. In almost all cases, either the findings resulted in no specific age recommendation or desexing at a later age (or not at all) is recommended; in only one case (male Doberman Pinschers) was early desexing (age <1 year) specifically recommended, and in that case leaving the dog intact was considered an equal alternative. The possible early spaying of Shih Tzus was also presented as a reasonable, though lesser, alternative to delaying spay past age 2 years. In several cases, delaying desexing is recommended based on risks which were statistically insignificant, or based on nebulous factors such as "musculoskeletal development" in the absence of any increase in specific diseases. The study was funded in part by breeder groups, which may or may not be relevant to the ultimate findings.

But wasn't there another Hart 2020 study looking at mixed breed dogs by different weight classes?

Yes there was (Hart et al 2020b). This study did a similar analysis for mixed breed dogs weighing <10 kg, 10-19 kg, 20-29 kg, 30-39 kg, and 40+ kg. The numbers for each mixed-breed weight category were quite a bit larger than those seen for individual breeds in the 35-breed study. No significant increase was seen in the evaluated cancers (lymphoma, mast cell tumor hemangiosarcoma, osteosarcoma) with desexing at any age in any weight category.

Does desexing dogs increase or decrease overall survival?

While there is evidence (above) that desexing variably increases the risk of certain cancers in dogs, this needs to be weighed against the impact of desexing on overall survival. If cancer accounts for a large percentage of deaths, then desexing should result in increased all-cause mortality. However, if cancer accounts for a small proportion of "early" deaths, then the impact of desexing on all-cause mortality should be largely independent of the cancer effect.

Several studies have examined the impact of desexing on all-cause mortality. O'Neill and colleagues (2013), in a study of 2481 dogs with confirmed deaths that had lived at least 3 years, found that spayed females lived approximately 10 months longer than intact females; similarly, both neutered and intact males lived almost 6 months longer than intact females.

Hoffman and colleagues (PLOS 2013) found that neutering increased lifespan in males by 14%, and spaying increased lifespan by 26% in female dogs. While the data in this study were incorrectly analyzed and difficult to interpret (the authors presented mean age, rather than median), their study suggests an overall benefit of desexing on longevity.

A study of 2,000,000 dogs found that desexed male and female dogs had slightly longer median lifespans than intact dogs. Intact females had the shortest median survival (13.77 years), intact males had marginally shorter survival than neutered males (14.09 vs 14.15 years) and spayed females had the longest survivals (14.35 years) (Urfer *et al* 2019). These findings were further substantiated in a second study by the same authors (Urfer *et al* 2020). When they examined dogs that had lived at least 5 years, intact females lived a median of 14.9 years, intact males lived 15 years, neutered males lived 15.2 years, and spayed females lived 15.9 years.

More recently, researchers from UCDavis examined factors impacting life-span in Golden Retrievers presenting to, and undergoing necropsy examinations at a referral institution (Kent *et al* 2018). While such a population would be biased (because most, if not all, of these dogs presented because of disease concerns), the study examined records of 652 Golden Retrievers. Of these, 445 had a diagnosis of cancer, while 207 did not. Median lifespan for all dogs was 9.15 years. Somewhat surprisingly, those dying of non-neoplastic causes had median lifespans of 6.9 years, compared to 9.8 years for those dying of cancer. A greater proportion of spayed females died of cancer than intact females, although the study had relatively few intact females (58). Intact males lived a median of 8.7 years, compared to 9.4 years for neutered males, 5.9 years for intact females and 9.5 years for spayed females. These relative differences between genders persisted whether examining dogs dying from non-neoplastic causes or cancer – in other word, intact females had shorter lifespans than other genders, and spayed females lived the longest.

These data show that desexing increases survival in dogs, and the effect is greatest in females. Furthermore, the effect persists even when considering breeds that are highly susceptible to cancer (such as Golden Retrievers). While none of the studies examined the age at desexing (which has been proposed as a factor in cancer development), it would be reasonable to assume that most of the dogs in these studies would have been desexed at <1 year of age. Consequently, while associations with desexing and risk of cancer development exist, the overall survival of dogs increases with desexing. Therefore, arguments of "increased cancer risk with desexing" can be refuted with these data showing that, on average, dogs will live longer if they are desexed.

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