

# Murphy Foundation Study Exposes Need for Revisionist Thinking about Canine Mammary Cancer and Pyometra: Two Killers??

Mammary cancer and pyometra are widely recognized as important, ovary-driven health hazards of pet dogs. Early ovariohysterectomy (spay) can reduce the incidence (occurrence) of these two diseases. But, until now, an estimate of the extent to which the development of mammary cancer or pyometra adversely influences overall longevity was missing.

New research, funded in part by the Rottweiler Health Foundation, addresses this critical knowledge gap, showing that, after accounting for late age at diagnosis and competing mortality from other diseases, these two diseases do not adversely impact life expectancy.

Veterinary scientists at the Gerald P. Murphy Cancer Foundation's Center for Exceptional Longevity Studies have reported their results of the first-ever breed-specific, life course analysis of the impact of mammary cancer and pyometra on life expectancy and premature mortality in dogs. Their analysis shows that at no time points during the life course was the current or future diagnosis of mammary cancer or pyometra associated with shortened survival compared to females who never developed these conditions.

The peer-reviewed results first appeared in July 2017 in the prestigious *The Veterinary Journal* (formerly *The British Veterinary Journal*), the world's oldest veterinary journal ([click here for full-text manuscript](#)).

"I believe what the research means is that when it comes to thinking about the impact that interventions like early ovariohysterectomy have on overall longevity, we need to start thinking differently. We need to look beyond the incidence of particular diseases. We need to consider the physiological trade-offs that impact longevity," said David J. Waters, DVM, PhD, the veterinary researcher who led the study.

"Our motivation for conducting this research was the need for generating the very best information so we can make responsible decisions for our pets," Waters said. He added that the results on canine mammary cancer and pyometra were not altogether unexpected.

"A lack of longevity disadvantage is an expected result for late-onset diseases with less than 50% case fatality like mammary cancer or diseases with very low case fatality like pyometra," Waters said.

The results might catch veterinarians and pet owners by surprise because no one had studied the problem carefully before. Nobody had sought to untangle the implications of disease incidence versus the lethality of these diseases. But fresh insights are precisely what biomedical researchers are expected to uncover if they are open to new ways of thinking, escaping the boundaries of their previous training.

The research team's openness to re-thinking the relationship between two ovary-driven diseases and longevity in dogs was a logical outgrowth of their pioneering work on the biology of exceptional longevity. In a previous study of female Rottweilers who reached exceptional longevity — living at least 13 years, which is more than 30% longer than average for this breed — keeping ovaries longer was associated with a longevity advantage (Waters et al., Aging Cell 2009; [click here for full-text](#)). To determine whether this clue obtained from a group of Rottweilers with highly successful aging might be a biological signal operational in members of this breed who experienced more typical longevity, the researchers re-tested in this study the association between years of ovary exposure and longevity in 242 females that did not reach exceptional longevity (average age at death = 9.9 years). Females with longer ovary exposure ( $\geq 4.3$  years) had a statistically significant 17 months longevity advantage over females with shorter ovary exposure. And just as expected, females with longer ovary exposure were more likely to be diagnosed with mammary cancer or pyometra.

“Reconciling the notion that keeping ovaries longer increases the development of both mammary cancer and pyometra, but also promotes longevity might seem counterintuitive, even problematic. It is not. The concept of whole organism thinking predicts that any intervention — including the decision to remove or conserve ovaries — would be associated with biological trade-offs,” explained Waters, who serves as Director of the Center for Exceptional Longevity Studies at the Murphy Cancer Foundation.

The concept of *whole organism thinking* was introduced into the veterinary literature in a perspective paper written by Dr. Waters back in 2014 ([click here for full-text of that paper](#)).

#### IMPLICATIONS OF THE STUDY

For veterinarians and pet owners, what implications does the new work hold? The scientific investigation was prompted by the growing imperative to find and implement effective strategies to promote longevity in pets and people. With this context in mind, the authors of the research paper summarize their progress, stating that the study points to two important conclusions (quoted from manuscript).

“First, our results fail to provide evidence that either mammary cancer or pyometra have an adverse impact on overall longevity. These findings call into question the argument that elective ovariohysterectomy should be advocated as a longevity-promoting intervention on the basis of protecting against disease conditions that display late-onset, moderate case fatality risk (mammary cancer) or low case fatality risk (pyometra). It is hoped that these results, which challenge some prevailing beliefs, will stimulate new starting points for use by a freshly motivated field of investigators.”

“Second, and perhaps more importantly, this study points to the need for redirecting our emphasis away from a disease incidence-only approach and toward evaluating the impact of particular diseases in the context of competing causes of mortality and overall longevity. If our intent is to design and implement strategies that will promote healthy longevity, we will need to embrace the idea of trade-offs. This maturation toward whole organism thinking will provide a necessary corrective against the natural preoccupation of specialized investigators who find their own investigations focused on a particular disease. Focusing solely on the avoidance of a single disease, rather than engaging in a life course analysis of all-cause mortality that takes into account physiological trade-offs, will only hinder the sound selection of such strategies.”

The new findings call into question the argument that any strategy, such as elective ovariohysterectomy, implemented to reduce the incidence of mammary carcinoma and pyometra, will beneficially impact overall longevity. And as veterinarians and pet owners continue to seek solid health recommendations, the new study calls attention to the knowledge gaps that have plagued previous attempts at informed decision-making.

“It would be reasonable to assert that if a particular disease condition — such as mammary cancer or pyometra — adversely impacts longevity, then reducing the incidence of that disease might merit serious consideration as a core principle of a health strategy intended to optimize overall longevity,” said Waters. “However, it is possible that after one accounts for factors such as age at onset and competing causes of mortality, a diagnosis of mammary cancer or pyometra may not cut short life expectancy. Prior to our study, no such analysis of these trade-offs was available to guide informed decision-making.”

Waters explained further: “What was lacking were breed-specific analyses that compared the overall longevity of females that *ever* develop mammary cancer versus females who *never* develop the disease. Our work takes an important first step toward addressing this knowledge gap.”

Waters points to the years of dedicated work that led to the new discovery. He says the new results help to validate the Murphy Foundation’s Center for Exceptional Longevity Studies’ bold strategy of conducting the first systematic study of exceptional longevity in pet dogs. Launched a decade ago, this scientific initiative has generated an Exceptional Longevity Database of more than 350 elite dogs who have lived the equivalent to 100 years in humans. In addition to the database and an expanding repository of biological specimens, Waters travels across North America making first-hand observations, studying these dogs in their homes.

“Without the clues that we collected from exceptionally long-lived Rottweilers about the impact of ovaries on longevity, we would have never been asking this new set of questions,” Waters acknowledged. “Not only is our understanding of highly successful aging being strengthened, the current report shows that at least some of the clues obtained from Rottweilers with highly successful aging are translatable to members of the breed that exhibit typical longevity.”

Asked about the generalizability of the research results to other breeds, Waters commented: “Based upon our study results and results of other investigators reported in the scientific literature, canine mammary cancer is a late-onset disease with a case fatality risk of about 40% — which means that less than half of females that develop mammary cancer will die of their disease. Because these key disease characteristics (age at onset, likelihood of lethality) in our study population are so consistent with previous reports, we believe our work provides a perspective on the impact of mammary cancer on longevity that may have important implications for other canine populations, including other breeds.”

To the authors’ knowledge, this work provides the first life-long analysis of the impact of mammary cancer on longevity in female dogs. In their paper, the authors situate the new results within the context of a much larger study of mammary tumors in a population of more than 80,000 insured female dogs in Sweden published more than a decade ago. That study reported data on mammary

tumor incidence, survival after mammary tumor diagnosis, and proportion of deaths attributable to mammary tumors (i.e., proportionate mortality) in females from age 3 years up to 10 years.

In some critical aspects, the results of the two studies are remarkably congruent. For example, Swedish investigators reported that 93% of female Rottweilers were not affected by mammary tumors until after age 8. In the Murphy Foundation study, 96% of Rottweilers were free of a diagnosis of mammary carcinoma during the first 8 years of life. However, estimates of the impact of these mammary tumors on overall longevity were not obtainable in the Swedish study because more than 50% of females with mammary tumors were alive at 10 years of age, therefore age at death and age-anchored life expectancy could not be ascertained. Moreover, in the Swedish study, mammary tumor diagnoses were not distinguished as benign or malignant tumors and no information was available on treatment. In contrast, all dogs in the Murphy Foundation study had histologically confirmed mammary cancer and each dog received conventional treatment, i.e. surgical treatment by veterinary practitioners. Overall, the proportion of deaths attributable to mammary tumors was 2.5% in the Swedish study, which parallels the 2.9% proportionate mortality attributable to mammary carcinoma reported in the Murphy Foundation study.

#### A LOOK INSIDE THE STUDY

In this historical cohort study of Rottweilers that lived in North America, questionnaires completed by owners and veterinarians were used to obtain lifetime health and medical information on 242 female Rottweilers, including years of lifetime ovary exposure, age at death, and cause of death. The risk for developing mammary cancer and pyometra increased with longer ovary exposure. Yet, longer ovary exposure ( $\geq 4.3$  years) was also associated with an overall longevity advantage — a 33% decrease in mortality, living 17 months longer than females with shorter ovary exposure ( $P = 0.002$ ). Analysis of age-anchored life expectancy showed that at no time points during the life course was the current or future diagnosis of mammary cancer or pyometra associated with shortened survival compared to females who *never* developed these conditions. For example, although 84% of mammary carcinoma cases had been diagnosed prior to 10 years of age, no deaths attributable to mammary carcinoma were observed during the first 10 years of life, an age which exceeded the average age at death of Rottweilers in the study population. In further analysis, the investigators used the same experimental methods to show that two other diseases widely believed to be “killers” — namely bone sarcoma and lymphoma — did significantly cut short life-expectancy and contributed to premature mortality. Taken together, these findings fail to support the notion that a strategy, such as elective ovariohysterectomy, implemented to reduce the incidence of mammary cancer and pyometra will beneficially impact overall longevity. Future efforts to find and implement effective longevity-promoting interventions must look beyond reducing the incidence of a particular disease to considering trade-offs.

In the new Murphy Foundation study, the authors address the strengths and limitations of single-breed studies. Recognizing the tremendous morphological diversity that exists across breeds of the canine species, it is altogether reasonable to question the extent to which the results from a single breed are translatable to other breeds. But this questioning is really no different than questioning whether the results of any health study can yield accurate predictions for other individuals — even members of the same breed — who were not involved in that particular study.

The authors believe each clinician will need to decide whether the results of this study of competing causes of mortality in Rottweilers are relevant to members of other breeds that share similar body size and overall disease spectrum, and thus share a similar set of mobility-threatening orthopedic diseases and a preponderance of particular classes of tumors (mesenchymal and lymphoid, rather than epithelial neoplasms). Seemingly, a sizeable list of dog breeds, such as Labrador retriever, Golden retriever, German Shepherd, Saint Bernard, Great Dane, Bernese Mountain Dog, and Newfoundland, would fall into this category.

Further, the authors encourage veterinarians and pet owners to consider that the Rottweiler breed is among the top 25% of breeds at highest risk for mammary cancer and the top 5% at highest risk for pyometra. This indicates that a minority of other breeds carry a stronger predisposition for developing these disease conditions.

Waters commented: “Today, single-breed studies such as the Golden Retriever Lifetime Study are being rightfully revered for their translational potential — not only to other dog breeds, but to humans. The challenge ahead is to see such studies — all health-related studies — as sources of clues, not proof, providing each clinician an opportunity to re-shape their beliefs, and providing the veterinary profession with new hypotheses that will help to re-frame ideological starting points.”

In the new report, the authors acknowledge that there are other considerations that figure into the decision by pet owners to pursue elective ovariohysterectomy that were not addressed by their study, such as limiting overpopulation of unwanted dogs, and other behavioral and quality of life issues.

“Broader dialogues concerning optimal timing and techniques of sterilization are certainly warranted. But focused studies such as this one can provide the essential starting points to launch such dialogue,” said Waters. “Our findings here that the two diseases considered to be the major health hazards of ovary conservation — mammary cancer and pyometra — are not associated with shortened longevity, situates whole organism thinking as all the more strategic as we undertake future research to advance our understanding of the physiological trade-offs provoked by elective endocrine organ removal.”

**To download a pdf of the manuscript titled “Life Course Analysis of the Impact of Mammary Cancer and Pyometra on Age-anchored Life Expectancy in Female Rottweilers: Implications for Envisioning Ovary Conservation as a Strategy to Promote Healthy Longevity in Pet Dogs”, [CLICK HERE](#) .**

For more info about this research, contact Ms. Cheri Suckow at 765-775-1005 or [murphyfoundation@gpmcf.org](mailto:murphyfoundation@gpmcf.org) .

#### About the Center for Exceptional Longevity Studies

The Center for Exceptional Longevity Studies seeks to identify important genetic, lifestyle, and environmental determinants of healthy longevity and to better understand the complex relationship between aging, cancer, and cancer avoidance. While the scientific community looks for reliable research approaches to verify exciting scientific leads, the Murphy Foundation sees enormous value in studying pet dogs living with their owners as a virtual aging laboratory. There is a big payoff for pursuing this kind of innovative thinking — an opportunity to promote healthy longevity in both pets and people. The Gerald P. Murphy Cancer Foundation is a 501 (c)(3) not-for-profit research institute.