A Healthier Respect for Ovaries 2015

David J. Waters, *DVM, PhD, Diplomate ACVS*
Director, Center for Exceptional Longevity Studies
Gerald P. Murphy Cancer Foundation

This article, originally written in 2010, has been updated to reflect our emerging perspective on the relationship between ovaries and healthy longevity, which is based on our continuing research.

A landmark study by my research group published in 2010 in *Aging Cell* revealed shortened longevity as a possible complication associated with ovary removal in dogs (1). This work represented the first investigation testing the strength of association between lifetime duration of ovary exposure and exceptional longevity in mammals. To accomplish this, we constructed lifetime medical histories for two cohorts of Rottweiler dogs living in 29 states and Canada: Exceptional Longevity Cohort = a group of exceptionally long-lived dogs that lived at least 13 years; and Usual Longevity Cohort = a comparison group of dogs that lived 8.0 to 10.8 years (average age at death for Rottweilers is 9.4 years). A female survival advantage in humans is well-documented; women are 4 times more likely than men to live to 100. We found that female Rottweilers were 2 times more likely than males to achieve exceptional longevity [Odds Ratio (95% confidence interval) = 2.0 (1.2 - 3.3); p = .006]. However, *removal of ovaries during the first 4 years of life erased the female survival advantage.* In females, this strong positive association between ovaries and longevity persisted in multivariate analysis that considered other factors, such as height, adult body weight, and having a mother with exceptional longevity.

On further analysis, we found female Rottweilers who kept their ovaries for at least 6 years were 4.6 times more likely to reach exceptional longevity (i.e. live >30 % longer than average) than females with the shortest ovary exposure (≤ 2 years). Our results support the notion that how long females keep their ovaries determines how long they live. And a further evaluation of female Rottweilers showed that the beneficial link between ovaries and longevity is *independent of a female's investment in reproduction*, i.e. number of pups, number of litters (2).

In the pages that follow, I have attempted to frame these findings in a way that will encourage veterinarians to venture beyond the peer-reviewed text and data-filled tables of our scientific manuscript to consider the pragmatic, yet sometimes emotionally charged implications of this work. Call it a primer for the dynamic discussions that will undoubtedly take place, not only between practitioners and pet owners, but also inside the veterinary profession. Call it a wake-up call for how little veterinarians have been schooled in the mechanistic nuts and bolts underlying the aging process. Call it an ovary story.

Do ovaries really promote longevity? Observed associations between exposures and outcomes are not always causal, so we explored alternative, non-causal explanations for the association between ovaries and exceptional longevity in our study. But we found no evidence that factors which may influence a pet owner's decision on age at ovary removal — for example, earlier ovariectomy in dogs with substandard conformation or delayed ovariectomy to obtain more offspring in daughters of long-lived mothers — could adequately account for the strong association.

There is another aspect of our data pattern that gives us further confidence that ovaries really do matter when it comes to successful aging. A simple explanation for the observation that ovaries promote longevity would be that taking away ovaries increases the risk for a major lethal disease. In Rottweilers, cancer is the major killer. We found, however, that by conducting a subgroup analysis that excluded all dogs that died of cancer, the strong association between intact ovaries and exceptional longevity persisted. *After excluding all cancer deaths*, females that kept their ovaries the longest were 9 times more likely to reach exceptional longevity than females with shortest ovary exposure (1). *Thus, we observed a robust ovarian association with longevity that was independent of cause of death,* suggesting that a network of processes regulating the intrinsic rate of aging and overall resilience are under ovarian control.

Interestingly, our findings in dogs surfaced just as data from women were calling into question whether those who undergo hysterectomy should have ovary removal or ovary sparing. In fact, our results mirror the findings from more than 29,000 women in the Nurses' Health Study who underwent hysterectomy for benign uterine disease (3). In that study, the upside of ovariectomy — protection against ovarian, uterine, and breast cancer — was outweighed by increased mortality from other causes. As a result, longevity was cut short in women who lost their ovaries before the age of 50 compared with those who kept their ovaries for at least 50 years. Taken together, the emerging message for dogs and women seems to be that when it comes to longevity, it pays to keep your ovaries. More recent data from Walter Rocca and colleagues at Mayo Clinic point to an association between ovary removal and increased risk for undesirable health outcomes ranging from dementia to glaucoma (4,5).

But before we all go out and buy T-shirts with some romantic imperative like "Save the Ovaries", perhaps we should step back and consider the following question: Why hadn't previous dog studies called our attention to this potential downside of ovariectomy? Reviewing the literature, an answer quickly bubbles up. No previous studies in pet dogs had rigorously evaluated the association between ovaries and longevity. Two frequently cited reports (6,7) provide limited guidance because: (1) longevity data were presented as combined mean age at death for a relatively small number of individuals of more than 50 breeds of different body size and life expectancy; and (2) ovarian status was reported as "intact" or "spayed", rather than as number of years of lifetime ovary exposure. In a follow-up study that investigated the consequences of this methodologic deficiency (8), we found that by using the common method of categorizing females as spayed or intact at the time of death (so-called dichotomous binning) — *ignoring the timing of spaying in each bitch* — a significant relationship between number of years of ovary exposure and longevity could be distorted. Because the reasons for ovariectomy (e.g., uterine infection, mammary cancer) increase with increasing age, it is expected that a large percentage of the oldest dogs are binned as "spayed" despite having many years of ovary exposure. For example, a dog who at age 8 undergoes ovariohysterectomy for pyometra and then lives until the ripe old age of 13 *would be binned as "spayed", despite 8 years of ovary exposure*. Our conclusion: The habit of veterinarians categorizing and reporting bitches as spayed or intact based upon gonadal status at time of death is inadequate for representing important biological differences in lifetime ovary exposure, which can lead to misleading assumptions regarding the overall health consequences of ovariohysterectomy (8).
For these reasons, in our research, we have employed a more stringent study design — restricting the study population to AKC registered, pure-bred dogs of one breed, carefully quantitating the lifetime duration of ovarian exposure — in order to side-step these shortcomings. Moreover, we reasoned that studying veterinary teaching hospital-based populations of dogs with artifactually low life expectancies (for example, 6.6 years is the median age at death for Golden Retrievers in the Veterinary Medical Data Base)(9,10) is an inappropriate vehicle to describe the influence that ovaries have on aging. So we

cast a wider net and collected data from Rottweiler owners nationwide, focusing our attention on exceptional longevity, not average age at death, as our study endpoint.

Why study exceptional longevity? Why not average longevity? We thought studying the most exceptionally long-lived individuals would tell us something about what it takes to age successfully (11,12). It's the same rationale used by Thomas Perls and investigators of the New England Centenarian Study (13) and by other scientists who study long-lived humans in other parts of the world (14). The approach even garners support from the mathematical field. In a seminal book on the origins of creative genius, the mathematician Jacques Hadamard wrote: "In conformity with a rule which seems applicable to every science of observation, it is the exceptional phenomenon which is likely to explain the usual one." (15) Hadamard was trying to understand how the brain gets creative so he studied people with extreme creativity. When it comes to studying aging, we're solidly in the Hadamard camp. That is why in 2005 we established the Exceptional Longevity Database, launching the first systematic study of the oldest-old pet dogs (16). And we've gone one step farther. Since 2010, we have been leading the way championing a different way of doing aging research — a unique out-of-the-laboratory-and-into-the-living-room approach studying the oldest-living dogs *in their homes* (17).

But folks in the opposing camp might justifiably fire back: "Don't study extreme longevity. Extreme longevity is much more about luck than it is about genes, or environment, or ovaries." So to address the possibility that the "strangeness" or outlier nature of dogs with exceptional longevity could be forging a misleading link between ovaries and longevity, we studied a separate cohort of Rottweiler dogs who had not reached exceptional longevity. This data set was comprised of 237 female Rottweilers living in North America that died at ages 1.2 to 12.9 years — none were exceptionally long-lived. Information on medical history, age at death, and cause of death was collected by questionnaire and telephone interviews with pet owners and local veterinary practitioners. In this population, we found females that kept their ovaries for at least 4 years had a statistically significant 37% reduction in mortality rate (1). This translated into a median survival of 10.4 years for females with more than 4 years of ovary exposure — 1.4 years longer than the median survival of only 9.0 years in females with shorter ovary exposure ($p < 0.0001$). *Taken together, if you take out ovaries before 4 years of age you cut longevity short an average of 1.4 years and decrease the likelihood of reaching exceptional longevity by 3-fold.*

Up to this point, my ovary story has centered around a summarizing of methodologies and results. The reader has been given opportunity to see the gist of our findings within the context of previous dog studies and emerging research in women. Now, let us pivot our attention away from the results to focus on the recipients of these results — DVMs and pet owners.

We can start by tackling the question: Just how receptive will DVMs be to these new research findings? It's hard for old dogs to learn new tricks. But one thing is sure — blossoming change is rooted in real communication. The anthropologist Gregory Bateson wrote: "The pre-instructed state of the recipient of every message is a necessary condition for all communication. A book can tell you nothing unless you know 9/10ths of it already." (18). I call this "Bateson's Rule of the 9/10ths". If Bateson is right, then we will want to do something about the pre-instructed state of veterinarians. Because when it comes to the biology of aging, the state is virtually a blank slate. None of us received training in the biology of aging as part of our DVM curriculum — whether we graduated 30 years ago or last summer. Therefore, most DVMs are ill-prepared to receive messages examining the mechanistic underpinnings of the aging process. I emphasized this deficiency in a recent paper titled: "Longevity in Pet Dogs: Understanding What's Missing" (10). A Batesonian prescription for positive change would be to ratchet up the biology

of aging IQ of practicing veterinarians. We agree. That is why we established the first gerontology training program for veterinarians in 2007 (19). We believe that by helping veterinarians "know" more about aging, they will be more able and more receptive to communicating the things that promote healthy longevity in their patients — things like preserving ovaries.

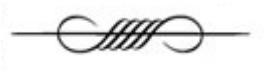
For sure, DVMs will be asked by pet owners to help them make their decision about age at spay in light of this new information. The question will be asked: Just how generalizable are these findings in Rottweilers to other segments of the pet dog population? It is impossible to say at this time. It will demand further study. Alas, 10 years from now, we might just find out that a longevity-promoting effect of ovaries in dogs is limited — limited to large breeds, urban but not rural dogs, or only those individuals with particular polymorphisms in insulin-like growth factor-1. These restrictions should not only be expected, they should be celebrated. It will mean that we have looked more deeply into how ovaries might influence healthy longevity. It will mean that our initial findings have been contextualized. And it is this contextualization of information that marks scientific progress — the kind of progress that guides sound clinical decision making. For it is context that determines meaning (20).

Our provocative findings mean that it's time to re-think the knee-jerk notion that taking away ovaries has no significant downside to a dog's healthy longevity. Recent research published by others on Golden Retrievers and Vizslas highlighting orthopedic conditions, cancer, and behavioral issues support this re-think (21,22). Perhaps it would help us if we thought of lifetime ovary exposure as *information* — information that instructs the organism. Just how long and how healthy a female lives reflects what her cells, tissues, and organs thought they heard from the message received. Of course in biology, there is no single message but a symphony of messages, enabling each individual to successfully respond to environmental challenges. Our findings suggest that ovaries orchestrate that symphony. Taking away ovaries early in life makes for muddled information, less than perfect music. I addressed this issue of muddling in a recent book chapter titled: "Caught in an Act of Convenience: Disentangling Our Thinking About the Influence of Ovariohysterectomy (Spaying) on Healthy Longevity in Dogs" (23).

Information muddling can ensnarl decision-making. Our research takes an important first step toward disentangling the thinking about ovaries and longevity. We should never be paralyzed by the incompleteness of our knowledge. *Our knowledge will always be incomplete* — subject to revision, primed for further inquiry. This uncertainty, although invigorating for the investigator, is often painful for the practitioner who seeks simple, fact-driven algorithms to guide his action. Just as scientists will be called upon to forge ahead with their scientific inquiries, so too will practitioners be counted on to master the uncertainty. Together, we will have to navigate what the philosopher Soren Kierkegaard called the gap "between the understanding and the willing." That is, we must ask the right questions and make smart choices so that our action (the willing) is in synch with our state of knowledge (the understanding) (24). Our progress will hinge on probing particulars. *Under what specific circumstances will a particular individual benefit from a particular lifestyle decision?* This is perhaps the most prescient, overarching question in the wellness and preventive medicine fields facing both human and veterinary health professionals today. I framed the challenge we face in a paper published in *Clinical Theriogenology* titled "In Search of a Strategic Disturbance: Some Thoughts on the Timing of Spaying" (25). How can we promote healthy longevity? Antioxidant supplementation or caloric restriction? Ovary removal or ovary sparing? *Are we smart enough to make spaying a strategic physiologic disturbance?*

Undoubtedly, there will be protagonists and antagonists in this ovary story. The protagonists will be open-minded to following a new script. They will embrace the idea of ovary sparing for critical periods, critical windows of time to maximize healthy longevity. They might even envision the need for some sort of "ovarian mimetic" in spayed dogs to optimize healthy aging. The antagonists in this story — the defenders of the old script — will dismiss as trivial the notion that ovaries regulate the rate of aging and influence healthy longevity. Lines will be drawn and opinions will fly. But *that's what healthy debate is* — antagonists and protagonists keeping a high priority issue front and center, not allowing it to fade into the woodwork. It would seem that, in light of the new scientific findings, a contemporary dialogue should balance the potential benefits of elective ovary removal emphasized in the old script (26) with the possible detrimental effects of ovary removal on healthy longevity.

A healthier respect for ovaries is a healthier respect for homeostasis, for overall health. Ovaries are not just reproductive units. Ovaries are endocrine organs, capable of exerting system-wide effects. Just how far-reaching are these effects, we are only just beginning to fully appreciate.



About The Gerald P. Murphy Cancer Foundation

The Murphy Cancer Foundation is a not-for-profit research organization focused on exploring the biological mechanisms that lead to highly successful aging and cancer avoidance. Dr. Waters and his colleagues at the Murphy Foundation's Center for Exceptional Longevity Studies are championing a brand new research approach. It hinges on the idea that pet dogs with extreme longevity — equivalent to humans who live to be 100 years old — offer a valuable scientific opportunity to uncover important clues to understanding what it takes for pets and people to age more successfully and avoid cancer. Our work on ovaries and longevity positions pet dogs, with their broad range of lifetime ovary exposure, to become one of biogerontology's new workhorses for identifying ovary-sensitive physiological processes that promote healthy longevity.

The Murphy Cancer Foundation's Center for Exceptional Longevity Studies is home to The Longevity Biorepository — the world's first collection of serum, blood cells, DNA and autopsy tissues from these exceptionally long-lived, cancer resistant dogs. The pioneering approach used by Dr. Waters and his research team is epitomized by The Old Grey Muzzle Tour — a cross-country scientific expedition that takes Dr. Waters out of the laboratory and into the living room to make first-hand scientific observations of the oldest-living dogs in their homes. The Murphy Cancer Foundation supports this effort as the essential fieldwork for making discoveries on what it means to age successfully — no different from scientists who go into the jungle to discover what it means to be "gorilla". What is front and center in our minds is how each of us can achieve successful aging and cancer avoidance. The spirit and scope of this win-win research are captured in Dr. Waters' recent TEDx talk titled "The Oldest Dogs as Our Greatest Teachers: Get the Words Out of Your Eyes." (https://www.youtube.com/watch?v=XS9fiDn4Qo8)

To learn more about the research and education efforts of the Murphy Cancer Foundation, visit www.gpmcf.org .

References

1. Waters DJ, Kengeri SS, Clever B, et al: "Exploring the mechanisms of sex differences in longevity: lifetime ovary exposure and exceptional longevity in dogs." *Aging Cell* 8:752-5, 2009

2. Kengeri SS, Maras AH, Suckow CL, et al: "Exceptional longevity in female Rottweiler dogs is not encumbered by investment in reproduction." *AGE* 35:2503-13, 2013

3. Parker WH, Broder MS, Chang E, et al: "Ovarian conservation at the time of hysterectomy and long-term health outcomes in the Nurses' Health Study." *Obstet Gynecol* 113: 1027-1037, 2009

4. Rocca WA, Shuster LT, Grossardt BR, et al: "Long-term effects of bilateral oophorectomy on brain aging: Unanswered questions from the Mayo Clinic Cohort Study of Oophorectomy and Aging." *Women Health* 5:39-48, 2009

5. Vajaranant TS, Grossardt BR, Maki PM, et al: "Risk of glaucoma after early bilateral oophorectomy." *Menopause* 21:391-8, 2014

6. Bronson RT: "Variation in age at death of dogs of different sexes and breeds." *Am J Vet Res* 43: 2057-9, 1982

7. Michell AR: "Longevity of British breeds of dog and its relationships with sex, size, cardiovascular variables and disease." *Vet Rec* 145: 625-629, 1999

8. 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* 76:1496-1500, 2011

9. Patronek GJ, Waters DJ, Glickman LT, et al: "Comparative longevity of pet dogs and humans: implications for gerontology research." *J Gerontol A Biol Sci Med Sci* 52: B171-8, 1997

10. Waters DJ: "Longevity in pet dogs: Understanding what's missing." *Vet J* 200:3-5, 2014

11. GMA Weekend: "Old dogs, new cures? Dogs help fight cancer" at http://gpmcf.org/ExternalPress/GMA_Weekend_041810.mpeg

12. Waters DJ: "The oldest dogs as our greatest teachers: Get the words out of your eyes." at https://www.youtube.com/watch?v=XS9fiDn4Qo8

13. Perls TT, Hutter Silver M, Lauerman JF: *Living to 100: Lessons in Living to Your Maximum Potential at Any Age*, New York, NY, Basic Books, 1999

14. Franceschi C, Motta L, Valensin S, et al: "Do men and women follow different trajectories to reach extreme longevity?" *Aging (Milano)* 12:77-84, 2000

15. Hadamard J: *The Psychology of Invention in the Mathematical Field*. New York, NY, Oxford Univ Press, 1945, p. 136

16. Waters DJ, Wildasin K: "Cancer clues from pet dogs." *Sci Am* 295:94-101, 2006

17. Gerald P. Murphy Cancer Foundation: "The Old Grey Muzzle Tour Facebook Page" at https://www.facebook.com/TheOldGreyMuzzleTour

18. Bateson G, Bateson MC: *Angels Fear: Towards an Epistemology of the Sacred.* New York, NY, Bantam, 1988, p 163

19. Gerontology Program for DVMs co-sponsored and organized by Gerald P. Murphy Cancer Foundation, Purdue University Center on Aging and the Life Course, P&G Pet Care

20. Waters DJ, Chiang EC, Bostwick DG: "The art of casting nets: fishing for the prize of personalized cancer prevention." *Nutr Cancer* 60:1-6, 2008

21. Torres de la Riva G, Hart BL, Farver TB, et al: "Neutering dogs: Effects on joint disorders and cancers in Golden Retrievers" *PLoS One* 8:e55937, 2013

22. Zink MC, Farhoody P, Elser SE, et al: "Evaluation of the risk and age of onset of cancer and behavioral disorders in gonadectomized Vizslas." *J Am Vet Med Assoc* 244:309-19, 2014

23. Waters DJ, Chiang EC: "Caught in an act of convenience: Disentangling our thinking about the influence of ovariohysterectomy (spaying) on healthy longevity in dogs." In *Dogs: Domestication History, Genetics, Behavior and Implications for Health*, Cohen KM, Diaz LR, Eds. Hauppauge, NY, Nova Science Publishers, 2013, p 115-120

24. Waters DJ: "In search of a strategic disturbance: Some thoughts on the timing of spaying." *Clinical Theriogenol* 3:433-37, 2011

25. Waters DJ, Waters LS:" On the self-renewal of teachers." *J Vet Med Educ* 38:235-41, 2011

26. Kustritz MV: "Determining the optimal age for gonadectomy of dogs and cats." *J Am Vet Med Assoc* 231:1665-75, 2007