



Canine Mammary Tumors

Bill Schiemann, Ph.D.

Although we are in the midst of the hot, sultry “Dog Days of Summer,” we can find comfort in knowing that Fall and its crisp, cool air will soon be upon us. This Fall and its accompanying October will mark the 27th year of the National Breast Cancer Awareness Month, which raises awareness for the disease and funds for research aimed at determining its causes, preventing its initiation, improving its diagnosis and treatment, and supporting those individuals affected by this deadly disease. The success of the annual campaign has been spectacular, resulting in a 24% decrease in the mortality of breast cancers between 1990-2000 primarily due to the combined actions of widespread screening mammography programs and the development of adjuvant chemotherapies. Despite these remarkable achievements, science and medicine cannot rest on their laurels as metastatic breast cancer remains the 2nd leading cause of death in woman in the United States, annually accounting for more than 40,000 deaths and 211,000 new cases of invasive breast cancer. Within the United States, 1 in 8 women can expect to be diagnosed with breast cancer during their lifetime, thus positioning this disease as the 2nd most prevalent cancer in women. Worldwide, metastatic breast cancer kills more than 500,000 women each year, making this disease the leading cause of death in women. Generally speaking, metastatic disease is incurable and results in a median survival of only 1.5 to 3 years

for patients harboring metastatic breast cancer. In fact, treatment goals for women with metastatic disease no longer aim to produce a cure, but instead focus on symptom management and prolonging the length and quality of life for these patients. Fortunately, the advent of new high-throughput genomic and proteomic sequencing technologies, coupled with new tumor imaging modalities, has ushered in a new era in biomedical research aimed at producing novel diagnostic tests capable of detecting the earliest stages of breast cancer in otherwise seemingly healthy women, and at providing “personalized” therapies tailored to the specific genetic makeup of a women’s tumor as opposed to the “one size fits all” therapies employed in years past. Thus, another significant decrease in breast cancer mortality rates may soon be realized as the impact of these new therapies and technologies gain widespread access to clinical settings.

So how do the aforementioned statistics relate to our female four-legged friends and their likelihood of developing canine mammary tumors? Well for one thing, cancer is now a leading killer of dogs, accounting for approximately 20% of all canine deaths and nearly 50% of deaths of dogs older than 10 years of age. Although not as common as lymphoid or soft tissue sarcomas, canine mammary tumors remain one of the Top 5 diagnosed malignancies

in dogs, affecting ~1-in-500 of our four-legged friends. Historically, the prevalence of mammary tumors is ~4-fold higher in dogs as compared to humans. Similar to human breast cancers, canine mammary tumors are the most common malignancy and killer of intact female dogs. In fact, the parallels existing between the development and metastatic progression of human breast cancers and canine mammary tumors is striking. For instance, correcting for life span differences between humans and dogs, it is readily apparent

that both female populations exhibit similar ages at disease onset (e.g., after 40 in humans and after 6 in dogs), and at peak incidence of disease (e.g., between 50-58

years in humans and 8-11 years in dogs). These findings suggest that human and canine mammary tumors develop and progress along similar pathological tracks, albeit more rapidly in our four-legged friends. Sequencing of the canine genome and comparing it to that of humans has amply proven the validity of this assumption and demonstrated the existence of extensive similarities in the DNA sequences of both species, particularly in genomic regions known to give rise to malignancies. Thus, genetic aberrancies detected in human breast cancers are also detected in canine mammary tumors and vice versa. Along these lines, it is important to note that human breast cancers are not a single disease entity, but are instead a group of 5 or more genetically distinct subtypes that dictate their clinical courses and responses to “subtype-specific” therapies. Analogous studies of

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canine mammary tumors point to a similar genetic stratification of canine mammary tumors; however, this wealth of information is only being exploited clinically to improve the treatment and overall survival of human breast cancer patients, not their canine counterparts.

Additional parallels between human and canine mammary tumors can be noted in several risk factors. For instance, cancer is a disease of aging and the incidence for developing mammary tumors increases in both

species with increasing age. Additionally, human and canine mammary tumors are regulated by ovarian hormones, particularly estrogen. The importance of

estrogen in driving the formation of canine mammary tumors is in evidence by the fact that spaying our four-legged female friends prior to their first estrous cycle affords them a 0.5% risk of developing mammary tumors, which increases to an 8% risk if spaying occurs after their second estrous cycle, and ultimately to a 26% risk if spaying transpires after the 2nd estrous cycle and prior to 2.5 years of age. Obesity is another risk factor for mammary tumor development that is shared by humans and dogs. Indeed, obesity elicits a 2-fold increase in breast cancer risk for women; it also plays a significant role in driving disease recurrence and worsening the prognosis of obese women, particularly in post-menopausal women. With respect to our four-legged friends, recent findings have associated juvenile canine obesity to increased risk of mammary tumor development. In fact, female dogs

with thin body conformations at 9-12 months of age exhibit a 99% reduced risk for mammary tumor development amongst spayed females, and a 40% reduced risk amongst non-spayed females. Finally, human and canine mammary tumors display a degree of genetic predisposition. For instance, breast cancer rates are 2-fold higher in women who have first-degree relatives with breast cancer as compared to those of the general population. Moreover, ~10% of human breast cancers arise from genetic inheritance of inactivating mutations in breast cancer susceptibility gene, BRCA1, an untoward event that is also detected in canine mammary tumors. Additionally, certain dog breeds appear especially predisposed to develop canine mammary tumors, particularly in Dobermans, Poodles, German Shepherds, Boxers, and English Springer, Brittany, and Cocker Spaniels.***

Lastly, human and canine mammary tumors possess additional parallels in terms of their developmental courses and prognoses. For instance, the acquisition of metastatic phenotypes is responsible for the deaths of ~90% of human breast cancer patients. This process is complicated by the fact that many breast cancers disseminate long before their primary tumors become symptomatic. In fact, 33% of women diagnosed with small tumors of the breast (4 mm) already harbor disseminated breast cancer cells in their bone marrow. Moreover, these micrometastases readily escape clinical detection by remaining dormant for years before reemerging as incurable secondary tumors that are insensitive to the very chemotherapies that originally attacked the primary tumor. The process of mammary tumor metastasis and its routes of dissemination in canines mirrors that

of humans. For instance, the 5 year survival rate for women who present clinically with localized disease is high at ~98%, a survival rate that drops precipitously to ~15% once the primary tumor has metastasized. Similar associations of metastasis to the survival of our four-legged friends has also been observed. Indeed, the 2 year survival rate for canines who present clinically with localized disease approaches 80%, but drops to only 14% in canine patients presenting clinically with evidence of lymph node metastasis. Generally speaking, 50% of canine mammary tumors are benign and 50% are malignant, with surgical resection representing the standard-of-care for tumors types. Of those tumors determined to be malignant and surgically removed, ~50% will recur and progress metastatic disease states, which similar to humans remains an incurable condition.

Treatment options beyond surgical resection remain limited and have yet to be standardized for individual canine mammary tumor subtypes. Typical treatment regimens may include radiation or administration of classical nucleotide antimetabolites or DNA damaging agents, such as Doxorubicin, Cisplatin, and Gemcitabine. More recently, incorporation of the taxanes Paclitaxel and Docetaxel, which kill cancer cells by preventing cell division during proliferation, has provided modest degrees of efficacy against canine mammary tumors. The failure of these treatment regimens likely reflects the “one size fits all” approach to treating canine mammary tumors as opposed to tailoring these therapies to the specific genetic profile of an individual tumor. Indeed, the “personalized” targeted therapy approaches that have been successful in treating human breast cancers

have yet to be translated to our four-legged friends. For instance, while the anti-estrogen agent Tamoxifen revolutionized the treatment of estrogen-responsive tumors in humans, incorporating similar anti-estrogen-based approaches in dogs has been unsuccessful and elicited intolerable side-effects. Likewise, incorporation of successful human “personalized” anti-breast cancer agents (e.g., Lapatinib, Trastuzumab/ Herceptin, Avastin, etc.) in canines has been slow and hampered by a lack of canine-specific diagnostic tests needed to stratify our four-legged friends into appropriate treatment groups. Thus, the rapid translation of human-based biomarkers and targeted chemotherapies to the treatment of canine mammary tumors will likely to provide new inroads towards improving the overall survival of our four-legged friends afflicted with this deadly disease. Along these lines, remember to be proactive and ask your veterinarian about new and innovative treatment options, and consider enrolling your pup in a clinical trial.

Information related to ongoing Canine Mammary Cancer Clinical Trial can be obtained at the following addresses:

Canine Mammary Cancer Clinical Trial
Auburn University College of
Veterinary Medicine
Annette Smith, D.V.M.
Oncology Service Director
Department of Clinical Sciences
Phone: 334-844-4690
Email: Smith30@auburn.edu

R. Curtis Bird, Ph.D.
Principal Investigator
Department of Pathobiology
Phone: 334-844-2707
Email: birdric@auburn.edu
Website: <http://www.vetmed.auburn.edu/home/practitioners/clinical-trials/canine-mammary-cancer>

***What is the incidence of mammary tumors in Weimaraners? I was unable to obtain information to adequately address this question. I did find a retrospective study that examined the incidence and survival rates of dogs with mammary tumors based on Swedish insurance claims for these canines between 1995-2002. The sample size included 80,000 insured female dogs representing 280 breeds. Unfortunately, Weimaraners were not included in the presented findings, which focused on 51 breeds. Several possibilities may explain this egregious omission. First, the Swedes do not own any Weimaraners. Second, Swedes do in fact own Weimaraners, but they do not feel the need to insure them. Lastly and most likely, Swedish Weimaraners developed mammary tumors at a low incidence, which was not reported.

Bill Schieman is a Cancer Biologist who Co-Directs the Breast Cancer Program and Leads the TGF-B Focus Group at the Case Comprehensive Cancer Center. He lives in the Greater Cleveland area with his wife, Barbara, and their two gray boys, Loki and Jacy.