Editorial

Canine Genetics Offers New Mechanisms for the Study of Human Cancer

Edouard Cadieu and Elaine A. Ostrander

Cancer Genetics Branch, National Human Genome Research Institute, NIH, Bethesda, Maryland

Perspective

In this month's *CEBP*, Antuofermo et al. (1) offer new insights into spontaneous intraepithelial lesions using the dog as a discovery tool. In humans, ~500,000 intraepithelial lesions are diagnosed every year, generally through mammographic screening (2). Intraepithelial lesions include breast hyperplasias, atypical hyperplasias, and carcinoma *in situ*, and all are considered risk factors for invasive breast cancer (3, 4). Thus, establishing an animal model for intraepithelial lesions is important for the development of both preventive measures and effective treatments and for better understanding of the etiology of the disease.

Using data from 200 dogs, Antuofermo et al. (1) describe both the histologic and immunohistochemistry of canine intraepithelial lesions, showing their similarity to human lesions. Of the 200 canine specimens considered, 93 benign and 119 malignant tumors were found, with intraepithelial lesions observed in 60 cases, 39 of which were associated with malignant tumors. Ductal carcinoma *in situ* was the most common intraepithelial lesion found in dogs, accounting for 32 cases, 29 (91%) of which were associated with malignant tumors. Ductal carcinoma *in situ* is also the most frequently diagnosed intraepithelial lesion in humans.

Estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 in adjacent nonneoplastic mammary tissue were evaluated by immunohistochemistry. Seventy percent of cells showed strong estrogen receptor immunoreactivity, with most ductal hyperplasias expressing estrogen receptor, which decreased as intraepithelial lesions increased in grade. In contrast, high-grade ductal carcinoma *in situ* was generally estrogen receptor negative, suggesting that the canine intraepithelial lesions might be a good model for estrogen receptor–negative tumors. Ki67 measures were also conducted: in humans, Ki67 indices are usually associated with increased tumor grade and poor response to therapy (5). In the dog intraepithelial lesions, estrogen receptor and Ki67 were found to be inversely associated, as has previously been reported (6). In highly proliferative lesions with increased Ki67, estrogen receptor was negative, but human epidermal growth factor receptor 2 was usually positive with a distribution that was similar to that reported for human intraepithelial lesions (7).

With 74 million dogs living in the United States (8), it is not surprising that man's best friend would emerge as an informative system for the study of precancerous lesions (9). Dogs live in our environment, eat our food, are exposed to the same carcinogens (10), and share similar immunologic features (11).

Cancer is at least as common in dogs as in humans. In a necropsy series of 2,000 dogs, 23% of all dogs and 45% of dogs older than 10 years died of cancer (12, 13). The spontaneous appearance, frequency, and treatment response of canine tumors often parallel human neoplasms (14-16) much better than, for instance, induced tumors in rodents. Canine malignancies that have been established as strong comparative models (17) for human cancers include transitional cell carcinoma of the bladder (17), non-Hodgkin's lymphoma (18, 19) and leukemia, osteosarcoma (20), melanoma (particularly oral melanoma; refs. 21, 22), and soft tissue sarcomas (23-25).

In dogs, hormonal cancers display interesting epidemiologic patterns. Although prostate cancer is among the most common cancers in men with 218,890 estimated new cases in 2007 (26), it is rare in dogs (27). Further, although high-grade prostate intraepithelial neoplasia (28) and bone metastasis similar to those observed in humans have been reported (29), the significance of those results is unclear (30). Some breeds of dog seem to be at a higher risk for the disease, such as the Bouvier de Flanders, Doberman pinschers, Shetland sheepdogs, and the Norwegian Elkhound; the strongest risk factor is castration (27, 31). This is the opposite of what is observed in humans, in which prostate cancer is virtually undiagnosed in castrated males (32, 33).

By comparison, the mammary gland is a common site of neoplasia in female dogs (12). Annual incidence rates are difficult to assess because most of the available data come from insurance databases in which younger dogs are overrepresented. Dobson et al. (34) estimated that the standardized incidence rate was 205 per 100,000 dogs per year. This is similar to the estimate of 145 per 100,000 female dogs per year reported by Schneider (35). The study of Schneider represents dogs from the Alameda Country Tumor Registry and Alameda Costa Counties Animal Neoplasm Registry, both of which include dogs of all ages. The median age at diagnosis for breast cancer in the Registry study was 11 years and

Cancer Epidemiol Biomarkers Prev 2007;16(11):2181–3

Received 10/8/07; accepted 10/8/07.

Requests for reprints: Elaine A. Ostrander, Cancer Genetics Branch, National Human Genome Research Institute, NIH, Building 50, Room 5351, 50 South Drive, Bethesda, MD 20892. Phone: 301-594-5284; Fax: 301-480-0472. E-mail: eostrand@mail.nih.gov

doi:10.1158/1055-9965.EPI-07-2667

6 months, which is equivalent to 62 years in the human (35). However, studies of dogs in Sweden, where animals are much less likely to be spayed, report considerably higher numbers (36).

There are marked differences in mammary cancer risk between breeds, with the English springer spaniel and Doberman pinscher having the highest risk, versus the rough coated collie, for which the risk is estimated to be almost 65-fold lower (36). The risk of breast cancer is eliminated in dogs that are spayed before they experience their first menstrual cycle. As with humans, incidence increases with age, and at 6, 8, and 10 years, 1%, 6%, and 13% of dogs across all breeds report at least one mammary tumor.

Although canine models of various cancers garner increasing interest as *in vitro* systems suitable for studies of basic biology and drug development, the fact that breed specificity is observed for many types of cancer has excited geneticists who are anxious to localize susceptibility genes that have proved intractable in human families and populations. Of significance has been a growing understanding of how distinct dog breeds relate to one another (37, 38). This allows researchers to select affected cases from breeds that probably share a common ancestry, and hence a common mutation, for whole-genome association studies. This scheme is being used to study a variety of cancers that appear in small numbers of related breeds like transitional cell carcinoma of the bladder, for which only five breeds are at increased risk: the Scottish (odds ratio, 19.89; 95% confidence interval, 7.74-55.72) and West Highland white terriers (odds ratio, 5.31; 95% confidence interval, 2.51-11.63), the Shetland sheepdog (odds ratio, 4.46; 95% confidence interval, 2.48-8.03), the beagle (odds ratio, 4.15; 95% confidence interval, 2.14-8.05), and the wire-haired fox terrier (odds ratio, 3.20; 95% confidence interval, 1.19-8.63; refs. 17, 39). Phylogenetic studies show that the terriers probably share a common ancestry, and combining data from the three breeds will probably not only allow the mapping of the disease locus but may also identify a minimal critical haplotype with a small number of candidate genes, as has been done for other canine diseases (37, 40). The non-terrier breeds are from distinct phylogenetic groups that may have unique mutations in the same gene or mutations in altogether different genes.

The last point is important. Just as human diseases feature extensive locus heterogeneity, so do dog diseases. However, dog breeds generally are characterized by closed breeding and relatively isolated populations, often with a small number of founders and popular sires whose gene pool is overrepresented in modern-day progeny. As a result, genetic studies of dogs are a useful mechanism for overcoming the genetic heterogeneity associated with many human cancers. That is, although there may be dozens of genes contributing to particular cancer susceptibilities in dogs as a whole, within any single breed there are likely to be only one or two. By knowing how breeds relate to one another, studies can be designed to optimize the chances for finding the small number of relevant genes.

Dogs have proved their utility in facilitating our understanding of human cancers in many ways: they have large and multiple litters, which offers a powerful system for doing linkage analysis, as was shown with kidney cancer in the German shepherd (41, 42). Whole-genome association studies are ongoing for a host of canine cancers that are of interest for human health and biology, including osteosarcoma, lymphoma, transitional cell carcinoma, soft tissue cancer, and squamous cell carcinomas; each study centered around a carefully chosen set of breeds. Finally, as several investigators have shown (43), including Antuofermo et al. (1), dogs experience many of the same precursor syndromes that herald metastatic disease in humans. Therefore, a clearer understanding of canine cancer syndromes will almost certainly lead to a better understanding of the key steps in the formation of human tumors.

Acknowledgments

We thank the many dog owners who continue to contribute DNA samples for our studies, and the American Kennel Club Canine Health Foundation and the Intramural Program of the National Human Genome Research Institute for continued support.

References

1. Antuofermo E, Miller MA, Pirino S, Xie J, Badve S, Mohammed S. Spontaneous mammary intraepithelial lesions in dogs—a model of breast cancer. Cancer Epidemiol Biomarkers Prev 2007:16:2247–56.
2. Silverstein MJ. Ductal carcinoma *in situ* of the breast. Ann Rev Med 2000;51:17–32.
3. Page DL, Dupont WD. Anatomic markers of human premalignancy and risk of breast cancer. Cancer 1990;15:1326–35.
4. Skinner KA, Silverstein MJ. The management of ductal carcinoma *in situ* of the breast. Endocr Relat Cancer 2001;8:33–45.
5. Shoker BS, Jarvis C, Clarke RB, et al. Estrogen receptor-positive proliferating cells in the normal and precancerous breast. Am J Pathol 1999;155:1811–5.
6. Yang WY, Liu CH, Chang CJ, Lee CC, Chang KJ, Lin CT. Proliferative activity, apoptosis and expression of oestrogen receptor and Bcl-2 oncoprotein in canine mammary gland tumours. J Comp Pathol 2006; 134:70–9.
7. Mylonas I, Makovitzky J, Jeschke U, Briese V, Friese K, Gerber B. Expression of Her2/neu, steroid receptors (ER and PR), Ki67 and p53 in invasive mammary ductal carcinoma associated with ductal carcinoma *in situ* (DCIS) versus invasive breast cancer alone. Anticancer Res 2005;25:1719–23.
8. American Veterinary Medical Association U.S. Pet Ownership and Demographics Sourcebook. Schaumburg, ILL: American Veterinary Medical Association; 2002.
9. Sutter NB, Ostrander EA. Dog star rising: the canine genetic system. Nat Rev Genet 2004;5:900–10.
10. Glickman LT, Raghavan M, Knapp DW, Bonney PL, Dawson MH. Herbicide exposure and the risk of transitional cell carcinoma of the urinary bladder in Scottish terriers. J Am Vet Med Assoc 2004;224: 1290–7.
11. Storb R, Thomas ED. Graft-versus-host disease in dog and man: the Seattle experience. In: Möller G, editor. Immunological reviews, no. 88. Copenhagen: Munksgaard; 1985. p. 215–38.
12. Vail DM, MacEwen EG. Spontaneously occurring tumors of companion animals as models for human cancer. Cancer Investigation 2000;18:781–92.
13. Bronson RT. Variation in age at death of dogs of different sexes and breeds. Am J Vet Res 1982;43:2057–9.
14. Dorn CR. Epidemiology of canine and feline tumors. Comp Cont Educ Pract Vet 1976;12:307–12.
15. Ostrander EA, Kruglyak L. Unleashing the canine genome. Genome Res 2000;10:1271–4.
16. Ostrander EA, Wayne RK. The canine genome. Genome Res 2005;15: 1706–16.
17. Knapp D, Glickman N, DeNicola D, Bonney P, Lin T, Glickman L. Naturally occurring canine transitional cell carcinoma of the urinary bladder: a relevant model of human invasive bladder cancer. Urol Oncol 2000;5:47–59.
18. Leifer CE, Matus RE. Canine lymphoma: clinical considerations. Semin Vet Med Surg Small Anim 1986;1:43–50.
19. Valli VE, Vernau W, de Lorimier LP, Graham PS, Moore PF. Canine indolent nodular lymphoma. Vet Pathol 2006;43:241–56.

20. Mueller F, Fuchs B, Kaser-Hotz B. Comparative biology of human and canine osteosarcoma. Anticancer Res 2007;27:155–64.
21. Bergman PJ. Canine oral melanoma. Clin Tech Small Anim Pract 2007;22:55–60.
22. MacEwen EG. Spontaneous tumors in dogs and cats: models for the study of cancer biology and treatment. Cancer Metastasis Rev 1990;9:125–36.
23. Moore PF, Rosin A. Malignant histiocytosis of Bernese mountain dogs. Vet Pathol 1986;23:1–10.
24. Affolter VK, Moore PF. Canine cutaneous and systemic histiocytosis: reactive histiocytosis of dermal dendritic cells. Am J Dermatopathol 2000;22:40–8.
25. Onions DE. A prospective survey of familial canine lymphosarcoma. J Natl Cancer Inst 1984;72:909–12.
26. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin 2007;57:43–66.
27. Teske E, Naan EC, van Dijk EM, Van Garderen E, Schalken JA. Canine prostate carcinoma: epidemiological evidence of an increased risk in castrated dogs. Mol Cell Endocrinol 2002;197:251–5.
28. Waters DJ, Hayden DW, Bell FW, Klausner JS, Qian J, Bostwick DG. Prostatic intraepithelial neoplasia in dogs with spontaneous prostate cancer. Prostate 1997;30:92–7.
29. Navone NM, Logothetis CJ, von Eschenbach AC, Troncoso P. Model systems of prostate cancer: uses and limitations. Cancer Metastasis Rev 1998;17:361–71.
30. Weaver AD. Fifteen cases of prostatic carcinoma in the dog. Vet Rec 1981;109:71–5.
31. Bryan JN, Keeler MR, Henry CJ, Bryan ME, Hahn AW, Caldwell CW. A population study of neutering status as a risk factor for canine prostate cancer. Prostate 2007;67:1174–81.
32. Wu CP, Gu FL. The prostate in eunuchs. Prog Clin Biol Res 1991;370:249–55.
33. Lytton B. Prostate cancer: a brief history and the discovery of hormonal ablation treatment. J Urol 2001;165:1859–62.
34. Dobson JM, Samuel S, Milstein H, Rogers K, Wood JL. Canine neoplasia in the UK: estimates of incidence rates from a population of insured dogs. J Small Anim Pract 2002;43:240–6.
35. Schneider R. Comparison of age, sex, and incidence rates in human and canine breast cancer. Cancer 1970;26:419–26.
36. Egenvall A, Bonnett BN, Ohagen P, Olson P, Hedhammar A, von Euler H. Incidence of and survival after mammary tumors in a population of over 80,000 insured female dogs in Sweden from 1995 to 2002. Prev Vet Med 2005;69:109–27.
37. Parker H, Kukekova A, Akey D, et al. Breed relationships facilitate fine mapping studies: a 7.8 kb deletion cosegregates with collie eye anomaly across multiple dog breeds. Genome Research. In press 2007.
38. Parker HG, Kim LV, Sutter NB, et al. Genetic structure of the purebred domestic dog. Science 2004;304:1160–4.
39. Knapp DW. Animal models: naturally occurring canine urinary bladder cancer. In: Lerner SP, Schoenberg MP, Sternberg CN, editors. Textbook of bladder cancer. Oxon (United Kingdom): Taylor and Francis; 2006. p. 171–5.
40. Goldstein O, Zangerl B, Pearce-Kelling S, et al. Linkage disequilibrium mapping in domestic dog breeds narrows the progressive rod-cone degeneration interval and identifies ancestral disease-transmitting chromosome. Genomics 2006;88:541–50.
41. Jonasdottir TJ, Mellersh CS, Moe L, et al. Genetic mapping of a naturally occurring hereditary renal cancer syndrome in dogs. Proc Natl Acad Sci U S A 2000;97:4132–7.
42. Lingaas F, Comstock KE, Kirkness EF, et al. A mutation in the canine BHD gene is associated with hereditary multifocal renal cystadenocarcinoma and nodular dermatofibrosis in the German Shepherd dog. Hum Mol Genet 2003;12:3043–53.
43. Waters DJ. High-grade prostatic intraepithelial neoplasia in dogs. Eur Urol 1999;35:456–8.

Canine Genetics Offers New Mechanisms for the Study of Human Cancer

Edouard Cadieu and Elaine A. Ostrander

Cancer Epidemiol Biomarkers Prev 2007;16:2181-2183.