Epidémiol. santé anim., 1997, 31-32

HOST RELATED RISK FACTORS FOR CANINE OSTEOSARCOMA

Ru G.[1], Terracini B.[1], Glickman LT.[2]

L'étiologie des ostéosarcomes chez le chien ou l'Homme est peu connue. L'incidence des ostéosarcomes humains est plus élevée durant la période de croissance du squelette ; chez le chien, un risque accru a été rapporté pour les grandes races. Une étude de type cas - témoins réalisée à partir de la base de données Veterinary Medical Data Base (VMDB) a été conduite pour tester l'hypothèse selon laquelle l'augmentation de la taille et du poids sont des facteurs de risque indépendants des ostéosarcomes du chien. De plus, le rôle d'autres facteurs inclus dans la base de données a été examiné. Les cas étaient constitués de 3062 chiens de pure race ayant un ostéosarcome et admis dans un des 24 hôpitaux vétérinaires des Etats-Unis et du Canada participant à l'étude, entre 1980 et 1994. Le groupe témoin était constitué de 3959 chiens de pure race ayant d'autres diagnostics tirés au sort en fonction de leur fréquence et appariés aux cas en fonction de l'établissement et de l'année du diagnostic. Les odds - ratio (OR) non ajustés ont mis en évidence une tendance linéaire significative pour l'augmentation du risque d'ostéosarcome avec l'âge, l'augmentation du poids vif, du poids standard et de la taille standard. En comparaison avec la race Berger Allemand, le risque d'ostéosarcome est plus élevé chez les chiens de race Irish Wolfhound (OR 18.9, Intervalle de confiance à 95% (IC) 7.0-50.7), Saint Bernard (OR 11.7, IC95% 5.9-23.2) et Danois (OR 5.2, IC95% 3.1-8.5) alors qu'il est diminué pour les petites races (OR<0.10). Un risque deux fois plus élevé a été observé pour les mâles et femelles castrés. Les estimations du risque pour la taille standard ajustées sur le poids standard, et vice versa, ont montré une association plus forte des ostéosarcomes avec l'augmentation de taille qu'avec celle du poids. Malgré les biais potentiels et les contraintes inhérentes à l'utilisation de registres hospitaliers, la relation entre le risque d'ostéosarcome et l'augmentation de taille apporte un argument supplémentaire en faveur du lien existant entre ce cancer et la croissance du squelette.

INTRODUCTION

Osteosarcoma in dogs and humans has many similarities including a predilection for metaphyseal regions of long bones, high-grade malignancy, a high rate of metastasis, and the lung as the most common site of metastasis. In both species the aetiology and the risk factors for osteosarcoma remain unknown. It has been suggested that host factors such as the rate of bone growth may be important in the development of osteosarcoma (Fraumeni, 1967). This hypothesis is consistent with earlier findings by Tjalma (1966), who related the risk of osteosarcoma in dogs with increasing body weight. Computerised hospital records of dogs from the Veterinary Medical Data Base (VMDB) were used for a case-control study to test the hypothesis that body size, as measured by height and body weight are risk factors for canine osteosarcoma. Moreover, the association of other host factors (i.e. age, sex, neutering status and breed) with canine osteosarcoma was explored.

MATERIALS AND METHODS

The following information is available in VMDB for each record: participating institution, patient identifying number, species, breed, sex and neuter status, age, weight, up to five diagnoses, diagnostic procedures completed, date of discharge. Records of all pure-bred dogs with a diagnosis of bone tumour were obtained by searching for the appropriate code (****.8760.*, osteoma-osteosarcoma) from January 01, 1980 to August 31, 1994. A control group was selected by frequency matching by institution and year of discharge an equal number of random records of pure-bred dogs seen for any other diagnostic reason, including immunisations or minor surgical procedures. After eliminating from the case group the records of dogs with either a diagnosis of osteosarcoma without histological or radiological confirmation or a diagnosis of osteoma, the case and the control series comprised respectively 3,062 cases and 3,959 controls. As age and weight data are treated as categorical, rather than as continuous variables, by the VMDB, the following age (years) and weight (kilograms) classes were used: age <2.0, 2.0 to 3.9, 4.0 to 6.9, 7.0 to 9.9, >10 and weight <23, 23 to 33, 34 to 44, >45. While body weight was recorded during each dog's visit, the individual height was not. As a proxy measure of body height, a variable called standard adult breed height for each dog was created by using published breed standards (Mandeville & Sidewater, 1987). Given a normal distribution of height in the controls, dogs were divided into quartiles in centimetres (<35.5, 35.5 to 54, 54.5 to 60.5, >61). Using a similar procedure, individual body weights were assigned using breed standards, both for dogs with missing values for body weight (n=1,579; 22.5%) and for all others (n=5,442; 77.5%). The standard weights were categorised using the same groups as for actual body weight.

Unadjusted odds ratio with 95% confidence limits (CL) were obtained for each potential risk factor. With regard to age, body weight, standard weight, and standard height, ORs were estimated separately for each stratum using the lowest category as the reference. The Mantel extension chi-square test was used to evaluate trends in the

[1] Department of Biomedical Sciences, and Human Oncology, University of Turin, via Santena 7, 10126, Turin, Italy
[2] Department of Veterinary Pathobiology, Purdue University, West Lafayette, Indiana 47907, USA

ORs across strata. Crude and age adjusted ORs and 95% CL for risk for individual breeds were calculated by comparing each breed with the German Shepherd breed, arbitrarily selected as the reference group. The risk by breed was estimated only for 15 breeds having a minimum of 100 dogs. To further evaluate the risk of osteosarcoma by neuter status, cases and controls were stratified by sex, breed, and institution. To characterise the relative importance of standard weight and standard height, the risk of osteosarcoma was estimated as a function of each, while controlling for the other and for age. Finally, host factors included in VMDB (i.e. age, sex, neuter status, breed, and body weight) that had biological or statistical significance (P value < 0.10) as potential risk factors and the stratification variables institution and year of diagnosis were included in a multivariate unconditional logistic regression analysis. In this model only dogs (n=4,223) from the 15 represented dog breeds were considered. German Shepherd breed was used as referent, and dummy variables were created for each breed.

RESULTS

A linear trend of increasing osteosarcoma risk was observed with increasing age (P<0.001). This pattern of risk by age was obtained also within each of the eight most represented breeds. In the unadjusted analysis there were no sex related differences in risk, but neutered dogs had twice the risk compared with sexually intact dogs (Table I). The association between risk of osteosarcoma and neutering was evident for both males (age adjusted OR 1.4, 95% CL 1.2-1.7) and females (OR 1.9, 95% CL 1.6-2.2). These findings were consistent for all the participating institutions and within most breeds. The Irish Wolfhound, Saint Bernard, and Great Dane breeds had the highest risk of osteosarcoma, whereas breeds of smaller size had lower risks. Risk increased with weight (P<0.001): the use of the actual body weight or the standard weight led to similar estimates, thus supporting the use of standard weight as a proxy measure of body weight. Increasing standard height was also associated with increasing osteosarcoma risk (P<0.001). Both the estimates of the OR for standard weight and standard height following adjustment for age only were similar to the unadjusted ORs. The OR for weight adjusted for height and age was less than the unadjusted OR for weight, although a residual effect of weight was evident for the largest dogs (> 45 kgs). In contrast the risk estimates for height after adjustment by standard weight were only slightly reduced compared to the risk for height alone (Table I). The logistic regression model confirmed most of the estimates obtained by the unadjusted analyses with an additional small increased risk for males. The osteosarcoma breed-risk ranking was only slightly affected by the adjustment for all other variables included in the model (i.e. sex, neuter status, age, and body weight).

Table I

Breed (n)	**OR [1]**	**95%CL**	**OR [2]**	**95%CL**
Irish Wolfhound (111)	18.0	7.9-43.5	18.9	7.0-50.7
Saint Bernard (230)	11.5	6.7-19.1	11.7	5.9-23.2
Great Dane (280)	5.2	3.6-7.5	5.2	3.1-8.5
Rottweiler (203)	2.0	1.4-2.8	3.5	2.2-5.5
Irish Setter (350)	4.5	3.3-6.1	3.2	2.2-4.6
Golden Retriever (537)	1.6	1.3-2.1	2.4	1.7-3.3
Doberman Pinscher (548)	2.5	2.0-3.3	2.2	1.6-3.0
Labrador Retriever (598)	1.0	0.8-1.3	1.3	1.0-1.8
German Shepherd (540) [5]	1.0		1.0	
Shetland Sheepdog (105)	0.3	0.2-0.5	0.7	0.3-1.4
Collie (122)	0.3	0.2-0.6	0.5	0.3-0.9
Miniature Poodle (166)	0.2	0.1-0.4	0.4	0.2-0.8
Miniature Schnauzer (116)	0.2	0.1-0.4	0.4	0.2-0.8
Dachshund (116)	0.1	0.0-0.1	0.1	0.1-0.4
Cocker Spaniel (201)	0.1	0.0-0.1	0.1	0.1-0.3
Sex	**OR [1]**	**95%CL**	**OR[2]**	**95%CL**
females	1.0		1.0	
males	1.0	0.9-1.1	1.3	1.1-1.6
Neutering	**OR [1]**	**95%CL**	**OR [2]**	**95%CL**
intact	1.0		1.0	
neutered	2.2	2.0-2.4	2.0	1.6-2.4

Age	**OR[1]**	**95%CL**	**OR[2]**	**95%CL**
<2 ys	1.0		1.0	
2-3.9	2.6	2.0-3.3	2.1	1.5-3.0
4-6.9	7.3	5.9-9.0	4.4	3.2-6.2
7-9.9	12.2	10.0-15.0	8.2	5.9-11.4
10>	9.9	8.0-12.2	9.8	7.0-13.8
Body weight	**OR[1]**	**95%CL**	**OR[2]**	**95%CL**
<23 kgs	1.0		1.0	
23-33	5.9	5.0-6.9	2.5	1.7-3.6
34-44	10.3	8.6-12.3	2.7	1.8-4.0
45>	22.8	18.1-28.9	2.8	1.7-4.7
Standard weight	**OR[1]**	**95%CL**	**OR[3]**	**95%CL**
<23 kgs	1.0		1.0	
23-33	5.5	4.8-6.5	1.4	1.1-1.8
34-44	7.8	6.5-9.1	1.1	0.5-2.2
45>	22.6	18.4-27.7	5.4	1.7-17.7
Standard height	**OR[1]**	**95%CL**	**OR[4]**	**95%CL**
<35.5 cms	1.0		1.0	
35.5-54	2.1	1.6-2.7	2.2	1.7-2.9
54.5-60.5	8.3	6.6-10.4	8.7	4.6-16.8
61>	15.8	12.7-19.7	4.8	1.6-14.8

(1) crude ORs ; [2] logistic regression-derived ORs adjusted for institution and year and, when appropriate, for breed, age, sex, neutering, and body weight; [3] ORs adjusted for age and standard height using the Mantel-Haenszel procedure; [4] ORs adjusted for age and standard weight using the Mantel-Haenszel procedure; [5] reference group. The breed risk ranking is based on adjusted ORs.

DISCUSSION

The present study confirmed that increasing age and increasing breed size are significant risk factors for osteosarcoma in dogs. Males had a small increased risk compared with females, which is similar to the

increased risk for males in humans. Also a twofold excess risk was observed among neutered dogs. Previously unreported findings included a significantly increased risk of osteosarcoma with increasing actual body weight adjusted for breed size, and vice versa, and with increasing standard height.

The study has some limitations. Sources of potential bias derive from the structure of VMDB, which does not include individual height. The use of proxy exposures such as standard height and standard weight does not allow for the study of individual variability within breeds, and may lead to misclassification. Nevertheless, when the analyses were limited to dogs for which actual weights were available, risk estimates for osteosarcoma based on actual or standard weights did not differ. As standard height and standard weight were highly correlated, the potential for effect modification could not be evaluated. With regard to the effect of neutering, unfortunately no information was available regarding when surgical neutering took place, i.e. either preceding or following onset of the tumour. Thus, the temporal sequence between the two events is uncertain. Nevertheless, most of the sarcomas occurred in older dogs whereas neutering presumably occurs in younger dogs, and owners would be unlikely to have such an elective surgical procedure performed on a dog diagnosed with an osteosarcoma. Also, there is no medical indication for neutering a dog with osteosarcoma.

The bimodal pattern of age risk reported for human osteosarcoma, which shows a major peak in the second decade of life and a smaller one at around age 70 (Parkin et al., 1992), was not apparent for dogs, even after performing the analysis within breeds of different size and therefore, different life span. A marginally increased risk for neutered dogs was previously reported. Using intact males as the reference category, an OR of 1.3 was observed for both neutered males and neutered females (Priester & McKay, 1980). The analysis of risk for neutering by institutions did not suggest regional differences. The higher risk for neutered dogs was consistent in the most represented breeds and unrelated to sex. The interpretation of a neutering effect on osteosarcoma risk, for both sexes, is not straightforward. Moreover, a hormonal mechanism has not been previously investigated even if bone growth is known to be influenced by hormonal patterns. One possible explanation is that the association with neutering is the result of confounding due to some unmeasured factor such as diet. For example, owners of neutered dogs may be more health conscious and thus more likely to feed their dogs a wide variety of mineral and vitamins supplements which may promote bone growth and increase osteosarcoma risk.

The overall risk pattern for osteosarcoma among the most common dog breeds suggests a major influence of the dogs' size, as in a previous study (Tjalma, 1966). However, a genetic susceptibility to osteosarcoma for individual breeds cannot be excluded. Patterns of familial aggregation of osteosarcoma have been shown by others (Bech-Nielsen et al., 1978) for Saint Bernards and we observed a wide range of risk of osteosarcoma among breeds of similar body size. To our knowledge, the role of height alone has not been previously investigated. A previous study (Tjalma, 1966) used standard weight as a proxy measure for body size. The findings of that study were consistent with the hypothesis proposed a decade before (Johnson, 1953) for the role of bone growth in children. The hypothesis was based on the observation that osteosarcoma occurred preferentially at sites of bone growth (i.e. metaphyses of long bones). Further evidence has been drawn from age and sex patterns of mortality from osteosarcoma. In both male and female children mortality from osteosarcoma correlates with the pubescent growth spurt with an earlier onset of osteosarcoma in females and an excess of osteosarcomas in males after age 13 (Miller, 1981). Fraumeni (1967) observed that children with bone cancer (both osteosarcoma and Ewing's sarcoma) were significantly taller at the time of diagnosis than controls, although this positive association was not confirmed in a more recent case-control study (Operskalski et al., 1987). The human data are consistent with the observations of our animal model suggesting that: a) more rapidly growing dogs are at the highest risk of osteosarcoma; b) there is a stronger and more consistent association of osteosarcoma risk with height than with weight; c) these findings can be explained, if it is assumed that height is a good surrogate measure for the rate of cell turn-over at the epiphyses of the long bones during the growth period. Finally, unlike previous studies (Tjalma, 1966), we used actual body weights rather than breed standards to confirm a significant role for this host factor. The risk of osteosarcoma increased with increasing weight, even after controlling for breed.

REFERENCES

Bech-Nielsen S., Haskins ME., Reif JS., Brodey RS., Patterson DF., Spielman R., 1978. Frequency of osteosarcoma among first-degree relative of St. Bernard dogs. JNCI 60, 349-353.

Fraumeni JF. ,1967. Stature and malignant tumors of bone in childhood and adolescence. Cancer 20, 967-973.

Johnson LC.,1953. A general theory of bone tumors. Bulletin of the NewYork Academy of Medicine 29, 164-171.

Mandeville JJ., Sidewater AB., 1987. The complete dog book. 17th ed. American Kennel Club. New York: Howell Book House.

Miller RW., 1981. Contrasting epidemiology of childhood osteosarcoma, Ewing's tumor, and rhabdomyosarcoma. JNCI 56, 9-14.

Operskalski EA., Preston-Martin S., Henderson BE., Visscher BR., 1987. A case-control study of osteosarcoma in young persons. Am.J. Epidemiol. 126, 118-126.

Parkin DM., Muir CS., Whelan SL., Gao YT., Ferlay J., Powell J., 1992. Cancer Incidence in Five Continents, Volume VI, IARC Scientific Publications No. 120, Lyon: International Agency for Research on Cancer.

Priester WA., McKay FW., 1980. The occurrence of tumors in domestic animals. Nat. Canc. Inst. Mon. 54, 169.

Tjalma RA.1966.Canine bone sarcoma: estimation of relative risk as a function of body size.JNCI36,1137-1150.