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## Canine neoplasia – Introductory paper

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The paper gives a brief introduction to canine oncology, including its comparative aspects as basis for recording tumours in the animal kingdom. In an abbreviated presentation of the Norwegian Canine Cancer Project for the years 1990 – 1998, the data (n=14,401) were divided into age groups, each of two years, into different categories of tumours, and into age and gender. As expected, cutaneous histiocytoma was the dominant tumour type in both sexes during the two first years of life. In the age group 2 – 3.99 years histiocytoma was still the largest group in males, but was surpassed by benign epithelial skin tumours in females. After the age of 4 years, benign epithelial skin tumours constituted the greatest circumscribed group in males, and mammary tumours in females, although the summated other tumours, not explained in this survey, dominated overall in males. Malignancies (cancer) were shown in the same way, by corresponding groups of gender and age. While mastocytoma was the most common tumour and non-Hodgkin's lymphoma the second most common during the two first years of life in females, the situation was reversed in males. Later, mammary tumours dominated in females, while different tumour types not further specified in this summarized report dominated in males, until the end of the age registration (above 14 years). Number, sex and location of most common tumours are shown in a tabular outline.

Comparative aspects between human and dog tumours are considered: mammary and testicular neoplasia seemed more frequent in dogs than in humans in Norway, while intestinal, pulmonary and prostatic malignancies were less common in dogs. In our study, vascular tumours and tumour-like lesions constituted about 3% of the total data. As benign vascular tumours are incompletely reported to the human Cancer Registry, no dependable comparison may be made, but malignant vascular tumours have been on the rise during the last decades in the Norwegian human population, more so in men than in women.

Finally, the article deals briefly with the development of endothelial cells, and the sparse information on causal factors of vascular tumours.

Key words: Dog, neoplasia, comparative aspects, population-based material, age, gender

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### 1. GENERAL CONSIDERATIONS ON ANIMAL ONCOLOGY

Recent decades have produced a growing interest for comparative oncology, largely due to the increasing understanding of the need for basic biological environmental monitoring systems. While primary concern is directed at mammals, even fish neoplasms have been used as indicators of environmental carcinogen concentration and a Registry of Tumors in Lower Animals has been established to gather information on tumours in fish and other poikilothermic

animals (1). Neoplasia in wild mammals is not considered common, probably due to the shorter lifespan of such animals (2). It must be admitted, however, that our knowledge of neoplasia in non-domestic animals is limited.

As far as domestic animals are concerned, the dog and cat are of special interest, since these species are more frequently affected by tumours than other animals. The “over-representation” of tumours in these species may be explained in part by the circumstance that only these animals are allowed to reach the “cancer age”, but may also be due to their close relationship to man in

respect to housing, environment and nourishment.

Prior to our study (1990–1998) there was a dearth of systematically-collected information on the occurrence of companion-animal tumours in Norway. Norway was considered well suited for such a project, since the canine population is quite controlled and stray dogs are unknown. Furthermore, almost all animals are sexually intact, so the incidence of tumours is not influenced by neutering. The following items were additional arguments for performing the study, as proposed also by others (3, 4):

- the canine lifespan is approximately 1/7 that of man, and the induction times of external carcinogenic factors are reduced correspondingly
- the canine species is divided into many phenotypically characteristic breeds. Although this does not strictly reflect the situation in man, pure breeds represent a valuable model for the study of the importance of inheritance versus environment in the development of cancer and other diseases
- the incidence of cancers in dogs may be compared with that in humans, but the relative risk of various types of cancer is different in the two species
- dog and man live in close contact, and are exposed to the same environmental influences
- increased information on the possible causes of cancer will allow better prevention and treatment in dogs
- cancer research based on recording spontaneously-occurring tumour incidence only in dogs does not imply any experimentation.

## 2. RESUME OF THE NORWEGIAN CANINE CANCER PROJECT 1990–1998 – RESULTS AND COMMENTS

This paper reports the total material gathered in The Norwegian Canine Cancer Project during the years 1990–1998. Veterinary surgeons in four counties (Akershus, Oslo and Troms; from 1991 also Finnmark) were invited to participate in the research project “Cancer in the Dog”. A free histopathological diagnosis was offered to

secure maximal approval, and our supposition is that participation was nearly complete. The registration programme was based on the premises presented above, and the population at risk contained a total of 14,401 tumours from 162 different pure breeds and from mixed breeds. A presentation of the total material has previously been given by Arnesen et al. (5).

The occurrence of tumours varied greatly among breeds and tumour types. About 50% of neoplasms were malignant. Locations are shown in Table 1. Tumours of the skin with adnexa and subcutaneous tissue dominated, as this heterogenous group constituted 51% of the total material; 22% exhibited malignant or pre-malignant features. The second largest group was mammary tumours, with an incidence of 30%. In contrast to others (6, 7), we diagnosed as many as 94% of these as malignant or pre-malignant. This discrepancy in malignancy has previously been discussed (5). A considerable proportion of mammary tumours (adenoma or carcinoma) is “complex”, in that they contain cellular elements derived from both secretory- and myoepithelial cells. The term “mixed” means containing a complexity of cellular units that include epithelium, myoepithelium and mesenchymal components of varying extent, frequently of cartilaginous and/or osseous character. This tumour type has been compared to the salivary pleomorphic adenoma in humans, which also contains myoepithelial cells and has been described as “mixed”; there is thus a difference in terminology, since “mixed” in the veterinary sense requires an additional mesenchymal component.

Among a total of 35 renal tumours are 18 cases of cystic renal adenocarcinoma in German shepherd dogs, first described in our laboratories in 1985 by Lium & Moe (8). This ailment is frequently combined with nodular dermatofibrosis. It is inherited in an autosomal dominant trait, and is of considerable comparative interest since it shows similarities with human polycystic renal disease, with increased risk of development of renal tumours. A later paper reports early cystic renal lesions in young German shepherd dogs, possibly representing early stages of this condition (9). The genetic background has also recently been studied (10, 11). Another report from our files is concerned with ocular tumours (12). An evident breed-depend-

TABLE 1. Number of tumours by location and sex. The Norwegian Canine Cancer Register 1990–98 (5)

Primary location*	Number of tumour diagnoses				Percent of total (N=14,401)	Percent pre-malignant/malignant
	Male	Female	Unknown	Total		
All	4,836	9,543	22	14,401	100	52
Skin with adnexa	3,388	3,995	18	7,401	51	22
Mammary gland	35	4,223	1	4,259	30	94
Oral cavity	300	233	1	534	3.7	31
Testis	345			345	2.4	**
Eye/eyelid	93	113	1	207	1.4	24
Vagina/vulva		172		172	1.2	8
Spleen	79	76	0	155	1.1	87
Lymph node	77	73	0	150	1	100
Skeleton (bone)	77	58	1	136	<1	98
Ovary		119		119	<1	72
Intestine	40	39	0	79	<1	68
Peritoneum/omentum/mesentery	54	23	0	77	<1	86
Liver and bile ducts	31	42	0	73	<1	89
Musculature	30	36	0	66	<1	55
Kidney	21	14	0	35	<1	94
Uterus/cervix		35		35	<1	26
Mediastinum, heart and thymus	18	15	0	33	<1	100
Urinary bladder and urinary tracts	5	26	0	31	<1	58
Lungs and bronchi	13	15	0	28	<1	96
Nasal cavity and sinuses	16	11	0	27	<1	96
Thyroid gland	13	14	0	27	<1	85
Stomach	13	11	0	24	<1	75
Central nervous system	9	15	0	24	<1	92
Salivary gland	11	11	0	22	<1	73
Adrenal	8	13	0	21	<1	48
Pancreas	11	10	0	21	<1	90
Pleura and pericardium	3	12	0	15	<1	100
Prostate	14			14	<1	100

\* Other and primary multicentric tumours (about 2%) are omitted from the table.

\*\* Estimation of malignancy uncertain.

ent occurrence was disclosed, both generally, and for certain tumour types (Table 2).

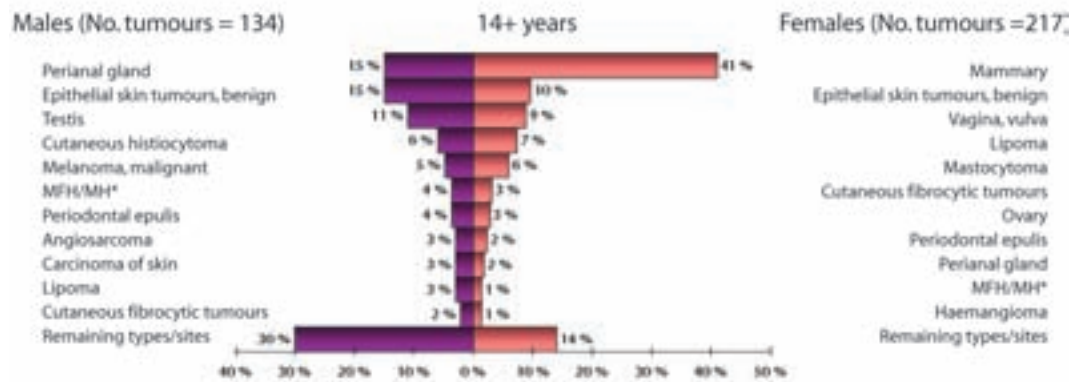
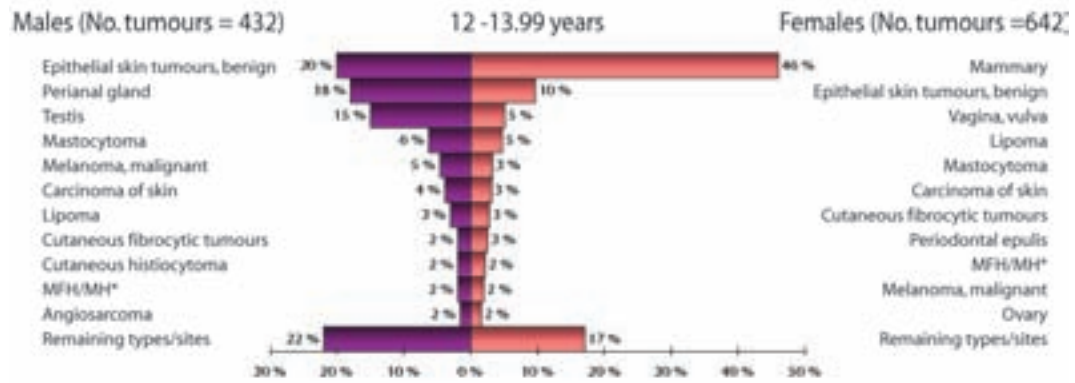
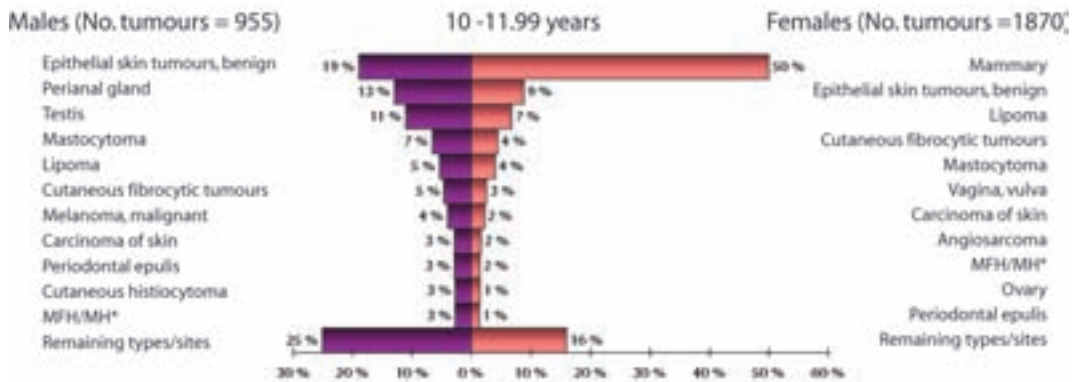
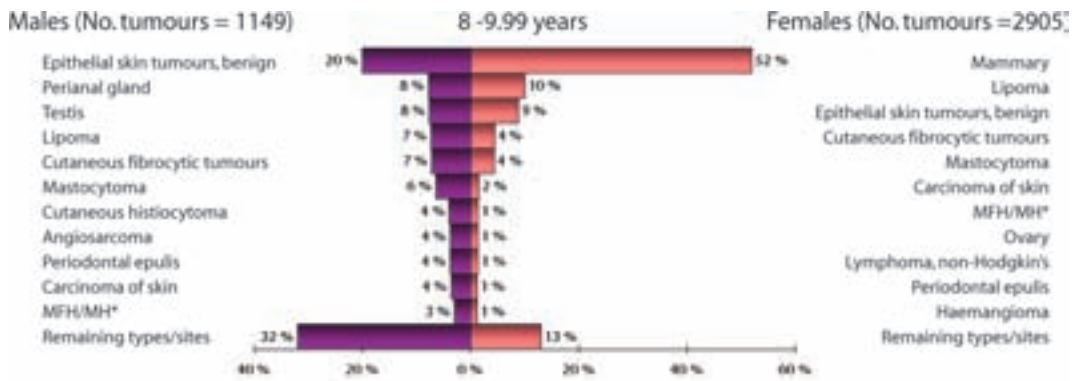
The most frequent types of benign and pre-malignant/malignant tumours, according to age and gender, are shown in figure 1. In the age group 0 – 1.99 years cutaneous histiocytoma, a benign tumour or tumour-like lesion now interpreted as derived from Langerhans' cells (13, 14), was the dominating tumour in both sexes, and most frequent in males. Benign cutaneous epithelial tumours were the second most common lesions; these lesions were more frequent in females than in males (17% and 11%, respectively). Benign skin tumours also constituted the greatest group in dogs age group 2 – 3.99 years (both sexes), with histiocytoma most frequent in males, and epithelial lesions in females. The third most frequent tumour group in fe-

males was mammary processes (10%). From 4 – 5.99 years benign epithelial skin tumours formed the major group in males, while in females mammary tumours had increased to 35%, and therewith became the prime female tumour. Benign skin tumours were still the next most common group in males, while benign epithelial skin processes were the second group in females. Mastocytoma, a pre-malignant/malignant tumour type most often located in the skin, was the third group in both sexes. In the age group 6 – 7.99 years, benign epithelial skin tumours dominated in males, at 21%, and mammary tumours in females, at 46%. Mastocytoma was the second most frequent tumour in males (9%), and benign epithelial skin tumours in females (13%). In third place, cutaneous fibrocytic tumours comprised 8% in males, and lipoma 11%



Fig. 1. Canine Tumours in Norway: The most frequent types of tumours (benign and malignant) 1990–98 by age and sex. Figure continues on next page.

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\* Malignant fibrous histiocytoma/Malignant histiocytoma

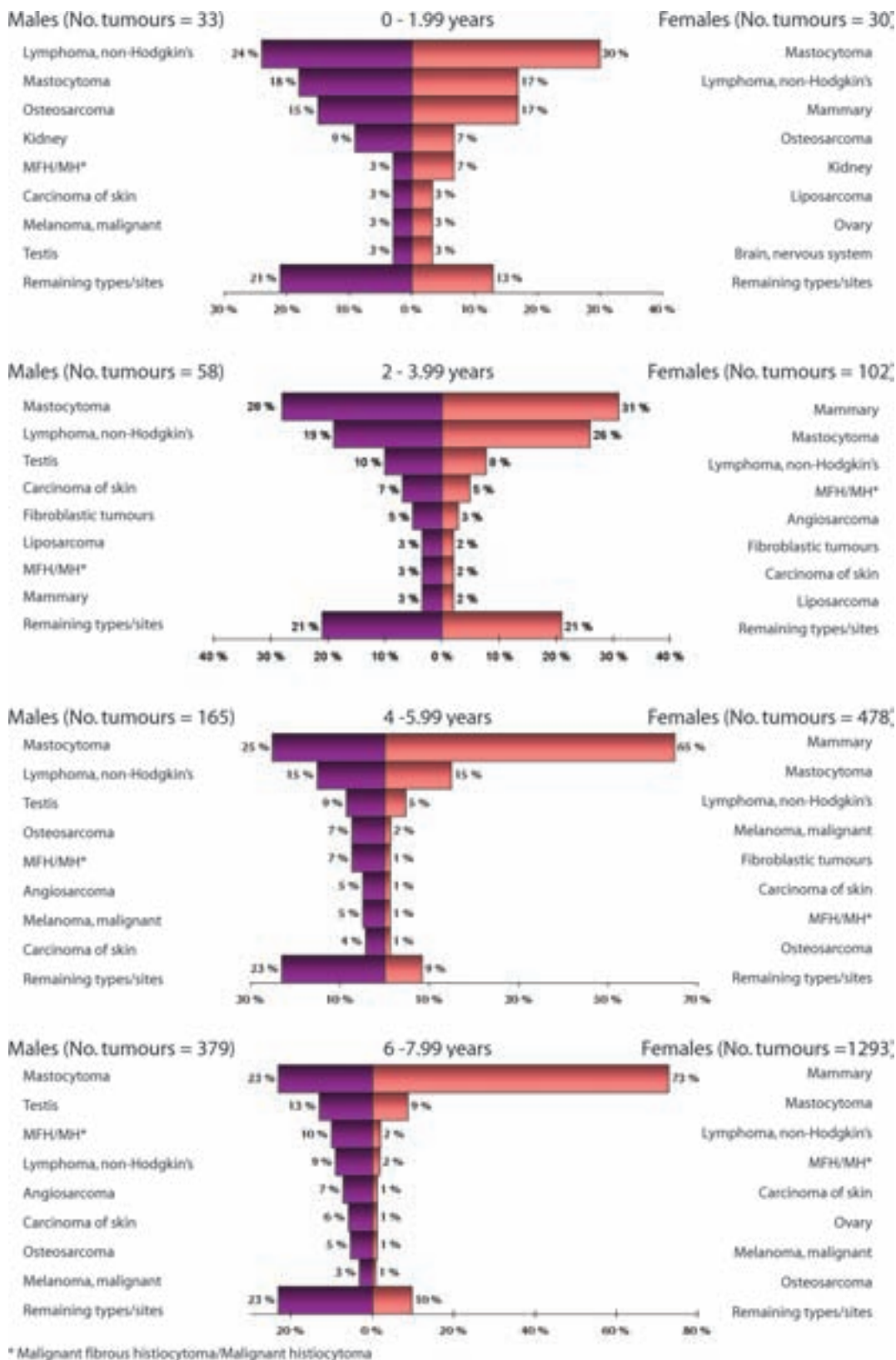
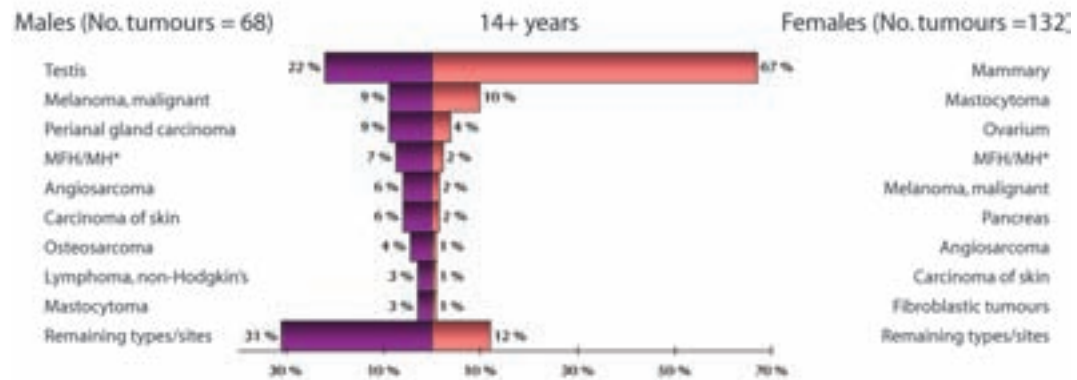
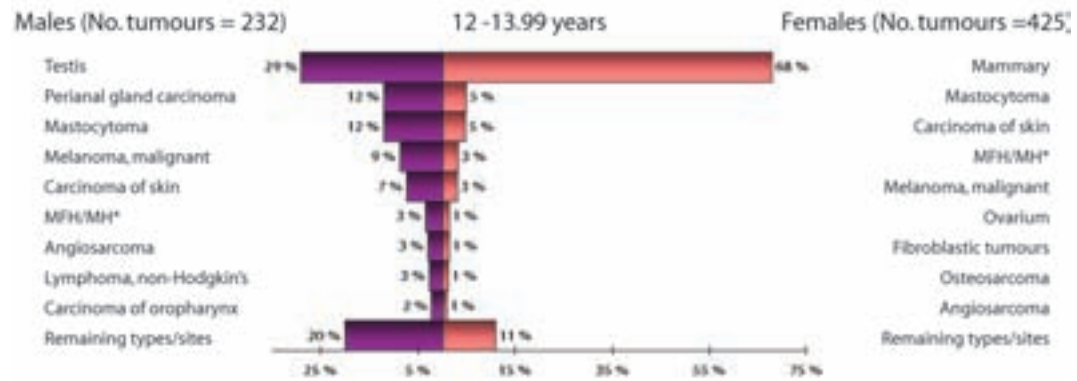
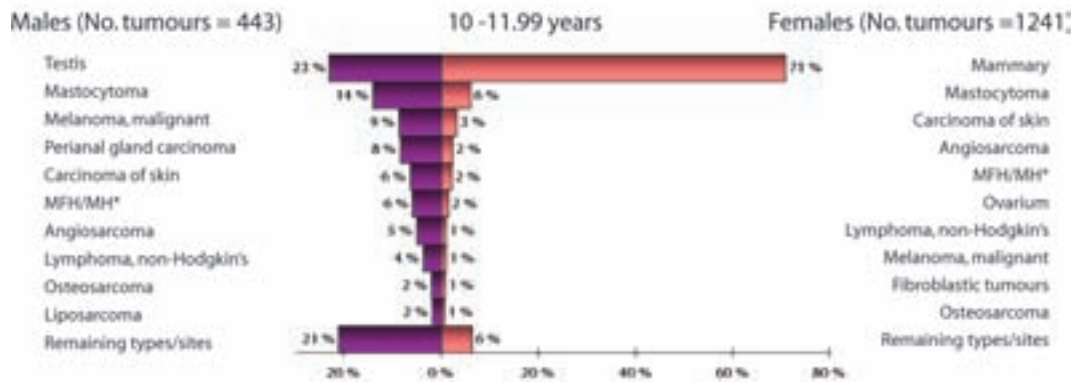
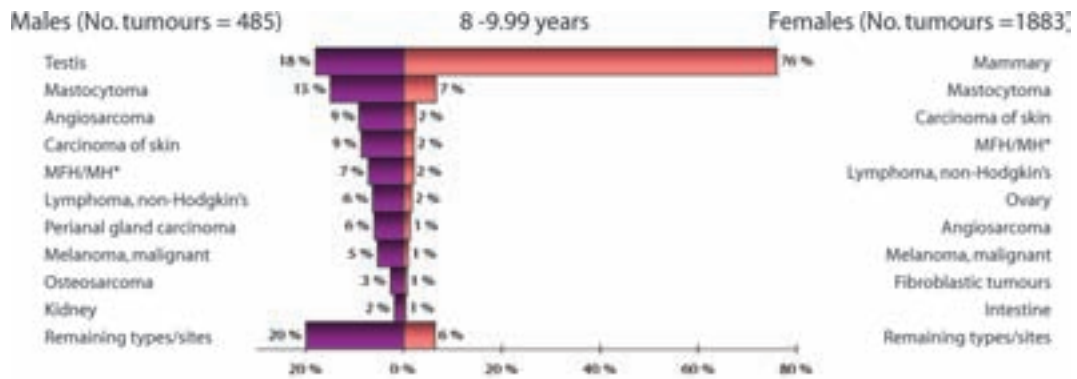


Fig. 2. Canine Cancer in Norway: The most frequent types of cancer 1990–98 by age and sex. Figure continues on next page.



\* Malignant fibrous histiocytoma/Malignant histiocytoma

TABLE 2. The relative risk ratio (RR) for all tumours, mammary tumours, testicular tumours, non-Hodgkin's lymphoma, malignant fibrous histiocytoma and malignant histiocytosis (MFH/MH), and osteosarcoma in 20 breeds. Breeds having >210 registrations per year (N) with the Norwegian Kennel Club (NKC) were included. The Norwegian Canine Cancer Register 1990–98

Breed	Regis- trations with NKC N	Total no tumour diag- noses n	Relative risk ratio (RR)*					
			All tumours	Mam- mary	Testis	Lym- phoma	MHF/ MH**	Osteos- arcoma
Boxer	315	647	385	283	369	690	154	251
Flat-coated retriever	545	811	279	114	49	361	767	338
Giant schnauzer, black	213	233	205	95	168	340	274	
English cocker spaniel	485	460	178	214	129	64	100	
Rottweiler	507	452	167	100	35	265	192	1,144
English setter	1,347	1,147	160	154	126	92	87	39
Bernese mountain dog	274	218	149	29	98	264	1,277	481
Dobermann	278	205	138	156	32	186	210	379
Laborador retriever	881	649	138	101	61	153	88	29
German pointer	655	461	132	172	55	32	104	80
Poodle (except Standard)	485	323	125	211	203		40	54
Golden retriever	1,459	926	119	98	190	163	127	108
Irish setter	358	212	111	130	100	116	54	220
Dachshund	714	364	96	194	125	43	41	73
German shepherd dog	2,826	1,401	93	126	73	88	48	37
Bichon frise	595	291	92	136	120		49	
New foundland	288	129	84	50	124	144	68	366
Gordon setter	456	192	79	60	59	136	107	115
American cocker spaniel	215	90	78	98		96	45	
Siberian husky	296	98	62	58	181	70	99	

\*  $RR = \left( \frac{n_s}{N_s} / \frac{n_t}{N_t} \right) \times 100$  is by definition the mean of the RR-values for each cancer category.

$n_s$  = number of tumours in the breed, 1990–1998;  $N_s$  = NKC's number of dogs registered for the breed, 1982–1997

$n_t$  = number of tumours for all breeds, 1990–1998;  $N_t$  = NKC's number of dogs registered for all breeds, 1982–1997

\*\* MFH/MH = Malignant fibrous histiocytoma/malignant histiocytosis

in females. In the age group 8 – 9.99 years benign epithelial skin tumours in males and mammary tumours in females still prevailed, while perianal gland tumours and lipoma had taken over as the second most common tumour types in males and females, respectively. Testicular tumours are the third most common group in males, at 8%, while in females benign epithelial skin tumours have this position. From 10 – 11.99 years of age benign epithelial skin tumours retained the primary position in males, and mammary tumours in females, with approximately the same incidence as in preceding age group (about 50%). Benign epithelial skin tumours were also the most common lesions from 12 – 13.99 years of age in males, while mammary tumours showed a slight decrease

compared with the preceding group of age in females. As in the two preceding age groups perianal gland tumours and testicular tumours followed skin tumours in males; benign epithelial skin tumours and tumours of vagina/vulva were the second and third group, respectively, in females. From 14 years of age perianal gland tumours and benign epithelial skin tumours were equally frequent in males (15%), while the frequency of mammary tumours had decreased to about 40% in females; benign epithelial skin tumours were still the second most common tumour also in females. Testicular tumours seemed somewhat reduced compared with the preceding age group (15% and 11%, respectively), while vaginal and vulval processes were nearly doubled.

Figure 2 shows the most frequent types of canine cancer by age and gender, comparable to cancer statistics in man. In the age group 0 – 1.99 year non-Hodgkin's lymphoma was the most frequent malignant tumour in males, with 24%, while mastocytoma constituted the largest number in females, with 30%. For the next most common cancer type, the sexes were reversed, 18% mastocytoma in males and 17% lymphoma in females; however, in females mammary cancer were of the same magnitude. In males mastocytoma was also prime in the age group 2 – 3.99 years, with 28%, while mammary cancer was the greatest type in females, i.e. 31%. The second most common malignant tumour was lymphoma in males and mastocytoma in females, with 19% and 26%, respectively. Also in the male age group 4 – 5.99 years mastocytoma was the most frequent type, with 25%; in females the percentage of mammary cancer had increased to 65%. Thereafter, the frequencies of lymphomas in males, and mastocytomas in females were equal (15%). In the age group 6 – 7.99 years mastocytoma still constituted the largest cancer type in males, with 23%; in females the percentage of mammary cancer had increased to 73. In this age group testicular tumours were of the next most common, 13%, in males, while mastocytoma was still the second most common cancer type in females. In the age group 8 – 9.99 years testicular tumours had increased to 18%, and represented the most common cancer in males, while mammary cancers reached their highest incidence, with 76%. Mastocytoma was the second most common cancer in both sexes, 15% in males and 7% in females. Angiosarcoma, which is of special interest in our study, is represented among males with 9%, i.e. the third most common cancer type. In the age group 10 – 11.99 years testicular tumours had increased to 23% and were still the most frequent cancer in males. Although there was a slight decline in the frequency of mammary cancer (71%), these tumours were still the most frequent female cancer type. Likewise, mastocytoma retained the second place in both sexes, with 14% in males and 6% in females. Among animals 12 – 13.99 years of age testicular tumours were still the most common cancer type, with 29%, while the corresponding most common cancer in females, mammary cancer, had declined to 68%. Mastocytoma was slightly reduced in both sexes, but still the second

most common cancer type, although perianal gland carcinoma was of equal magnitude in males. In animals more than 14 years of age, sex-related cancers, testicular tumours in males, and mammary cancer in females, were still represented with the highest incidence, although there seemed to be a slight reduction in both sexes; mastocytoma retained second place in females, while malignant melanoma had occupied the second place in males.

### 3. SOME COMPARATIVE ASPECTS ON CANINE AND HUMAN NEOPLASIA

When compared with the statistics of the human Cancer Registry of Norway, mammary and testicular neoplasms, and also osteosarcomas were found to be more frequent in dogs than in people, while malignancies of the intestine, lung and prostate were less common in dogs. In previous studies in these laboratories a close morphologic resemblance of the canine non-Hodgkin's lymphoma to the human counterpart has been shown (15); also the occurrence of non-Hodgkin's lymphoma was approximately equal in both species (Table 3).

Vascular tumours and tumour-like lesions constitute 3% (439/14401) of the registered tumours in our study (16). Information from the human Cancer Registry shows that benign vascular lesions are incompletely reported to the Registry (17, 18). The incidence of malignant vascular tumours rose from 1981 through the 1980's to the 1990's, when the age-adjusted incidence was nearly doubled in males; in females there was an increase of about 20% (Tables 4 and 5). Malignant vascular tumours are more common in both sexes in the urban than in the rural Norwegian sub-population (Tables 4 and 5), indicating a difference in contributing factors between urban and rural environments.

### 4. ENDOTHELIAL CELL DEVELOPMENT, VASCULOGENESIS AND VASCULAR TUMOURS

The vascular endothelial cells (EC) originate from stem cells/angioblasts in embryonic mesoderm, although, the detailed molecular events involved in EC differentiation remain uncertain

TABLE 3. *A comparison of the incidence of cancer at particular locations in people and dogs (Based on 1994 report of the Cancer Registry of Norway and the Norwegian Canine Cancer Register 1990–98) (5)*

Malignant tumours (Cancer)	Human		Dog	
	Number	%	Number	%
All sites	19,284	100	7,467	100
Intestine	2,871	15	54	0.7
Prostate	2,330	12	14	0.2
Mammary	2,156	11	4,011	54
Lung and bronchi	1,773	9	27	0.4
Testis	198	1.0	345	4.6
Skeleton/bone	40	0.2	133	1.8
Lymphoma	603	3.1	251	3.4

TABLE 4. *Annual incidence rates per 10 million of malignant vascular tumours of skin (C44) in the Norwegian population 1981–2000 by sex, calendar period, and urban/rural districts. (No of cases in parenthesis)*

Age (year)	Urban		Rural	
	1981–90	1991–2000	1981–90	1991–2000
<b>Males</b>				
0–19	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
20–39	45.1 (13)	42.5 (14)	2.8 (1)	6.0 (2)
40–59	57.8 (11)	70.5 (18)	7.8 (2)	20.4 (6)
60–79	111.1 (16)	138.5 (20)	164.0 (31)	104.8 (18)
80+	571.2 (11)	541.7 (14)	804.1 (24)	416.1 (14)
All	58.1 (51)	65.1 (66)	48.8 (58)	34.6 (40)
Adjusted	40.2	41.1	22.0	18.8
<b>Females</b>				
0–19	0.0 (0)	0.0 (0)	2.9 (1)	0.0 (0)
20–39	0.0 (0)	6.2 (2)	0.0 (0)	0.0 (0)
40–59	15.5 (3)	4.0 (1)	16.4 (4)	0.0 (0)
60–79	46.8 (9)	65.1 (12)	99.6 (21)	41.4 (8)
80+	173.6 (8)	266.9 (16)	249.9 (12)	335.6 (20)
All	21.3 (20)	29.1 (31)	32.4 (38)	24.4 (28)
Adjusted	8.2	11.0	15.5	6.6

(19, 20). Vascular and haematopoietic tissues develop together, with formation of “blood islands” within the primitive yolk sac of the embryo (21) and cell-cluster proliferations arising in the embryonic aorta from the aorta-gonad-mesonephros region (22, 23). Angioblasts and haematopoietic stem cells are ultimately derived from a common precursor, the putative haemangioblast (24, 25). Angioblasts form the outer layer of ECs encasing the “blood islands”, and haematopoietic stem cells populate the inner cluster from which the first embryonic blood cells develop. Within the embryo, the first angioblasts arising from the lateral mesodermal plate and cardiac crescent assemble into the endocardium of the early heart tube (21, 26). Other angioblasts form a plexus of ECs at the base of the primitive heart tube, which assemble

into the vitelline vessels and thus allow blood cells initially located in the region of yolk sac to circulate within the body, and populate the mesenchyme throughout the foetus (21). Recently, it has been demonstrated that circulating “blood island”-derived cells contribute to the genesis of both extra- and intraembryonic blood vessels in the early quail embryo (27). This finding establishes that the embryonic vasoformation is a composite of two processes: 1) the direct *in situ* formation of blood vessels from mesoderm-derived angioblasts, and 2) incorporation and differentiation of circulating endothelial progenitor cells into forming embryonic vasculature (27). Bone marrow-derived endothelial progenitor cells or angioblasts have been identified from peripheral blood in the adult as well (28, 29), and recently, adult peripheral

TABLE 5. Annual incidence rates per 10 million of malignant vascular tumours of all sites and of skin (C44) in the Norwegian population 1981–2000 by sex, calendar period. (No of cases in parenthesis)

	Age (year)	All sites		Skin	
		1981–90	1991–2000	1981–90	1991–2000
<b>Males</b>					
	0–19	5.1 (3)	5.2 (3)	0.0 (0)	0.0 (0)
	20–39	40.3 (26)	48.2 (32)	21.7 (14)	24.1 (16)
	40–59	60.6 (27)	125.6 (69)	29.2 (13)	43.7 (24)
	60–79	195.2 (65)	183.5 (58)	141.1 (47)	120.2 (38)
	80+	856.0 (42)	521.1 (31)	713.3 (35)	470.6 (28)
	All	78.9 (163)	89.0 (193)	52.8 (109)	48.9 (106)
	Adjusted	50.9	63.1	30.1	29.5
<b>Females</b>					
	0–19	5.3 (3)	7.3 (4)	1.8 (1)	0.0 (0)
	20–39	18.0 (11)	22.0 (14)	0.0 (0)	3.1 (2)
	40–59	38.9 (17)	37.7 (20)	16.0 (7)	1.9 (1)
	60–79	121.6 (49)	111.2 (42)	74.4 (30)	53.0 (20)
	80+	318.8 (30)	334.6 (40)	212.5 (20)	301.2 (36)
	All	52.1 (110)	54.2 (120)	27.5 (58)	26.6 (59)
	Adjusted	28.9	31.2	12.1	8.8

blood CD34+ stem cells are shown to transdifferentiate into cardiomyocytes, mature ECs, and smooth muscle cells *in vivo* (30).

Vasculogenesis refers to *de novo* organization of ECs from stem cells or angioblasts into vessels in the absence of pre-existing vascular structures, and contrasts with angiogenesis, which implies the formation of new microvessels as a result of EC proliferation, migration, branching and intussusceptive growth from existing capillaries (24). Angiogenesis occurs during embryogenesis and in the postnatal state. Vasculogenesis has been largely restricted to early embryogenesis, however, recent studies on bone marrow-derived stem cells (CD34+, CD133+) with haematopoietic and endothelial potential isolated in peripheral blood of adult species are consistent with postnatal vasculogenesis (29, 31, 32). These findings indicate postnatal neovascularization sites by incorporation of circulating endothelial progenitor cells that differentiate into endothelial cells *in situ*, and suggest that vasculogenesis and angiogenesis may constitute complementary mechanisms also for postnatal physiological and pathological neovascularization (29, 32). The induction of angioblasts to differentiate into ECs, organise into a vascular network, and subsequently populate the specialised vascular bed of an organ, results from a complex genetic program. The transcriptional processes that regulate the first steps in vasculogenesis are not well defined (20). However, HoxB5 is necessary and suf-

ficient to activate the cell-intrinsic events that regulate the differentiation of angioblasts and mature endothelial cells from their mesoderm-derived precursors (20). Dyscontrolled vasculogenesis with accumulated transcriptional abnormalities may result in neoplasia, and development of vascular tumours.

## 5. VASCULAR NEOPLASIA – AETIOLOGY AND OCCURRENCE

Congenital haemangiomas, by some interpreted as hamartomas, are very common in the human being. Haemangiomas are also well known in adults; this topic is detailedly described in a following paper (16). Chronic lymphoedema, sometimes combined with irradiation, are considered to be important predisposing factors for angiosarcomas in man (33). It is known that exposure to AsO<sub>3</sub> or vinyl chloride has given rise to hepatic angiosarcomas, and that angiosarcomas in this site also have been reported as sequela to the application of thorium dioxide, the contrast medium Thorotrast, previously used for cerebral angiography (33, 34, 35, 36). Information on causal factors is otherwise rather limited, but angiosarcomas have occasionally been reported adjacent to deposits of foreign material, associated with renal transplantation, and in connection with rare genetic abnormalities (33).

Vascular tumours are described in a number of animal species, also in wild animals (2). In addition to dogs, haemangiomas are known in cattle, horses and cats (37). Among domestic animals, angiosarcomas are by far best known in dogs. While most authors point out German shepherd as the breed most commonly affected (37–43), Priester reports that angiosarcoma is most frequent in the boxer, and in further declining frequency in the Great Dane, German shepherd and English setter (44); the last observation, reporting the boxer as the most exposed breed is in accordance with our population-based observations (45). Breed differences are not known in other animal species (37). Genetic studies are few, but angiosarcoma associated with tumour suppressor gene p53 mutation has been reported in a cat (46) and in a dog (47). A recent study indicates that mutations of PTEN tumour-suppressor gene participate in the origin and behaviour of canine haemangiosarcoma (48). Solar irradiation has been suggested responsible in some dermal canine cases (49, 50), but such a possibility seems unlikely in our material, as also doubted in humans (33). Application of 1,2-dimethylethylhydrazine dihydrochloride in mice (51, 52) and dimethylnitrosamine in mink have produced hepatic vasoproliferative lesions interpreted as angiosarcomas (53, 54).

Some years ago Oksanen assumed an increase of angiosarcomas in Finnish dogs (55), but this hypothesis was not supported by epidemiological data. An increase of angiosarcoma frequency has also been suggested in the cat (50). Apart from Priester (44) and our own investigation no population-based study seems to exist on the incidence in animals. Therefore, for comparative reasons, the increasing frequency of vascular tumours in man shown in this paper should stimulate further studies in dogs.

The authors wish to thank IT-Adviser Steinar Hansen, Cancer Registry of Norway, for preparation of figures 1 and 2.

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