Available online at www.sciencedirect.com
SCIENCE DIRECT

ELSEVIER

Preventive Veterinary Medicine 69 (2005) 109–127

PREVENTIVE VETERINARY MEDICINE

www.elsevier.com/locate/prevetmed

Incidence of and survival after mammary tumors in a population of over 80,000 insured female dogs in Sweden from 1995 to 2002

Agneta Egenvall [a,*], Brenda N. Bonnett [b], Patrik Öhagen [a], Pekka Olson [c], Åke Hedhammar [d], Henrik von Euler [d]

[a] *Department of Clinical Sciences, Faculty of Veterinary Medicine and Animal Science, Swedish University of Agricultural Sciences, SE-750 07 Uppsala, Sweden*

[b] *Department of Population Medicine, Ontario Veterinary College, University of Guelph, Guelph, Ontario, Canada N1G 2W1*

[c] *Agria Insurance, PO 70306, SE-107 23 Stockholm, Sweden*

[d] *Department of Small Animal Clinical Sciences, Faculty of Veterinary Medicine and Animal Science, Swedish University of Agricultural Sciences, SE-750 07 Uppsala, Sweden*

Received 8 July 2004; received in revised form 25 January 2005; accepted 26 January 2005

Abstract

The main objective of this study was to describe the incidence of mammary tumors (MTs) and the survival after MTs, in female dogs between 3 and 10 years of age (insured for veterinary care and with life insurance in a Swedish animal-insurance company) from 1995 to 2002. Measures of incidence are presented crudely, by breed and across age categories and birth cohorts (1991–1998). The survivals until MT diagnosis and after a MT diagnosis were computed. The overall incidence for any MT claim was 111 dogs per 10,000 dog-years at risk (DYAR). The overall MT rate in the 1992 and 1993 birth cohorts was 154 dogs per 10,000 DYAR. The incidence for any MT claim increased with age and varied by breed, from 319 dogs per 10,000 DYAR in the English springer spaniel to 5 dogs per 10,000 DYAR in the rough-haired collie. At the ages 6, 8 and 10 years, 1%, 6% and 13% respectively, of all

* Corresponding author. Tel.: +46 18671369; fax: +46 18673545.
E-mail addresses: agneta.egenvall@kv.slu.se, agneta.egenvall@kirmed.slu.se (A. Egenvall).

0167-5877/$ – see front matter
doi:10.1016/j.prevetmed.2005.01.014

females had at least one MT claim. The MT mortality was 6 deaths per 10,000 DYAR and increased with age. The overall-case fatality was 6%.

Keywords: Dog; Insurance; Database; Mammary tumor; Breed; Cox regression; Life-table; Cohort analysis; Poisson regression; Longitudinal study

1. Introduction

Mammary tumors (MT) are the most-common type of tumor in intact-female dogs (Brodey et al., 1983). There is little information concerning the current incidence of canine MT. Among commonly cited studies, Schneider (1970) reported an incidence of 145 per 100,000 dog-years at risk in female dogs in California, USA. Recently, Dobson et al. (2002) reported a standardized-incidence rate for MT of 205/100,000 dogs/year, based on a defined population of insured dogs in the UK.

In addition to the high incidence and potential of being fatal, similarities with human breast cancer have prompted several studies on the incidence and factors affecting the incidence of MT in female dogs (Schneider, 1970; Owen, 1979; MacEwen, 1990; Knapp and Waters, 1997; Schafer et al., 1998). High-risk breeds vary depending on study and geographic location. Toy and miniature poodles, English springer spaniels, Brittany spaniels, cocker spaniels, pulis, English setters, pointers, German shepherds, Maltese, Yorkshire terriers and dachshunds have been reported to have increased risk of developing MT, suggesting a genetic component (Mac Vean et al., 1978; Kurzman and Gilbertson, 1986; Boldizsar et al., 1992; Yamagami et al., 1996; Moe, 2001). The age of onset (Priester, 1979; Boldizsar et al., 1992; Moe, 2001), the effect of spaying (Misdorp, 1988; Rutteman et al., 2003) and hormonal treatments (Misdorp, 1988; Donnay et al., 1993; Stövring et al., 1997) were studied.

The risk of developing MTs in dogs is significantly decreased by ovariohysterectomy at an early age as illustrated by an increasing risk of developing MTs of 0.5%, 8%, to 26%, depending on whether ovariohysterectomy is performed before the 1st, 2nd, or any estrus thereafter, respectively (Schneider et al., 1969). Although earlier disputed there is also recent evidence for the importance of timing of spaying on survival of dogs with MTs. In a study by Sorenmo et al. (2000) dogs that were spayed <2 years before MT surgery had a significantly longer overall survival compared to the group of intact dogs and dogs that were spayed >2 years before MT treatment.

The Agria insurance database (Agria Insurance, PO 70306, SE-107 23 Stockholm, Sweden) has been used to study mortality up to an age of 10 years and morbidity up to an age of 12 years in Swedish dogs (Egenvall et al., 2000a,b,c, 2001). It has been shown that the dogs in this database are representative of Swedish dogs in general and that the database contains large numbers of individuals of breeds seen worldwide. The demographic validity (breed, age, gender) of the database is excellent, while the diagnostic validity in general is satisfactory (Egenvall et al., 1998). In other work by us, among insured females (up to 12 years of age), in 1996 1.4% had at least one veterinary-care claim reimbursed with a diagnosis of MT (unpublished data). Despite the lack of verification and classification by histology and life-insurance coverage only until 10 years of age, it is a large database that allows estimation of breed, age and geographical effects on canine MTs in a well-defined population of dogs. Unfortunately, neuter status is not recorded in this insurance database, but only a small proportion of Swedish bitches, approximately 7%, are neutered (Egenvall et al., 1999).

The main objectives of this study were to describe the incidence of MT and survival after MT in female dogs, between 3 and 10 years of age, insured for veterinary care and with life insurance in Agria during 1995–2002. This includes measures of incidence crudely, by breed and across age categories and birth cohorts (1991–1998) and survival until and after a MT diagnosis crudely and by breed (only for survival until). Variables for geographic location and urban/other location were used to adjust for potential confounding.

2. Materials and methods

2.1. The insurance database

There are two types of insurance for dogs offered from Agria. Veterinary-care insurance has no age limit and reimburses the owner most of the fee if the dog receives costly veterinary care. Dogs can also be life insured, but only up to 10 years of age. With life insurance the owner will generally be reimbursed if the dog dies/is euthanized. Whether the dog dies or undergoes euthanasia cannot be differentiated in the database. Most insured dogs have both types of insurance. Some dogs ($n = 805$) that were settled for life insurance, without actually dying/being euthanized were omitted from the present study. The insurance process has been described in detail (Egenvall et al., 2000a,b,c). In the present study dogs had to be insured before 3 years of age to be included (8% of the dogs in the database entered after 3 years of age).

2.2. Data management

Data from the insurance database were downloaded to a personal computer. Variables used were diagnoses for claims (both for veterinary care and life insurance), dates when dogs entered or left the insurance program, the types of insurance for which dogs were enrolled, breed, date of birth, date of death, gender (male or female) and postal code of the owner. All males were eliminated from further analysis.

Breeds were classified according to the Swedish Kennel Club breed-classification system. In the analysis, some breeds were combined because they were considered to be the same. For example, ‘‘dachshund miniature’’ included all dachshund miniature variants, ‘‘dachshund normal-size’’ included all except long-haired dachshunds, ‘‘German pointer’’ included both smooth-haired and wire-haired German pointers, and ‘‘poodle’’ included miniature and toy poodles.

Many dogs originally insured before 1993 had year of birth accurately recorded (Egenvall et al., 1998), but it had not been possible to register the date and month of birth. However, most of the dogs have had their date and month of birth updated since then. The dogs with only year of birth recorded were considered to have been born the 2nd of July.

For analyses which required dogs to be in chronological-age categories, these were assigned based on the age of the dog on the 1st of January (i.e. <1, $1 < 2$, ..., $9 < 10$ years).

The owner's postal code (the last registered) was used to identify where in Sweden the dog lived. Three different regions were defined: south, middle and north. Dogs were also recorded as living in either an urban environment, based on whether the owner resided in one of the three largest cities in Sweden or elsewhere in Sweden (urban = Stockholm, Göteborg or Malmö; versus 'other'). Because not all postal codes could be matched to geographic location, 0.06% of the dogs lacked information for geographic location/urban versus other.

Diagnostic codes had been assigned by the attending veterinarian based on a hierarchically constructed diagnostic registry with approximately 8000 codes (Swedish Animal Hospital Organisation, 1993). In this registry there is only one code for MT, which means that the cases cannot be separated by histologic type or criteria of malignancy.

We assumed that essentially no dogs develop MTs before 3 years of age and the few ($n = 69$) claims for MT in the studied population before this age were excluded from further analysis. Data for the years 1995–2002 were available, and the main analyses included data from the birth cohorts 1992–1999. The analyses that were based on age categories included data on birth cohorts 1991–1998. Accordingly, all estimates refer to female dogs $\geq$3 years and $<$10 years of age, alternatively age categories $3 < 4$–$9 < 10$, where age categories were used for analysis.

An individual was considered to be an incident-case of MT at the time of the first-recorded diagnosis. Dogs could have either (i) one or more veterinary-care claims for MT, (ii) just a life claim for MT (e.g. a primary-life claim event) or (iii) both one or more veterinary-care claims and a life claim for MT (either simultaneous or subsequent). In the insurance database, the recording of disease events for dogs with multiple receipts does not allow for a clear differentiation between ongoing-original events versus recurrent or new cases of a disease. If a dog had two or more receipts for veterinary care or life insurance with a diagnosis of MT $>$ 6 months apart, we arbitrarily considered that the dog had experienced a second MT event (either a recurrence or a new MT).

2.3. Analyses

Descriptive statistics are presented on the number of bitches in the analysis, the number with a claim(s) for MT (by insurance type), the distribution of veterinary receipts in those settled for at least one MT event and the incidence of multiple MT events. Crude and breed-specific age distributions for MT cases are presented.

Incidence rates were calculated with exact denominators. Each animal contributes to the denominator the exact time they were at risk (dog-years at risk, DYAR) in the database. The incidence rates are multiplied by 10,000 to be interpreted as the number of dogs with MT per 10,000 DYAR. These incidence densities only pertain to risk between 3 and 10 years of age. (Note that the data are imbalanced such that dogs in earlier birth cohorts, e.g. dogs born in 1992, provide data for all ages, while later birth cohorts only provide data for a younger and shorter part of the lifespan.) Several analyses were performed separately on data for the two full 7-year birth cohorts (1992 and 1993).

Incidence-rate calculations were done for the overall-withdrawal rate (based on all dogs that leave the database, including those dying), overall-mortality rate (with any diagnosis assigned, excluding dogs that were dead but not claimed) and for rates for claims coded with the diagnosis MT. The rates for MT were related to the first receipt with the diagnostic code MT, for having multiple events (receipts >6 months apart) for MTs and for mortality because of MT. The denominator for the multiple-event rate includes the time contributed (starting at age 3 years) by all dogs in the study population until the second MT event or censoring occurred. Standard errors (S.E.) for incidence rates were constructed taking the root of the number of cases and dividing by the DYAR (Breslow and Day, 1987), then multiplying by 10,000. Case fatality (CF) is evaluated as the proportion of cases with a MT life-insurance diagnosis out of all dogs with MT.

Age and birth-cohort-specific incidence rates were constructed for the first MT diagnosis. The age-category-specific rates were averaged over the birth cohorts.

Breed-specific incidence rates related to the first MT diagnosis were constructed for the most common breeds (those with the most DYAR). Incidence rates related to the first MT diagnosis were constructed stratified by geographic location and urban versus other.

The crude and breed-specific proportions of bitches that were claimed for MT up to certain ages (6, 8, 10 years) was calculated for the breeds with >50 cases of MT, using the baseline-survival statement from Cox regression (and without independent variables). Each dog was entered January 1st, 1995 or later at the date of enrolment and removed either when it had a MT event or when the dog left insurance. Dogs not removed before December 31st, 2002 were considered withdrawn at that date. For the analysis, we assumed that the risk of MT before 3 years of age is 0. Age-specific and breed- and age-specific incidence rates were constructed using the SMOOTH macro (Allison, 1995), which computes age-specific hazards (densities or more-general rates) from the baseline-survival function computed by PHREG (SAS Institute Inc., Cary, NC, 27513, USA). This provides a smoothed estimate of the hazard curve using a kernel-smoothing method. The WIDTH parameter was set to one-fifth or one-tenth of the range of event times. Overall and MT-specific mortalities were constructed using the same method.

A multivariable Cox regression was developed using as covariates the 38 breeds with most DYAR (marked with [c] in Table 1) (entered as 37 dummies with mongrels as the primary baseline), geographic location (baseline = north) and the variable urban/other (baseline = other). The outcome was time to the first MT event. All possible two-way interactions were tested between the variables that stayed in the model after backward main-effect reduction based on Wald's criterion. The proportional-hazards assumption was investigated by plotting the natural logarithm of the cumulative hazard stratified by each included covariate (log–log plots; from Cox regressions without covariates as described above) against the log of DYAR. Because of the large sample size a P-value of 0.01 was considered significant in the final-multivariable models, also, the interactions were added at $P < 0.01$. Overall-model fit was using Cox-Snell residuals (Dohoo et al., 2003). Model fit was also inspected using plots of martingale and deviance residuals against DYAR and against covariates. Confidence intervals presented for hazard ratios are 99% (99% CIs). The statistical-software program SAS (SAS Institute Inc., Cary, NC, 27513, USA) was used to analyse the data, the procedure PHREG was used for Cox-proportional hazard regression.

Table 1
The incidence (per 10,000 dog-years at risk) of mammary tumors (MT) from a female population of dogs ($\geq$3 and <10 years of age) insured in Agria[a] for veterinary care and with life insurance from 1995 to 2002

Breed[b] (risk-rank for MT)	Number of dogs	Number of cases	Median age at diagnosis (in years)	Incidence rate	Standard error
American cocker spaniel (5)	558	33	7.7	192	33
Beagle[c] (29)	720	23	7.0	95	20
Bearded collie[c] (45)	773	14	7.1	50	13
Bernese mountain dog[c] (41)	857	14	7.6	54	15
Bichon frisé[c] (8)	830	47	7.3	172	25
Border collie[c] (43)	1909	31	7.8	51	9
Borderterrier (24)	781	30	6.9	116	21
Boxer[c] (3)	709	55	6.4	256	34
Cairn terrier[c] (12)	1058	55	7.2	148	20
Cavalier King Charles spaniel[c] (38)	1867	41	7.5	64	10
Dachshund (smooth/wirehaired, normal size) [c] (27)	2883	109	7.6	104	10
Dalmatian[c] (36)	626	16	7.7	72	18
Doberman[c] (2)	468	36	6.7	297	49
Drever[c] (39)	2274	45	7.6	62	9
Elkhound[c] (32)	1347	33	8.4	80	14
English cocker spaniel[c] (13)	1306	58	7.6	142	19
English springer spaniel[c] (1)	2101	226	6.9	319	21
Finnish hound[c] (50)	809	4	6.8	17	9
Finnish spitz[c] (47)	620	8	7.8	40	14
Flatcoated retriever[c] (31)	1293	39	7.0	94	15
German pointer[c] (16)	1218	51	7.5	128	18
German shepherd[c] (9)	6088	322	7.1	170	9
Golden retriever[c] (35)	4511	118	7.7	73	7
Irish setter[c] (19)	636	28	6.9	126	24
Jack russell[c] (26)	902	29	7.2	105	19
Jamthund[c] (21)	1501	47	6.1	122	18
Labrador retriever[c] (28)	3942	133	7.1	96	8
Leonberger (7)	464	24	6.5	176	36
Miniature dachshund[c] (20)	3104	133	7.4	126	11
Miniature schnauzer[c] (33)	861	21	7.7	77	17
Miniature/toy poodle[c] (15)	1587	70	8.0	136	16
Mongrel[c] (25)	3108	111	6.9	116	11
Munsterländer (30)	436	15	7.4	95	24
Newfoundland (49)	457	3	6.3	21	12
Nova Scotia duck tolling retriever (17)	610	25	6.6	126	25
Papillon[c] (10)	806	39	7.7	158	25
Petite bassett griffon (18)	635	25	7.6	126	25
Rottweiler[c] (22)	1575	56	7.3	121	16
Rough-haired collie[c] (51)	1284	2	7.9	5	3
Samoyed (37)	479	11	7.9	72	22
Shetland sheepdog[c] (46)	1151	18	7.9	47	11
Shih-tzu (34)	601	14	7.0	74	20
Softcoated wheaten terrier[c] (4)	782	48	6.8	199	29
Standard poodle[c] (23)	778	29	7.7	120	22
Standard schnauzer (14)	474	20	7.5	142	32

Table 1 (*Continued*)

Breed[b] (risk-rank for MT)	Number of dogs	Number of cases	Median age at diagnosis (in years)	Incidence rate	Standard error
Swedish hound[c] (44)	1477	25	7.3	50	10
Tervueren (42)	514	9	7.0	51	17
Tibetan spaniel (48)	430	4	7.4	29	14
Wachtel dog (11)	551	26	7.7	149	29
West highland white terrier[c] (40)	711	15	8.6	60	15
Yorkshire terrier[c] (6)	628	40	8.1	188	30

[a] Agria Insurance, PO 70306, SE-107 23 Stockholm, Sweden.

[b] Breeds with >1000 dog-years at risk in each breed.

[c] Breeds with >2000 dog-years at risk in each breed.

Poisson regression, using the SAS procedure GENMOD, was used for the cohort analysis (cohort-age-period analysis) (Holford, 1983; Moolgavkar et al., 1998). The denominator in each cell was the DYAR appropriate for that cell; the natural logarithm of this was used as offset in the model. The aim was to model the effect of three variables: period, cohort and age category. Five models were constructed—(a) ‘‘age’’ effect, (b) ‘‘period’’ effect, (c) ‘‘period-and-age’’ effect, (d) ‘‘cohort’’ effect and (e) ‘‘cohort-and-age’’ effect. The period and cohort effects were modelled using dummy variables. Age was modelled as a linear effect after verifying that the age variable was linearly related to the outcome. Interactions were not considered for inclusion. Confidence intervals for incidence density-rate ratios (IDRRs) are 99% CIs. Model fit was inspected by plotting deviance residuals against covariates and predicted values. Over-dispersion was not directly evaluated because each dog belonged to multiple records (e.g. by period and cohort) in the dataset. However, subsets of the data (e.g. mainly age in period 2001 and 2002) could be analysed with respect to single-risk factors. These analyses produced results that were similar to the results from the whole dataset.

The causes of death (MT, other tumors or other causes) are reported for dogs that had a diagnosis of MT. This included only claimed deaths where a diagnosis was assigned.

The survival in dogs after the diagnosis MT is reported using life-table analysis, using the SAS procedure LIFETEST. In these analyses dogs with a MT-life claim within 30 days from first MT-claim were excluded.

Cox-proportional regression, using the PHREG procedure, with the event of MT as a time-dependant covariate was used to analyse whether an MT event had any impact on survival. The deaths were all dogs with an assigned life-insurance diagnosis during the study period; the rest were considered as censored. The time at original diagnosis of MT was modelled excluding dogs with a MT-life claim within 30 days from first MT-claim. Also the time of multiple events of MT was modelled as a time-dependant covariate, both separately and together with the time of original MT-diagnosis. These models were done ignoring breed on the whole dataset and separately by breed using data on the 13 breeds with the most MT cases. In the breed-stratified models the *P*-value was set to 0.05, while in the overall model a 99% CI was used (because the breed-specific populations were generally much smaller than the total population).

3. Results

3.1. The population

In the main analyses over 80,000 bitches were included at any time during the study period, accounting for over 250,000 DYAR; there were >48,000 bitches at the end of year 2002. The females were from over 280 different breeds and they were born during 1992–1999. Their ages ranged from 3 years to 10 years of age. The number of years each dog contributed ranged from a few days to 7 years, with 2.9 years as median (mean 3.2 years). In the age-category-based analyses, data on over 80,000 bitches were used, accounting for over 270,000 DYAR.

3.2. Withdrawal and overall mortality

The overall mortality (Fig. 1) with an assigned diagnosis was 248 (S.E. 3) deaths per 10,000 DYAR (incidence for bitches ≥3 years up to 10 years) and the withdrawal was 1245 (S.E. 7) per 10,000 DYAR.

3.3. Morbidity related to MTs

Of the 2925 bitches that had at least one receipt with the diagnosis MT, 2858 had veterinary-care events registered (98%). Of the 1793 MT cases in the 1992 and 1993 birth

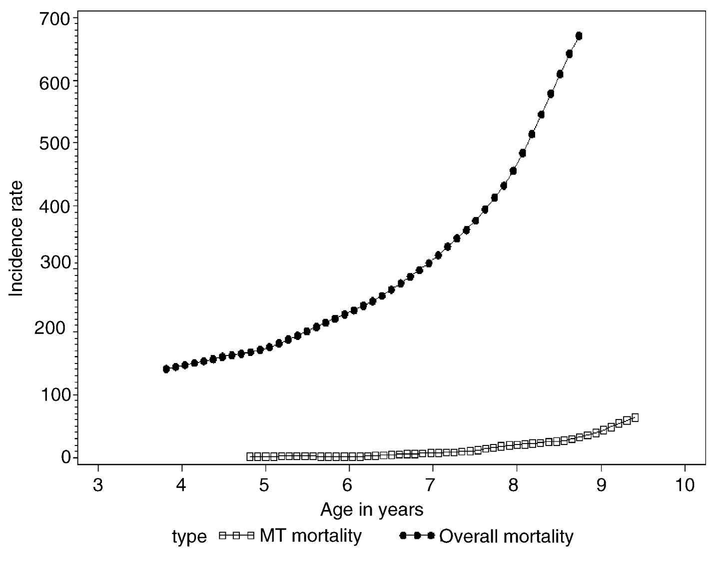

Fig. 1. Age-specific mortality rate (per 10,000 dog-years at risk) with respect to the diagnosis mammary tumor (MT) for females dog insured at Agria (a) for veterinary care and with life insurance 1995–2002. Note: (a) Agria Insurance, PO 70306, SE-107 23 Stockholm, Sweden, (b) smoothing procedure makes the graph lines span different-age intervals.

cohorts, 1740 had veterinary-care events registered (97%). In the age-category-based analysis there were 3852 cases (for the cohort analysis).

Of the 2858 dogs with at least one receipt for veterinary care with the diagnosis MT, 61% of the dogs had only one receipt, 25% of the dogs had two receipts and 15% of the dogs had more than two receipts. The total number or receipts for veterinary care with a diagnosis of MT was 4677.

The overall-incidence density related to the first MT diagnosis was 111 (S.E. 2) per 10,000 DYAR (incidence for bitches $\geq$3 years up to 10 years). The overall MT rate in the 1992 and 1993 birth cohorts was 154 (S.E. 4) per 10,000 DYAR. The median age of the MT cases was 7.3 years, ranging from 3.0 years to 10.0 years. Table 1 presents the breed-specific incidence rates in 51 breeds with a denominator of at least 1200 DYAR.

Table 2 presents the cumulative crude and breed-specific probability, from Cox regression, of not yet developing a MT at age 8 and 10 years for the breeds with at least 50 MT cases. At 6 years of age the proportion that had not developed a MT was 98.6% (95% CI: 98.5, 98.7) in the whole dataset and 98.5% (95% CI: 98.4, 98.7) in the 1992 and 1993 birth cohorts. For the breeds reported in Table 2 this estimate for 6 years of age varied between 95% and 99%.

Fig. 2 presents the incidence rates for having a MT claim for all dogs in the study, by age category and birth cohort (1991–1998). Fig. 3 demonstrates the age-specific incidence rate from Cox regression related to the first MT diagnosis.

Table 2
The proportion of bitches not affected by mammary tumors (MT) at 8 and 10 years of age in 13 breeds with at least 50 cases of MT in dogs insured at Agria[a] during 1995–2002, the number MT deaths and case fatality

	8 years (cohort 1992–1995)		10 years (cohort 1992–1993)		MT mortality	
	Percent	95% CI	Percent	95% CI	No.	CF[b]
Boxer	86	82, 90	77	70, 94	6	11
Cairn terrier	92	90, 95	85	81, 89	2	4
Dachshund (smooth/wirehaired, normal size)	95	94, 96	89	86, 91	2	2
English cocker spaniel	94	91, 96	82	77, 87	2	3
English springer spaniel	85	83, 87	68	64, 73	10	4
German pointer	94	91, 96	85	81, 89	4	8
German shepherd	91	90, 93	80	77, 82	34	11
Golden retriever	97	96, 97	92	90, 94	6	5
Labrador retriever	96	95, 97	90	88, 92	4	3
Miniature dachshund	94	93, 95	85	81, 89	2	2
Miniature/toy poodle	95	93, 97	81	77, 86	1	1
Mongrel	94	93, 96	87	84, 90	6	5
Rottweiler	93	90, 95	84	79, 89	4	7
All dogs	94.5	94.2, 94.7	86.9	86.4, 87.5	167	6
1992–1993 birth cohorts	94.4	94.1, 94.8	86.9	86.3, 87.5	136	8

It is assumed that no females develop MT before 3 years of age.
[a] Agria Insurance, PO 70306, SE-107 23 Stockholm, Sweden.
[b] Case fatality% = the number dead with MT assigned as diagnosis/divided by all dogs with MT × 100.

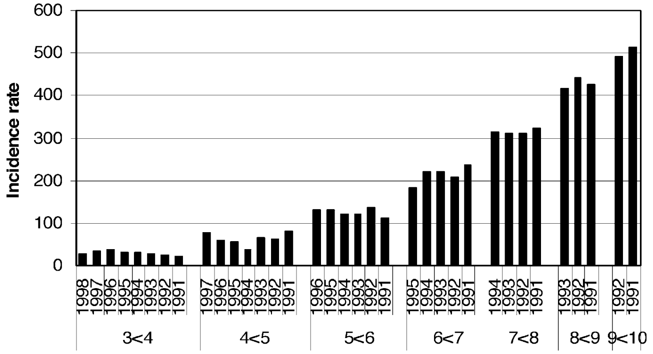

Fig. 2. Incidence rate (per 10,000 dog-years at risk, DYAR) for the first diagnosis of mammary tumor in all breeds by age category (3 < 4 up to 9 < 10) and birth cohorts (1991–1998). Data are from dogs insured for life and veterinary care at Agria (a) between years 1995 and 2002. Cases range from 21 to 262 in each bar (b). Note: (a) Agria Insurance, PO 70306, SE-107 23 Stockholm, Sweden. (b) The average-incidence rate for age category 3 < 4 was 29 per 10,000 DYAR, for the other age categories 63 (age category 4 < 5), 126 (5 < 6), 215 (6 < 7), 315 (7 < 8), 429 (8 < 9) and 502 (9 < 10) cases per 10,000 DYAR.

The incidence rate of MTs in the southern region of Sweden was 102 (S.E. 3) per 10,000 DYAR, 127 (S.E. 3) per 10,000 DYAR in the middle region and 82 (S.E. 5) per 10,000 DYAR in the northern region. In dogs with urban residence the incidence rate of MTs was 138 (S.E. 5) per 10,000 DYAR compared to 103 (S.E. 2) per 10,000 DYAR in dogs from other areas.

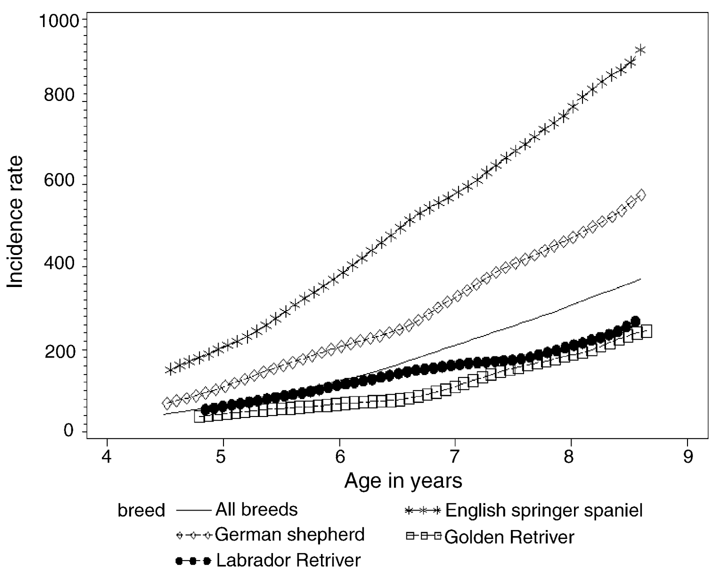

Fig. 3. Age-specific (for all breeds) and breed- and age-specific incidence rates (per 10,000 dog-years at risk) of mammary tumors for female dogs of four breeds insured for veterinary care and with life insurance at Agria (a) 1995–2002. The incidences are developed using Cox regression.

Table 3
Hazard ratios (HRs) with 99% confidence intervals (99% CIs) from Cox regression of time to the first veterinary-care event with the diagnosis mammary tumor

Breed	Hazard ratio	99% CI
Doberman	3.2	2.0, 4.9
English springer spaniel	2.7	2.2, 3.3
Boxer	2.3	1.6, 3.3
Softcoated wheaten terrier	1.7	1.2, 2.5
German shepherd	1.5	1.3, 1.8
Labrador retriever	0.8	0.6, 1.0
Drever	0.6	0.4, 0.8
Golden retriever	0.6	0.4, 0.7
Cavalier King Charles spaniel	0.5	0.4, 0.8
Border collie	0.5	0.3, 0.8
Swedish hound	0.5	0.3, 0.8
West highland white terrier	0.4	0.2, 0.9
Shetland sheepdog	0.4	0.2, 0.7
Bearded collie	0.4	0.2, 0.9
Finnish spitz	0.4	0.2, 1.0
Finnish hound	0.2	0.05, 0.6
Rough-haired collie	0.04	0.006, 0.2
Baseline (BL) breeds	1	–
Urban	1.3	1.1, 1.4
Other—BL	1	–
Middle region	1.2	1.1, 1.4
North and south region-BL	1	–

The data are from female dogs 3–10 years old insured at Agria (Agria Insurance, PO 70306, SE-107 23 Stockholm, Sweden.) during 1995–2002. The model includes data from 38 breeds (see Table 1), using data on 59,047 bitches.

3.4. Multivariable modeling of MT morbidity

Of the 38 breeds with at least 2000 DYAR (see Table 1) entered in the Cox model where the time to first MT event was modelled, 17 breeds stayed in the final model (Table 3). The dataset consisted of 59,047 dogs with 2185 MT cases. Middle region was also retained in the final model (southern and northern residence as baseline). No interactions were significant at $P \leq 0.01$ (or even at $P \leq 0.05$). The baseline breeds are those of the 38 (see Table 1) breeds that are not in the model. The log–log plots demonstrated that the proportional hazards assumption was justified. In the martingale and deviance plots the largest residuals belonged to dogs that became cases early in life (just after 3 years of age). No systematic pattern was found in the residual plots against covariates. The plot of Cox-Snell residuals demonstrated an overall good fit.

The dataset used in the Poisson models (Table 4) consisted of 80,189 dogs, including 3852 MT cases (the dataset used in the univariable age-category-based analysis). In the regressions all included variables were highly significant at $P < 0.0001$ using the type-3 criterion except that cohort (in the age-cohort model) had $P = 0.44$. The interpretation is that there are age and period effects; however, no (significant or real) cohort effect. In general, the deviance residual plots were judged to be satisfactory.

Table 4
Incidence density-rate ratios (IDRRs) from Poisson regression for the age and period and the age and cohort model

Variable	Level	Age-period model		Age-cohort model	
		IDRR	99% CI	IDRR	99% CI
Age		1.6	1.5, 1.6	1.6	1.6, 1.6
Period	1995 (BL[a])	1.0	–	–	–
	1996	1.9	1.1, 3.5	–	–
	1997	1.9	1.1, 3.3	–	–
	1998	2.4	1.4, 4.2	–	–
	1999	2.2	1.3, 3.8	–	–
	2000	2.2	1.3, 3.8	–	–
	2001	2.1	1.2, 3.7	–	–
	2002	2.0	1.2, 3.5	–	–
Cohort	1991 (BL)	–	–	1.0	–
	1992	–	–	1.0	0.9, 1.1
	1993	–	–	1.0	0.9, 1.2
	1994	–	–	1.0	0.9, 1.2
	1995	–	–	1.0	0.8, 1.2
	1996	–	–	1.0	0.8, 1.3
	1997	–	–	1.0	0.7, 1.4
	1998	–	–	0.6	0.4, 1.1

The outcome is the initial mammary-tumor claim. Data are from Agria (Agria Insurance, PO 70306, SE-107 23 Stockholm, Sweden.) and from the years 1995–2002 (n = 80,189).
[a] Baseline.

3.5. Mortality and multiple events related to MTs

Eleven hundred twenty nine bitches had receipts with the diagnosis MT with different-claim dates (irrespective of whether for life insurance or for insurance for veterinary care). Of these, 356 bitches (12% of the 2858 bitches with "not only" life-insurance claims settled) had receipts that were >6 months apart and therefore were defined by us as multiple events. The maximum time elapsed between the receipts was 5.7 years. The incidence rate for multiple events was 13 (S.E. 0.7) per 10,000 DYAR.

The proportion of all deaths that were due to MTs was 2.5%. Further, of all 2925 dogs with a MT event 167 dogs (CF 6%) had a life-insurance event with the diagnosis MT during the study period. In the 1992 and 1993 birth cohorts, 136 of 1793 dogs (CF 8%) had a life-insurance event with the diagnosis MT. The breed-specific case fatality is shown in Table 2, for the 13 breeds with over 50 dogs claimed for MT. (Only 35 dogs were classified as both having multiple events and having a MT life-insurance event.)

The mortality rate due to MT was 6 (S.E. 0.5) deaths per 10,000 DYAR. Fig. 1 demonstrates the age-specific MT mortality rates.

In total 6060 of the dogs in the study population died with a diagnosis assigned. (Of the insured population that die before 10 years of age, 28% die/are euthanised without a diagnosis, for example because of behavioural problems or pet-owner mismatch, unpublished data.) Of the 2295 MT cases, 414 died or were euthanized with an assigned diagnosis during the study period. Of those, as reported above, 167 dogs (40%) were

Table 5
Cumulative non-cause-specific survival from first mammary-tumor (MT) diagnosis using life-table analysis

Time interval	All cohorts (309 dead of 2820)		1992 and 1993 cohorts (242 dead of 1709)	
	P (survival)	S.E.	*P* (survival)	S.E.
$0 < 1$[a]	1.00	–	1.00	–
$1 < 2$	0.94	0.01	0.93	0.01
$2 < 3$	0.88	0.01	0.87	0.01
$3 < 4$	0.83	0.01	0.81	0.01
$4 < 5$	0.77	0.01	0.74	0.02
$5 < 6$	0.73	0.02	0.70	0.02
$6 < 7$	0.66	0.04	0.63	0.04

Data are from dogs insured at Agria (Agria Insurance, PO 70306, SE-107 23 Stockholm, Sweden.) during 1995–2002, followed from 3 to 10 years of age. Dogs with a MT life-insurance claim within 30 days of first diagnosis were excluded ($n = 105$ for "all" and 84 for "1992 and 1993 cohorts").

[a] Years after first MT claim (dogs that die up to but not including 1 year after first MT-diagnosis will be noted as dead at the time interval $1 < 2$).

assigned a diagnosis of MT, 103 dogs (25%) died due to tumor other than MT and 144 (35%) had a non-tumor diagnosis. In the 1992 and 1993 birth cohorts, of the 1793 MT cases 326 dogs died with a diagnosis assigned. Of these, 136 (42%) had a MT diagnosis, 69 (21%) had an other-tumor diagnosis and 121 (37%) had a non-tumor diagnosis.

Table 5 shows the survival in yearly intervals after diagnosis (not adjusted for age) in the whole dataset ($n = 82132$, excluding 105 dogs with a MT life event within 30 days of first

Table 6
Hazard ratios, in brackets if $P \geq 0.05$, from Cox regression with previous claim of MT[a] and with multiple MT-events[b], included as time-dependant covariates

Breed	No. dying (any diagnosis)	Previous MT claim[c]	Multiple events
Boxer	89	1.2[d]	2.5[d]
Cairn terrier	47	1.6[d]	0.0[d]
Dachshund (smooth/wirehaired, normal size)	220	0.7[d]	0.0[d]
English cocker spaniel	96	1.6[d]	1.0[d]
English springer spaniel	128	1.5[d]	2.5[d]
German pointer	74	3.1	13.4
German shepherd	624	1.5	4.1
Golden retriever	220	1.5[d]	5.5[d]
Labrador retriever	206	2.1	2.6[d]
Miniature dachshund	207	1.7[d]	5.3
Miniature/toy poodle	76	1.6[d]	6.6[d]
Mongrel	122	2.1[d]	4.0[d]
Rottweiler	153	2.1	4.4[d]

The outcome is time to death from any assigned diagnosis. Regressions were performed separately by breed on data on 13 breeds insured at Agria (Agria Insurance, PO 70306, SE-107 23 Stockholm, Sweden.) during 1995–2002.

[a] MT-mammary tumor.

[b] MT events more than 6 months apart.

[c] Cases that died within 30 days of first MT event excluded.

[d] Effects were nonsignificant.

diagnosis). In the non-breed-specific models the effect of previous MT was significant. The hazard ratio was 1.7 (99% CI: 1.4, 2.0) with $P < 0.0001$. In the model with multiple events the hazard ratio was 2.9 (99% CI: 2.0, 4.1), $P < 0.0001$. In the model with both effects the hazard ratio for previous MT was 1.5 (99% CI: 1.3, 1, 8), $P < 0.0001$ and for multiple events 1.9 (99% CI: 1.3, 2.8), $P < 0.0001$. The effect of the time-dependant covariates for each of the 13 breeds with the most MT cases are shown in Table 6 for previous MT and for multiple events.

4. Discussion

4.1. The population and the database

The Agria insurance database contains approximately one-third of the Swedish dog population (Egenvall et al., 1999). However, dogs older than 10 years are not covered by life insurance and mongrels are under-represented. Several aspects of the Swedish population are similar to other-dog populations. However, few dogs are neutered, e.g. only 7% of the bitches (Egenvall et al., 1999). Spaying of bitches in Sweden often takes place because of medical reasons, e.g. pyometra, and hence not very early in life (Egenvall et al., 2001). Unfortunately, neuter status is not recorded in the database.

Because a secondary database cannot be expected to have completely accurate recording of diagnoses, an insurance database will not capture exactly the total incidence of MTs. The general-diagnostic validity of the data in the Agria database is "adequate": >80% in the groups analyzed (Egenvall et al., 1998). We presumed that the MT diagnosis is relatively straightforward compared to many diagnoses because it can be made using visual inspection and palpation. Also, most of the dogs will be treated by surgery, which will give the treating veterinarian a possibility to view/dissect or send a biopsy from the lump. However, some dogs assigned as cases will have very mild or benign disease. In general, the histology report will not be finalized at the time of submitting the claims for veterinary care. It is a limitation to these data that no information on malignancy or cell type is included in the diagnosis. (Neither is information on the type of treatment provided available.)

In a study by Hellmen et al. (1993) it was shown that the disease entity "MT" is fairly accurately used as a clinical diagnosis in Sweden. Out of 202 histologically and DNA-content-investigated tumors, only nine (4%) were considered as non-MT (four "other tumors" and five mammary dysplasias). Thus, the use of this large insurance database to study MT in dogs is justified, even in the absence of histologically-confirmed diagnoses.

The inclination to seek veterinary care when the animal has a lump will differ by personality and type of owner, and breed. Some owners will know to palpate the mammary glands because these owners have encountered MT before. In some dogs it will be easier to find a lump (shorthaired, lean dogs). When in relation to the discovery of the lump owners seek veterinary care will also vary. Most insured dogs will have anything but miniscule lumps examined. Surgery is most often the treatment of choice and any surgery is likely to exceed the deductible, making it probable that the database captures most insured dogs seen by veterinarians because of MTs. However, relatively small non-growing lumps might not be excised and if the deductible is not reached the event will not be registered in the database. In cases of uncertainty, some veterinarians might be hesitant to assign a tumor diagnosis on the receipt to avoid labeling the dog before the diagnosis is confirmed.

4.2. Analytical issues and issues with interpretation

We used the data to calculate incidence measures, even if it could be argued that the disease might have been prevalent for some time when the owner seeks veterinary care. Incidence was appropriate because most dogs were followed since they were young (and MT free), owners are likely to take the dog to a veterinarian if they encounter this problem, veterinarians are likely to correctly diagnose MTs and MTs are likely to be covered by the insurance policy. The most correct way to express the incidence could be to say that it is the incidence for veterinary-care events/life-insurance events related to MTs.

The aim was to study a disease that occurs mainly after 5 years of age and there were eight calendar years of data available. Therefore, only cases occurring after 3 years of age/ in age category $3 < 4$ were included. In the full database some cases of MTs were found in young dogs in these birth cohorts during the study period (4 cases <1 year, 24 cases between 1 and 2 years of age, and 41 cases between 2 and 3 years of age, data not shown). These low numbers justify the exclusion of the youngest cases and it has been reported that only 1.52% of MT cases were below 4.8 years of age (Schneider, 1970).

It is important to examine breed-specific information on disease risk because breeds differ to a great extent with respect to conformation, usage and genetics, and from this insurance database it is possible to produce such estimates with reasonably large denominators and many cases. However, in some instances (for example CF for MT or in survival until MT for relatively low denominator/numerator breeds), it is difficult to produce estimates that have statistically sound and biologically meaningful information. (Therefore, fewer results are shown for some breeds than others.)

The geographic and rural/other variables were included mainly to control for otherwise unidentified confounding. This decision was based on previous results where these variables influenced the proportion of dogs receiving veterinary care (Egenvall et al., 2000a). Keeping only the variables and terms that were significant in the multivariable Cox model, middle versus south and north had a slightly higher risk of MTs. The reason could be different inclination to seek or availability of veterinary services in different areas of Sweden. There might also be biological reasons behind incidence differences in different geographical areas, but this is difficult to explore using these insurance data. Priester (1979) found that the rate of benign MTs varied considerably between geographic areas of North America, but that the rate of malignant MTs was more similar across regions.

Cohort analysis was performed with the aim to determine the combined effect of age, period and cohort with respect to the first MT claim. Unfortunately, to model age, period and cohort simultaneously is a statistical challenge and many statisticians argue against this (Holford, 1983; Moolgavkar et al., 1998). Hence, this was not attempted. Obviously, the cohort approach would be even more useful if a longer time period could be analysed.

Examining survival after MT (e.g. Table 5) mainly aims to be a comparison to similar statistics in other studies on the survival after MT diagnosis. Another survival analysis (e.g.

Table 6) compares the survival in dogs with and without previous MTs, which has not been as thoroughly investigated in the literature. Disadvantages in the survival calculations were the large amount of censoring (e.g. at age 10) and the lack of histological classification. Another drawback with the analysis is that, by breed, the numerators get quite small. Benefits with the present study are that the population is relatively similar to the base population and that it is unlikely that censoring would be different with and without previous MT.

4.3. Morbidity

Many reasons are possible for differences found among studies. Literature on the incidence of MTs reflect many-different designs, with respect to how representative the study population is of the base population. There might be unexplored regional differences and breed distributions might differ. Performed studies span a number of decades and owners' tendencies to seek veterinary care will likely have increased over time. The present study includes no old cases or very-young cases but in general includes somewhat younger cases than a cross-section of the population. Because of these reasons, comparison across studies must proceed with caution.

In the following sections, in general, the quoted figures from other studies pertain to the overall results, for example not considering whether MTs were malignant or benign. Citing studies that could claim they compare to a representative base population to estimate overall incidence of MTs, Schneider (1970) estimated the overall rate of MTs in dogs to be 14.5 cases per 10,000 DYAR (age-adjusted 20.3 cases per 10,000 DYAR). Mac Vean et al. (1978) found the overall MT rate to be 6.1/1000 dogs that were seen by a veterinarian during the study year. Dobson et al. (2002) reported that the age-standardized incidence rate of MTs was 205 cases per 100,000 dogs/year using data from an insurance database. Our estimate on the two longer-followed birth cohorts, also from an insurance database, was 154 cases per 10,000 DYAR. Comparing these two latter studies, done out of similar databases, but where in the present study cases were not verified to the same extent as by Dobson et al. (2002), our estimates were over 5–7 times higher than those from Dobson. This is likely because we have not included young dogs, few Swedish dogs are neutered and some non-MT cases might have been included. There may be differences in insurance coverage between these two countries. Hypothetically, if Swedish owners of insured dogs and their veterinarians are relatively aggressive in detecting and treating suspected MTs this might also influence the higher morbidity and lower CF in this study.

The bulk of the literature suggests that the incidence of MT increases with age (Schneider, 1970; Mac Vean et al., 1978; Priester, 1979)—as we also found.

One major prerequisite to identification of a breed as high or low risk in a study is sufficient individuals for valid interpretation. The risk rank for the breeds naturally varies by study, but many similarities are found. For example, we confirm the very-high risk of MTs in English springer spaniels (Frye et al., 1967; Priester, 1979; Arnesen et al., 2000; Moe, 2001). The Doberman in the present study has a higher hazard-ratio point estimate than the English springer spaniel (Table 3) which is opposite to the direction of the incidence rates in Table 1. This is likely a reflection of a generally lower-age distribution in the Doberman compared to the English springer spaniel (unpublished results).

There were multiple events in 13% of the dogs with MT, which includes deaths due to MT. The rate of multiple events was approximately two times the MT mortality rate. Else and Hannant (1979) found that overall 17.3% of their studied MT-cases ($n = 226$) recurred, when studying cases accruing during a time period of 36 months. We think that the magnitude of the arbitrary 6 months time period to separate MT events into ‘‘multiple MT events’’, likely reflects the true biology of the disease in most cases, but obviously not all.

The cohort analysis demonstrated, as anticipated, a strong age effect and a significant but smaller period effect, while the cohort effect was non-significant. Our results demonstrate that analysis of cohort effects must also consider analysing age and period effects. The slight increase in risk across the calendar years might be explained by increased utilization of veterinary care because owners become more and more aware that this disease can be treated by surgery. Also the increase in the cost of veterinary care over time might affect the period effect ‘‘positively’’ as more cases exceed the deductible.

4.4. Mortality

The actual survival after a MT diagnosis has been studied extensively (Bostedt and Tammer, 1995; Simon et al., 1996; Wey et al., 1999) with most studies presenting a shorter survival than in the present study. We could not calculate median survival because we still had >50% alive because dogs were censored at 10 years of age and probably also because our cases were relatively young and therefore likely had a better prognosis. During the first year after a MT claim 6–7% of the dogs died (due to any cause) and for those dogs that were followed 3 years almost 20% had died. Misdorp (1988) reported that dogs with benign MTs were relatively younger compared to dogs with malignant MTs and Bostock (1975) reported that there was an increase in age of onset of carcinomas with increase in malignancy. The slightly reduced survival in the two fully followed cohorts than in the total study population is likely due to age differences.

In our study the survival of dogs that had MTs was less than in non-MT cases. Schneider et al. (1969) found that excess mortality due to MT was concentrated in the first year, when 2.5 times more dogs died, either naturally or by euthanasia, than expected.

Four breeds out of 13 showed significantly increased risks of mortality when taking previous MT claims into account, with hazard-rate point estimates between 1.5 and 3.1. Reasons that the effect of a previous MT claim on mortality was only significant in some breeds could include, e.g. the power was comparatively lower in the stratified analyses and there might be actual breed differences in survivability (e.g. with/without surgery). Breed differences with respect to developing different types of MTs have been reported (Priester, 1979) and different genetic predisposition to various types of MTs in Sweden might affect the results.

The rate of multiple events was analyzed as a time-dependant covariate, as to whether it alone, or together with a primary MT claim, affected the survivability. The overall effect of multiple events was highly significant (hazard ratio 2.9), but in the stratified analysis it was only significant in four breeds (out of 13) with point estimates for the hazard ratio between 3.5 and 13.4. The overall effect of multiple events was still significant in the model with previous MT claim also included, but with a ‘‘low’’ hazard ratio of 1.9.

4.5. Conclusion

We have presented the incidence of MT in female dogs between 3 and 10 years of age of numerous breeds in a population of over 80,000 insured Swedish dogs representing over 250,000 DYAR. The incidence rates of 1 1 1 (for all dogs) and 154 initial diagnoses of MT per 10,000 DYAR in two birth-cohorts followed from 3 to 10 years of age is higher than reported from some other populations. This might be due in part to the age structure of the study population and because these are mainly intact bitches. There are marked differences between breeds with English springer spaniels, Dobermans and boxers having the highest risk and numerous breeds having a significantly reduced risk of MT compared to other breeds.

Acknowledgement

This work has been supported by grants from the Foundation for Research, Agria Insurance.

References

Allison, P., 1995. Survival Analysis Using the SAS® System: A Practical Guide, first ed. SAS Institute Inc, Cary, 292 pp.

Arnesen, K., Gamle, H., Glattre, E., Grondalen, J., Moe, L., Nordstoga, K. 2000. The Norwegian Canine Cancer Register 1990–1998. Report from the project "Cancer in the dog". Eur. J. Comp. Anim. Pract. 11, 159–169.

Boldizsar, H., Szenci, O.M., Muray, T., Csenki, J., 1992. Studies on canine mammary tumours. 1. Age, seasonal and breed distribution. Acta Vet. Hung. 40, 75–87.

Bostedt, H., Tammer, I., 1995. Kausustischer beitrag zur Prognose bei Mammtumoren des Hundes. Praktische Tierarzt 10, 921–924.

Bostock, D.E., 1975. The prognosis following the surgical excision of canine mammary neoplasms. Eur. J. Cancer 11, 389–396.

Breslow, N.E., Day, N.E., 1987. Statistical methods in cancer research, first ed. The Design and Analysis of Cohort Studies, vol. 2International Agency for Research on Cancer, Lyon, 406 pp.

Brodey, R.S., Goldschmidt, M.H., Roszel, J.R., 1983. Canine mammary gland neoplasms. J. Am. Anim. Hosp. Assoc. 19, 61–90.

Dobson, J.M., Samuel, S., Milstein, H., Rogers, K., Wood, J.L.N., 2002. Canine neoplasia in the UK: estimates of incidence rates from a population of insured dogs. J. Small Anim. Pract. 43, 240–246.

Dohoo, I., Wayne, M., Stryhn, H., 2003. Veterinary Epidemiologic Research, first ed. AVC Inc., Charlottetown, 706 pp.

Donnay, I., Rauis, J., Wouters-Ballman, P., Devleeschouwer, N., Leclercq, G., Verstegen, J.P., 1993. Receptors for oestrogen, progesterone and epidermal growth factor in normal and tumorous canine mammary tissues. J. Reprod. Fertil. Suppl. 47, 501–512.

Egenvall, A., Bonnett, B.N., Olson, P., Hedhammar, Å., 1998. Validation of computerized Swedish dog and cat insurance data against veterinary practice records. Prev. Vet. Med. 36, 51–65.

Egenvall, A., Hedhammar, Å., Bonnett, B.N., Olsson, P., 1999. Survey of the Swedish dog population: age, gender, breed, location and enrolment in animal insurance. Acta Vet. Scand. 40, 231–240.

Egenvall, A., Bonnett, B.N., Olson, P., Hedhammar, Å., 2000a. Gender, age, breed and geographic pattern of morbidity and mortality in insured dogs during 1995 and 1996. Vet. Rec. 146, 519–525.

Egenvall, A., Bonnett, B.N., Olson, P., Hedhammar, Å., 2000b. Gender, age and breed pattern of diagnoses for veterinary care events in insured dogs during. Vet. Rec. 146, 551–557.

Egenvall, A., Bonnett, B.N., Shoukri, M., Olson, P., Hedhammar, Å., Dohoo, I., 2000c. Age pattern of mortality in eight breeds of insured dogs in Sweden. Prev. Vet. Med. 1503, 1–14.

Egenvall, A., Hagman, R., Bonnett, B.N., Hedhammar, Å., Olson, P., Lagerstedt, A.-S., 2001. Breed Risk of pyometra in insured dogs in Sweden. J. Vet. Int. Med. 15, 530–538.

Else, R.W., Hannant, D., 1979. Some epidemiological aspects of mammary neoplasia in the bitch. Vet. Rec. 104, 296–304.

Frye, F.L., Dorn, C.R., Taylor, D.O.N., Hibbard, H.H., Klauber, M.R., 1967. Characteristics of canine mammary gland tumors cases. Anim. Hosp. 3, 1–12.

Hellmen, E., Bergström, R., Holmberg, L., Spångberg, I.-B., Hansson, K., Lindgren, A., 1993. Prognostic factors in canine mammary tumors: a multivariate study of 202 consecutive cases. Vet. Pathol. 30, 20–27.

Holford, T.R., 1983. The estimation of age, period and cohort effects for vital rates. Biometrics 39, 311–324.

Knapp, D.W., Waters, D.J., 1997. Naturally occurring cancer in pet dogs: important models for developing improved cancer therapy for humans. Mol. Med. Today 3, 8–11.

Kurzman, I.D., Gilbertson, S.R., 1986. Prognostic factors in canine mammary tumors. Semin. Vet. Med. Surg. (Small Anim.) 1, 25–32.

MacEwen, E.G., 1990. Spontaneous tumors in dogs and cats: models for the study of cancer biology and treatment. Cancer Metast. Rev. 9, 125–136.

Mac Vean, D.W., Monlux, A.W., Anderson, P.-S., Silberg, S.L., Rozsel, J.F., 1978. Frequency of canine and feline tumors in a defined population. Vet. Pathol. 15, 700–715.

Misdorp, W., 1988. Canine mammary tumours: protective effect of late ovariectomy and stimulating effects of progestins. Vet. Q. 10, 26–33.

Moe, L., 2001. Population-based incidence of mammary tumours in some dog breeds. J. Reprod. Fertil. Suppl. 57, 439–443.

Moolgavkar, S.H., Lee, J.A.H., Stevens, R.G., In Rothman, K.J., Greenland, S., 1998. Analysis of vital statistics data. Modern epidemiology, second ed. Lipincott-Raven Publishers, Philadelphia, pp. 481–498.

Owen, L.N., 1979. A comparative study of canine and human breast cancer. Invest. Cell Pathol. 2, 257–275.

Priester, W.A., 1979. Occurrence of mammary neoplasms in bitches in relation to breed, age, tumour type, and geographical region from which reported. J. Small Anim. Pract. 20, 1–11.

Rutteman, G.R., Kirpensteijn, J., In Dobson, J.M., Lascelles, B.D.X., 2003. Tumours of the mammary glands. BSAVA manual of canine and feline oncology. BSAVA, Gloucester 234–242.

Schafer, K.A., Kelly, G., Schrader, R., Griffith, W.C., Muggenburg, B.A., Tierney, L.A., Lechner, J.F., Janovitz, E.B., Hahn, F.F., 1998. A canine model of familial mammary gland neoplasia. Vet. Pathol. 35, 168–177.

Schneider, R., Dorn, C.R., Taylor, D.O.N., 1969. Factors influencing canine mammary cancer development and postsurgical survival. J. Natl. Cancer Inst. 43, 1249–1261.

Schneider, R., 1970. Comparison of age, sex and incidence rations in human and canine breast cancer. Cancer 26, 419–4126.

Simon, D., Goronzy, P., Stephan, I., Meyer-Lindberg, A., Aufderheide, M., Nolte, I., 1996. Mammatumoren beim Hund: Untersuchung zu Vorkommen und Verlauf der Erkrankung (Mammary tumours in the dog: frequency and course). Praktische Tierarzt 77, 771–782.

Sorenmo, K.U., Shofer, F.S., Goldschmidt, M.H., 2000. Effect of spaying and timing of sapying on survival of dogs with mammary carcinoma. J. Vet. Int. Med. 14, 266–270.

Stövring, M., Moe, L., Glattre, E., 1997. A population-based case-control study of canine mammary tumours and clinical use of medroxyprogesterone acetate. APMIS 105, 590–596.

Swedish Animal Hospital Organisation (Svenska djursjukhusföreningen) 1993. Diagnostic registry for the horse, the dog and the cat (Diagnosregister för häst, hund och katt). Taberg, Tabergs tryckeri.

Wey, N., Kohn, B., Gutberlet, K., Rudolph, R., Brunnberg, L., 1999. Mammatumore bei der Hündin: klinische Verlaufsstudie (1995–1997). Mammary tumours in the bitch: clinical follow-up study (1995–1997). Kleintierpraxis 44, 561–632.

Yamagami, T., Kobayashi, T., Takahashi, K., Sugiyama, M., 1996. Prognosis for canine malignant mammary tumors based on TNM and histologic classification. J. Vet. Med. Sci. 58, 1079–1083.