312 (2025) 106359

Contents lists available at ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

The epidemiology of mammary tumours in insured female dogs in Sweden

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ARTICLE INFO

Keywords:
Canine
Mammary tumour
Cancer
Tumour
Insurance
Breed risks
Cohort

ABSTRACT

Mammary tumour (MT) is the most common neoplasia in bitches. This study explored the incidence and cause-specific mortality rates of and risk factors for MT in dogs insured by Agria Djurförsäkring in Sweden, 2011–2016. The study population included just over 600,000 dogs, and 13,109 females had veterinary care claims for MT. The incidence rate in females was 157 cases per 10,000 dog-years at risk (95 % confidence interval (CI): 154–160). The breeds at highest risk of MT were the Kerry blue terrier (relative risk (RR) 4.72, 95 % CI 2.58–7.92) and English springer spaniel (RR 3.32, 95 % CI: 3.02–3.63), while the breeds at lowest risk were the German spitz (RR 0.06, 95 % CI: 0.00–0.33) and English bulldog (RR 0.07, 95 % CI: 0.00–0.37). The median age at first MT diagnosis was 8.94 years (interquartile range (IQR) 7.43–10.5). The Dogue de Bordeaux (median age at diagnosis 5.30 years) and Irish wolfhound (6.42 years) were youngest at diagnosis, and the Miniature dachshund (10.9 years) and West Highland white terrier (11.0 years) were oldest. Higher odds of MT were found in bitches with a history of pseudopregnancy (OR 2.10, $P < 0.001$) and acute mastitis (OR 4.93, $P < 0.001$). In total, 486 bitches died of MT-related causes at a median age of 9.32 years (IQR 8.37–9.99). The Large Munsterlander had the highest risk of MT-related death (RR 40.3, 95 % CI: 8.28–118.4). In conclusion, MT mainly affected middle-aged to older bitches. Large breed-related differences in the risk of MT and age at diagnosis were found.

Introduction

Mammary tumours (MT) are reported to be the most common neoplasia in bitches, accounting for 54–70 % of all cancer cases in females and 1.9–2.2 % of all cancer cases in males (Merlo et al., 2008; Pastor et al., 2018; Vascellari et al., 2009; Vascellari et al., 2016). The incidence of MT in bitches varies in the literature depending on the study population and methodology, from 19.2 cases per 10,000 dog-years at risk (DYAR) based on data from the Animal Tumour Registry in Italy between 1985 and 2002 (Merlo et al., 2008), to 134.1/10,000 bitches per year based on primary veterinary care data from the UK in 2016 (Varney et al., 2023). Approximately 40–50 % of the MT in bitches are malignant (Gedon et al., 2022; Hampe and Misdorp, 1974; Salas et al., 2015). There are several risk factors for MT development, such as age, neuter status, overweight/obesity, and breed (Edmunds et al., 2023; Gedon et al., 2022; Lim et al., 2015; Merlo et al., 2008; Tesi et al., 2020; Varney et al., 2023). The median age at diagnosis is reported to be 8–10 years (Edmunds et al., 2023; Varney et al., 2023). The risk of MT in general is higher in intact than in neutered females, although a higher risk of malignant tumours has been described in neutered females compared to intact (Edmunds et al., 2023; Gedon et al., 2022; Gruntzig et al., 2016; Varney et al., 2023). Moreover, early spaying is reported to completely or partially protect from the development of MT, although the scientific evidence for this association has been questioned (Beauvais et al., 2012; Schneider et al., 1969; Stavisky and White, 2022). Breeds with an increased risk of MT include the Boxer, Dobermann, English cocker spaniel, English setter, English springer spaniel, Irish soft coated wheaten terrier, Lhasa apso, Miniature dachshund, Pomeranian, Staffordshire bull terrier, Toy poodle, and Yorkshire terrier (Edmunds et al., 2023; Egenvall et al., 2005; Varney et al., 2023). An earlier study using insurance data from Sweden reported that 12 % of the bitches with MT were affected multiple times, i.e. were diagnosed with MT twice at least six months apart (Egenvall et al., 2005). Mammary tumours are described to have the highest cause-specific mortality of all tumours,

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https://doi.org/10.1016/j.tvjl.2025.106359
Received 2 October 2024; Received in revised form 14 April 2025; Accepted 15 April 2025
Available online 18 April 2025

reported to be 5–6 deaths per 10,000 DYAR (including benign and malignant tumours combined) (Bonnett et al., 2005; Egenvall et al., 2005).

Several studies have explored the epidemiology of MT in dogs using different data sources, such as primary-care veterinary data from the VetCompass Programme in the UK, data on cases presented for histopathological evaluation at laboratories, and data from cancer registries (Edmunds et al., 2023; Gruntzig et al., 2016; Salas et al., 2015; Varney et al., 2023). Data from Agria Djurförsäkring in Sweden from 1995 to 2006 have also been used, but studies using recent insurance data are lacking (Egenvall et al., 2005; Jitpean et al., 2012). A benefit of using insurance data in epidemiologic research is the inclusion of both clinical events and the healthy background population (Egenvall et al., 2009). Agria Djurförsäkring (Agria Djurförsäkring, Stockholm, Sweden) is a leading pet insurance company based in Sweden with operations in nine markets across Europe. Agria Djurförsäkring insured approximately 38 % of the Swedish dog population in 2016, and Sweden has the highest insurance coverage for the dog population worldwide; around 90 % of the population was insured in 2017 (Agria Djurförsäkring, 2017; Olsson, 2020).

This study aimed to explore the incidence and cause-specific mortality rates of MT and breed and age as risk factors for MT development in a population of female dogs insured by Agria Djurförsäkring in Sweden, 2011–2016. An additional aim was to describe the occurrence of other diagnoses in females with MT and evaluate risk factors (age, breed) for multiple MT events (defined as two MT events at least six months apart).

Materials and methods

Data

This study included dogs insured by Agria Djurförsäkring in Sweden between 1 January 2011 and 31 December 2016, and comprised two parts: 1) A cohort study evaluating the incidence rate and cause-specific mortality rates of MT, the occurrence of multiple MT events, and age and breed as risk factors for MT development, and 2) A case-control study examining other diagnoses in bitches with MT compared to control bitches.

The dogs were either insured for veterinary care, life, or both. The data included information about age, breed, sex (female/male, not neuter status), date of insurance enrolment and termination, dates and diagnostic codes for veterinary care claims and life insurance settlements during the study period (if any), and type of insurance policy. The breeds and breed groups were classified according to the Federation Cynologique Internationale and the Swedish Kennel Club (Federation Cynologique Internationale, 2024; Svenska Kennelklubben, 2024). The date of and age at first MT diagnosis were based on the date of the first registered claim for MT during the study period. If a dog had more than one veterinary care claim for MT, it was considered to have multiple MT events if the claims were at least six months apart (either a recurrence or a new MT). The remaining bitches with MT were considered to have one MT event, i.e. only one MT claim or several MT claims within six months. Males were included in the total number of cases and calculation of the incidence of MT but were excluded from further analyses. Dogs were excluded in case of missing information regarding age, breed, date of insurance enrolment, or sex.

The veterinary care insurance reimbursed costs associated with veterinary care (such as veterinary examinations, treatments, and diagnostics), while the life insurance provided compensation equivalent to the value of the dog in case of death or euthanasia. The owner could choose between the available deductible limits at insurance enrolment. The total veterinary cost over rolling 125-day periods had to exceed the insurance deductible for an insurance claim to be reimbursed. If receipts from several veterinary appointments were submitted together, these were usually recorded as separate claims, but on the same date. Each insurance claim had one or several diagnostic codes attached, chosen by the examining veterinarian from a national hierarchical diagnostic registry (Egenvall et al., 2009; Svenska Djursjukhusföreningen, 1993). Two diagnostic codes were available for MT: mammary tumour and tumour of the teat.

The life insurance policy terminated at eight, ten, or twelve years of age, depending on breed (see Supplementary Table 1 for more information). The dogs could be enrolled in veterinary care insurance at any age, but in life insurance only before four years of age (for breeds with insurance termination at eight years of age) or six years (for all other dog breeds). It was not possible to differentiate between natural death and euthanasia.

Statistical analysis

The data analysis was performed in R version 4.2.1 (R Core Team, 2022). Categorical variables are presented as numbers and percentages per category, and continuous variables as median (IQR), except for the total insurance duration for the population, which is presented as median (range). The Shapiro-Wilk test was used to assess the normality of continuous variables, in combination with visual assessment of histograms. The total DYAR were calculated by summing the insurance duration for all dogs during the study period. For example, a dog that was insured from 1 January 2011–31 December 2011 contributed one DYAR to the total DYAR. Age differences were explored with the Wilcoxon rank sum test. The incidence rate of MT, and age and breed as risk factors for MT was evaluated using veterinary care claims in veterinary care-insured dogs. The cause-specific mortality of MT and age and breed as risk factors for MT-related death was evaluated using life claims in life-insured dogs (as cause and date of death only were available in dogs with life insurance). In addition, the time from the first MT diagnosis to death was evaluated in dogs with both veterinary care and life insurance.

The first MT claim in dogs with veterinary care insurance was used for incidence calculation, and the DYAR were based on the time to that claim. The incidence rate was expressed as the number of dogs with one or multiple MT events per 10,000 DYAR. In dogs with life insurance, time to MT-related death was used for the calculation of cause-specific mortality, which was expressed as the number of dogs that died of MT-related causes per 10,000 DYAR. The relative risks (RR) for breed, breed groups, and sex were calculated by dividing the incidence rate of the subgroup of interest by the incidence rate of all other dogs. The risk of multiple MT events compared to one MT event was calculated using the time from the first to the second event in dogs affected by multiple events, and the time from the first event to censoring (i.e. termination of the insurance or end of the study period) in dogs with one MT event. The R package “epitools” was used to generate confidence intervals based on the Poisson distribution, and the package “forestplot” to generate forest plots of breed risks (Epitools; Gordon and Lumley, 2019). Bonferroni (BF) correction, based on the number of comparisons, was used to correct for multiple comparisons to avoid type I error. P-values < 0.05, after correction, were considered to indicate statistical significance. The “ggplot2” package was used to generate the plot for age-specific incidence rate, using only the first MT claim for each affected dog (Wickham, 2016).

Each dog with MT was matched to five controls without claims for MT based on age, insurance duration, and breed, to assess the odds of MT in dogs with other diagnoses and the risk of subsequent diagnoses in dogs with MT. The matchit() function from the package “MatchIt” was used, with nearest neighbour matching on propensity scores (Ho et al., 2011). All veterinary care claims in the cases and the controls were grouped based on the organ system, according to the diagnostic registry (Svenska Djursjukhusföreningen, 1993). These were further classified as “prior” or “subsequent” (occurring prior or subsequent to the first MT claim in cases and the date of matching in controls). Conditional logistic regression was performed to compare other diagnoses in cases and

controls using the clogit() function from the "survival" package (Therneau, 2021). To analyse the risk of subsequent MT in dogs with other diagnoses, the other diagnosis was set as the main exposure variable and the MT as the outcome. The MT diagnosis was set as the main exposure variable and the other diagnosis as the outcome in the analysis of subsequent diagnoses. Other diagnoses on the date of the MT diagnosis were not included. Further, the odds of MT in bitches with specific diagnoses of the reproductive organs (pyometra, pseudopregnancy, acute mastitis, ovarian cysts, and ovarian tumours) were evaluated using conditional logistic regression as previously described.

Results

The number of MT cases and the incidence rate of MT

The study population included just over 600,000 dogs insured by Agria Djurförsäkring (2011–2016). There were 13,428 dogs affected by MT, of which 13,349 (99.4 %) were females and 79 (0.59 %) were males. There were 13,186 dogs that had a total of 22,868 veterinary care claims for MT (Table 1), and the median number of claims per dog was 1 (IQR 1–2). In females, MT claims accounted for 4.84 % of all claims during the study period. The total incidence rate of MT in the study population was 76.2 (95 % CI: 74.9–77.5) cases per 10,000 DYAR. The incidence rate in females was 157 (95 % CI: 154–160) cases per 10,000 DYAR and in males 0.86 (95 % CI: 0.68–1.08) cases per 10,000 DYAR. The risk of MT was higher in females than in males (RR 182.3, 95 % CI: 145.8–231.2, $P < 0.001$). There were 488 dogs with life claims for MT (Table 1). The results under the following subheadings are reported for the bitches in the study population.

Age at diagnosis

The median age at first diagnosis of MT during the study period was 8.94 years (IQR 7.43–10.5). The age-specific incidence rate peaked in dogs aged 10–11 years, at 464.2 cases per 10,000 DYAR (Table 2).

The age at diagnosis varied significantly with breed. Breeds older and younger at first diagnosis are presented in Table 3.

Breed-related risk of MT

In total, there were 19 breeds with an increased risk of MT and 22 breeds with a decreased risk, after Bonferroni correction (Fig. 1). The full list of high- and low risk breeds without Bonferroni correction is presented in Supplementary Figures 1 and 2, respectively. The breeds at highest risk were the Kerry blue terrier (RR 4.72, 95 % CI 2.58–7.92), English springer spaniel (RR 3.32, 95 % CI: 3.02–3.63), and Irish soft coated wheaten terrier (RR 2.75, 95 % CI 2.42–3.11), while the breeds at lowest risk were the German spitz (RR 0.06, 95 % CI: 0.00–0.33), English bulldog (RR 0.07, 95 % CI: 0.00–0.37), and Rough collie (RR 0.12, 95 % CI: 0.06–0.21).

The breed groups at the highest and lowest risk of MT were dachshunds (RR 1.52, 95 % CI 1.40–1.64) and spitz and primitive types (RR 0.73, 95 % CI 0.68–0.78), respectively (Fig. 2).

Multiple MT events

In total, 1726/5786 (29.83 %) of the bitches with more than one insurance claim for MT had two claims at least six months apart, and were thus considered having multiple MT events according to the definition of the study (13.2 % of all bitches with veterinary care claims for

Table 1
Descriptive features of dogs insured by Agria Djurförsäkring in Sweden during 2011–2016.

	Veterinary care insurance	Life insurance
The total duration of insurance (years)	> 1.7 million	> 1.1 million
Insurance duration, median (range)*	2.68 y (9.15 w – 6.00 y)	2.51 y (9.15 w – 6.00 y)
Sex (%)		
Female	49.1 %	49.5 %
Male	50.9 %	50.5 %
Number of dogs with claims for MT**	13,186	488
Female	13,109	486
Male	77	2
Median age (years) at first MT claim (veterinary care insurance) or MT-related death (life insurance)	8.94 (IQR 7.43–10.5)	9.32 (IQR 8.39–9.99)

MT: mammary tumour, *IQR:* interquartile range
* Per dog, during 2011–2016
** A dog with both a veterinary care claim and life insurance settlement due to MT is included in both columns

Table 2
The age-specific incidence rate of mammary tumours in bitches insured by Agria Djurförsäkring in Sweden, 2011–2016.

Age group (years)	Incidence rate (95 % confidence interval)
0-< 1	0.45 (0.09–1.31)
1-< 2	3.81 (2.60–5.37)
2-< 3	6.24 (4.66–8.18)
3-< 4	19.3 (16.4–22.5)
4-< 5	42.3 (37.9–47.0)
5-< 6	93.6 (87.0–100.6)
6-< 7	164.3 (155.3–173.7)
7-< 8	258.1 (246.3–270.4)
8-< 9	385.4 (370.0–401.3)
9-< 10	442.7 (424.5–461.4)
10-< 11	464.2 (443.1–486.1)
11-< 12	440.1 (416.0–465.3)
12-< 13	365.2 (338.0–394.0)
13-< 14	286.2 (253.9–321.5)
14-< 15	278.1 (231.2–331.9)
15-< 16	130.2 (79.5–201.0)

Table 3
Breeds significantly older or younger* at first diagnosis of mammary tumours (MT) compared to all other breeds, in a study population of dogs insured by Agria Djurförsäkring in Sweden (2011–2016). The overall median age at first MT diagnosis was 8.94 years (IQR 7.43–10.5).

Breed	Median age at first MT diagnosis	IQR
Younger at diagnosis		
Dogue de Bordeaux	5.30	4.42–6.27
Irish wolfhound	6.42	5.51–7.70
French bulldog	6.82	5.33–8.52
Boston terrier	6.86	5.82–7.97
Great Dane	7.06	5.88–8.00
Cane corso	7.16	6.20–8.97
Dobermann	7.59	6.74–8.81
Miniature pinscher	7.60	6.58–8.82
Boxer	7.72	6.64–8.66
Rottweiler	8.10	6.86–9.45
English springer spaniel	8.19	6.54–9.65
Swedish elkhound	8.31	6.99–9.71
German shepherd dog	8.62	7.40–9.84
Mixed breed	8.80	7.22–10.3
Older at diagnosis		
Jack Russell terrier	9.55	7.99–11.0
Medium poodle	9.60	8.23–11.4
Border collie	9.69	8.43–11.3
Standard dachshund	9.71	8.31–11.2
Standard poodle	9.91	8.34–11.1
Norwegian elkhound grey	9.92	8.80–11.1
Shetland sheepdog	10.0	8.66–11.2
Miniature dachshund	10.9	8.95–12.0
West Highland white terrier	11.0	9.12–12.0

* After Bonferroni correction based on the number of comparisons, n = 232 (i.e. number of breeds with veterinary care claims for MT)

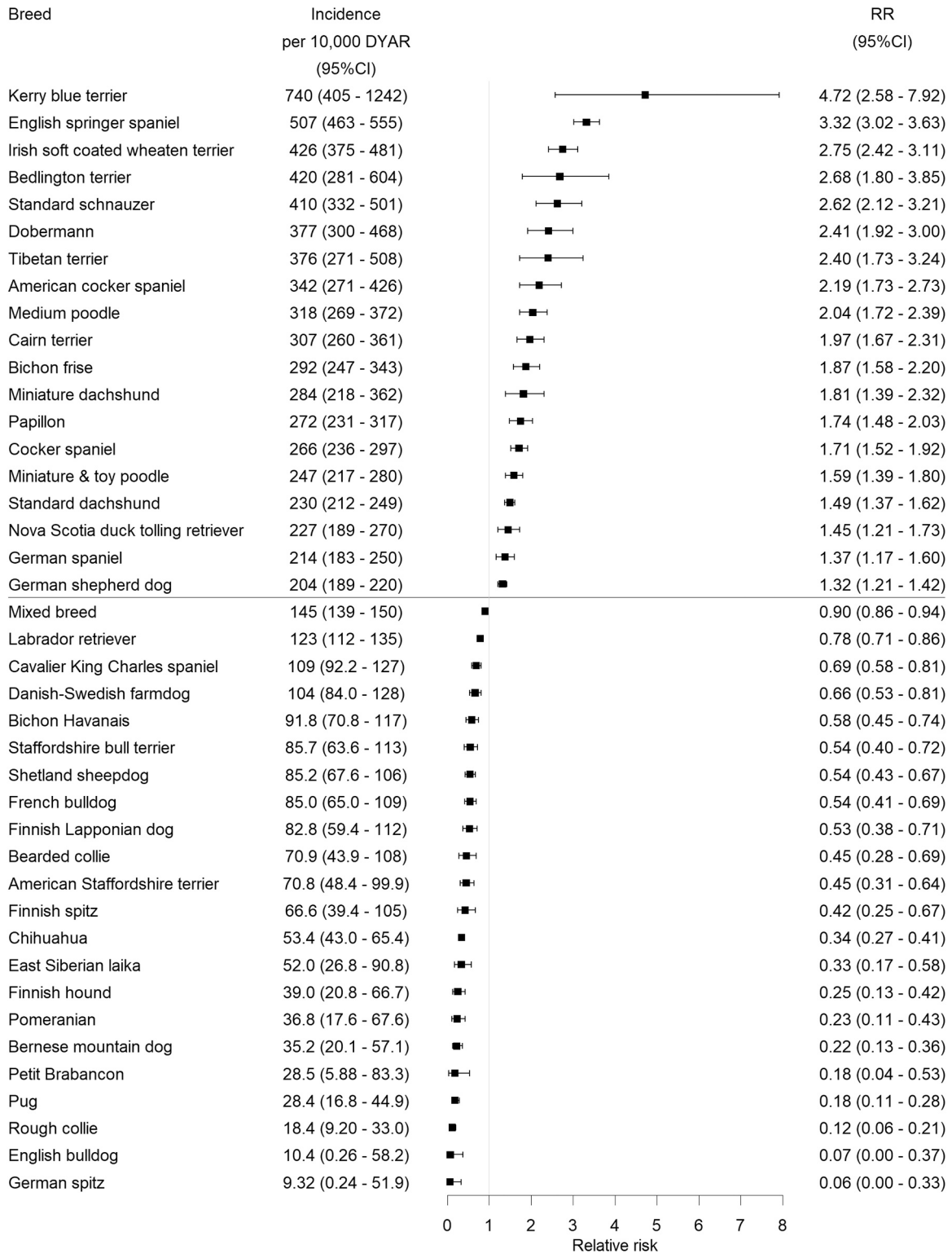

Fig. 1. Dog breeds with an increased or decreased risk of mammary tumours (relative to the rest of the population with the breed excluded) in a cohort of bitches insured by Agria Djurförsäkring in Sweden (2011–2016). All relative risks (RR) were significantly different from one after the Bonferroni correction based on the number of breeds included in the comparison (n = 330). *CI* confidence interval, *DYAR* dog-years at risk.

MT). Bitches with multiple MT events were younger at first diagnosis (median age 8.24 years, IQR 6.97–9.48) than bitches with one MT event (median age 9.06, IQR 7.50–10.59) (Wilcoxon rank sum test, $P < 0.001$). The Norwich terrier (RR 8.11, 95 % RI 1.67–23.74), Fox terrier (RR 2.20, 95 % CI: 1.20–3.70), Papillon (RR 1.58, 95 % CI: 1.10–2.21), and English springer spaniel (RR 1.27, 95 % CI 1.01–1.57) had an increased risk of multiple events compared to having one event ($P < 0.05$). The Golden retriever (RR 0.58, 95 % CI 0.39–0.84), Labrador retriever (RR 0.58, 95 % CI: 0.40–0.80), Miniature schnauzer (RR 0.45, 95 % CI 0.22–0.84), Drever (RR 0.41, 95 % CI 0.13–0.96), and Flat coated retriever (RR 0.26, 95 % CI 0.05–0.77) had a decreased risk of multiple events ($P < 0.05$). No breeds had a significantly increased/

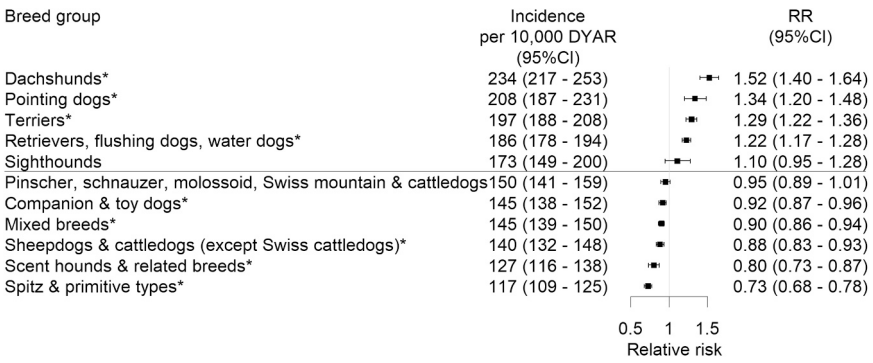

Fig. 2. The risk of mammary tumours in breed groups (relative to the rest of the population with the breed group excluded) in a cohort of bitches insured by Agria Djurförsäkring in Sweden (2011–2016). *Breed groups with a relative risk (RR) significantly different from one after the Bonferroni correction based on the number of comparisons (n = 11). *CI* confidence interval, *DYAR* dog-years at risk.

decreased risk of multiple MT events after Bonferroni correction.

The median age at death in dogs with one MT event was 9.24 years (IQR 8.26–9.95), compared to 9.36 years (IQR 8.51–10.1) in dogs with multiple MT events (Wilcoxon rank sum test, $P = 0.274$).

Other diagnoses in dogs with MT

Of the 13,109 bitches with veterinary care claims for MT, 6011 (45.9 %) had claims for other diagnoses before the first MT claim, and 8792 (67.07 %) had subsequent claims for other diagnoses. Diagnoses affecting the integumentary (21.3 %) and gastrointestinal (13.8 %) systems were most common before MT was diagnosed (Table 4), while diagnoses affecting the integumentary (21.2 %) and urogenital (18.3 %) systems were most common subsequent to an MT diagnosis (Table 5). Of the bitches with MT, 0.42 % and 1.28 % had a history of pseudopregnancy and acute mastitis, respectively. The corresponding percentages in bitches without MT were 0.20 % and 0.26 %. Higher odds of subsequent MT was found in bitches that had been diagnosed with pseudopregnancy (OR 2.10, $P < 0.001$) and acute mastitis (OR 4.93, $P < 0.001$), while no increased odds of subsequent MT was found in bitches that had been diagnosed with with pyometra (OR 0.97, $P = 0.411$), ovarian cysts (OR 1.10, $P = 0.739$), or ovarian tumours (OR 1.18, $P = 0.648$).

Table 4
Prior diagnoses* by organ system in bitches with mammary tumours (n = 13,109) and control bitches without veterinary care claims for mammary tumours (n = 65,545) matched on age, breed, and duration of veterinary care insurance in a cohort of dogs insured by Agria Djurförsäkring in Sweden (2011–2016). Significant *P*-values are in bold and indicate increased odds of a subsequent claim for mammary tumour in dogs with a diagnosis in that organ system.

Organ system	Cases (%)	Controls (%)	Odds ratio	*P*-value **
Cardiovascular	155 (1.18)	721 (1.10)	1.08	0.412
Endocrine	164 (1.25)	840 (1.28)	0.98	0.776
Gastrointestinal	1811 (13.8)	7610 (11.6)	1.22	**< 0.001**
Hematopoietic	131 (1.0)	572 (0.87)	1.15	0.159
Hepatic	187 (1.43)	802 (1.22)	1.17	0.057
Integumentary	2795 (21.3)	10,970 (16.7)	1.36	**< 0.001**
Musculoskeletal	1242 (9.47)	5432 (8.29)	1.16	**< 0.001**
Neurologic	195 (1.49)	855 (1.30)	1.14	0.095
Ophthalmic	497 (3.79)	2173 (3.31)	1.15	0.006
Other (general/ unspecific)	1552 (11.8)	6170 (9.41)	1.30	**< 0.001**
Respiratory	283 (2.16)	1320 (2.01)	1.07	0.284
Urogenital	1682 (12.8)	7326 (11.2)	1.17	**< 0.001**
All diagnoses combined	6011 (45.9)	25,816 (39.4)	1.32	**< 0.001**

* Relative to the first veterinary care claim for mammary tumours during the study period, or the date of matching for the controls.

** Significance level 0.05/13 (number of comparisons of prior and subsequent diagnoses) = 0.004

Table 5
Subsequent diagnoses* by organ system in bitches with mammary tumours (n = 13,109) and control bitches without veterinary care claims for mammary tumours (n = 65,545) matched on age, breed, and duration of veterinary care insurance in a cohort of dogs insured by Agria Djurförsäkring in Sweden (2011–2016). Significant *P*-values are in bold and indicate increased odds of a subsequent claim for a diagnosis within the organ system in bitches with MT compared to controls.

Organ system	Cases (%)	Controls (%)	Odds ratio	*P*-value **
Cardiovascular	347 (2.65)	1315 (2.00)	1.33	**< 0.001**
Endocrine	354 (2.70)	1197 (1.83)	1.49	**< 0.001**
Gastrointestinal	2026 (15.5)	7290 (11.1)	1.46	**< 0.001**
Hematopoietic	376 (2.87)	1193 (1.82)	1.59	**< 0.001**
Hepatic	427 (3.26)	1376 (2.10)	1.57	**< 0.001**
Integumentary	2780 (21.2)	8665 (13.2)	1.77	**< 0.001**
Musculoskeletal	1401 (10.7)	5227 (7.97)	1.38	**< 0.001**
Neurologic	369 (2.81)	1290 (1.97)	1.44	**< 0.001**
Ophthalmic	631 (4.81)	2030 (3.10)	1.59	**< 0.001**
Other (general/ unspecific)	2385 (18.2)	7038 (10.7)	1.85	**< 0.001**
Respiratory	612 (4.67)	1931 (2.95)	1.61	**< 0.001**
Urogenital	2402 (18.3)	7114 (10.9)	1.85	**< 0.001**
All diagnoses combined	7262 (55.4)	25,607 (39.1)	1.32	**< 0.001**

* Relative to the first veterinary care claim for mammary tumours during the study period, or the date of matching for the controls.

** Significance level 0.05/13 (number of comparisons of subsequent diagnoses) = 0.004

Mammary tumour-related death

The cause-specific mortality of MT in bitches was 8.92 (95 % CI: 8.14–9.74) deaths per 10,000 DYAR. Of the 13,109 bitches with veterinary care claims for MT, 8127 (62.0 %) were life insured of which 869 (10.7 %) died during the study period. In total, 246 (28.3 %) of these died of MT-related causes (3.03 % of the bitches with a veterinary care claim for MT and a life insurance).

In total, 486 bitches died of MT-related causes during the study period. Thus, 240 bitches had no veterinary care claim for MT prior to MT-related death. The median age at MT-related death was 9.32 years (IQR 8.37–9.99), compared to the age at death in all life insured bitches that died of other reasons, which was 7.57 years (IQR 5.01–9.15, Wilcoxon rank-sum test, $P < 0.001$). In bitches with MT, age at death did not differ in those with a prior veterinary care claim for MT compared to those with no such claim (9.25 years, IQR 8.36–9.93, and 9.37 years, IQR 8.49–10.0, Wilcoxon rank sum test, $P = 0.211$). The median time from the first veterinary care claim for MT to MT-related death was 9.14 weeks (IQR 0 days–0.76 years).

Five breeds had an increased risk of MT-related death, of which the Large Munsterlander had the highest risk (RR 40.3, 95 % CI: 8.28–118.4, Fig. 3).

There were five breeds significantly older than others at MT-related death (after Bonferroni based on the number of breeds with life insurance settlements related to MT, n = 96): Irish soft coated wheaten terrier (10.5 years, IQR 9.76–11.3), Miniature schnauzer (10.8 years, IQR 10.5–11.0), Papillon (10.9 years, IQR 10.0–11.9), Cairn terrier (11.3 years, IQR 10.0–11.9), and Welsh springer spaniel (11.4 years, IQR 11.1–11.6).

Discussion

This study aimed to explore the epidemiology of MT in an insured, Swedish dog population. The incidence of MT in bitches was 157 cases per 10,000 DYAR, compared to the 111 cases per 10,000 DYAR reported by Egenvall et al. (2005) using insurance data in Sweden 1995–2002, 19.2 cases per 10,000 DYAR reported by Merlo et al. (2008) using data from the Animal Tumour Registry of Genoa, Italy 1985–2002, and the 134.1 cases per 10,000 bitches per year reported by Varney et al. (2023) using primary veterinary care data from the UK 2016. Thus, the incidence rate of MT in the current study was higher than previously reported. The study by Egenvall et al. (2005) included bitches between three and ten years of age, compared to the current study which included bitches of all ages. Including older dogs could explain the higher incidence rate, as the risk of MT increases with age (Edmunds et al., 2023; Egenvall et al., 2005; Priester, 1979; Varney et al., 2023). This is supported by the higher age at MT diagnosis in the current study, compared to the study by Egenvall et al. (2005) (median age 8.9 years, compared to 7.3 years). However, it cannot be excluded that the incidence of MT has increased with time, which has been reported previously (Vascellari et al., 2016). This could be due to factors such as breed popularity (i.e. an increased popularity of high-risk breeds) and a general increased longevity of dogs (Inoue et al., 2018). A lower proportion of neutered dogs in Sweden compared to the UK could contribute to the higher incidence observed in this study compared to the study by Varney et al. (2023), as early neutering is reported as a protective factor (Sanchez-Vizcaino et al., 2017; Statistics Sweden, 2012; Stavisky and White, 2022). The incidence rate of MT in males was in line with what Merlo et al. (2008) reported (0.86 vs. 0.21 cases per 10,000 DYAR).

The median age at first MT diagnosis in bitches was 8.94 years which is similar to earlier reports, although age-related inclusion criteria for the study populations vary slightly (Edmunds et al., 2023; Rodriguez et al., 2022; Varney et al., 2023). Further, the incidence rate of MT increased with age, peaking in bitches 10–11 years old. This is in agreement with the results by Merlo et al. (2008), reporting a peaking incidence in bitches > 9–11 years of age. Large breed-related differences in age at diagnosis were found in the current study; the median age at first diagnosis varied from 5.30 years in the Dogue the Bordeaux to 11.0 years in the West Highland white terrier. In general, breeds diagnosed at younger ages were large-sized, and breeds diagnosed at higher ages were small-sized, a pattern that has been observed before (Salas et al., 2015). The negative correlation between longevity and increasing bodyweight could contribute to this observation, as smaller dogs generally live longer than larger dogs (O'Neill et al., 2013). The findings highlight the importance of regular mammary palpation in middle-aged and older bitches, but also in young bitches, especially of large breeds.

Several of the high-risk breeds have already been identified in previous studies, such as the English springer spaniel, Irish soft coated wheaten terrier, Bedlington terrier, Dobermann, Medium, Miniature, and Toy poodle, Cairn terrier, Bichon frise, Miniature and Standard dachshund, Cocker spaniel, and German shepherd dog (Edmunds et al., 2023; Egenvall et al., 2005; MacVean et al., 1978; Priester, 1979; Rodriguez et al., 2022; Varney et al., 2023; Vascellari et al., 2016). Others are not commonly reported as high-risk breeds in previous studies, such as the Kerry blue terrier, Standard schnauzer, Tibetan terrier, American cocker spaniel, Papillon, Nova Scotia duck tolling retriever, and German spaniel. The majority of the high-risk breeds were of small or medium size. Smaller dogs can be lifted and carried by their owners, potentially increasing the chance of detecting MT, which possibly contributed to this trend (Edmunds et al., 2023).

Of the low-risk breeds, the Staffordshire bull terrier, Labrador retriever, Cavalier King Charles spaniel, Chihuahua, and Pomeranian have been reported both as high-risk and low-risk breeds previously (Edmunds et al., 2023; Egenvall et al., 2005; Priester, 1979; Rodriguez et al., 2022; Varney et al., 2023; Vascellari et al., 2016). Some new low-risk breeds were identified, including the Danish-Swedish farm dog, Bichon Havanais, English and French bulldog, Finnish Lapponian dog, Finnish spitz, East Siberian laika, Bernese mountain dog, Petit brabancon, and German spitz, while some, such as the Shetland sheepdog, Bearded collie, Finnish hound, Pug, American Staffordshire terrier, and Rough collie, have been reported as low-risk breeds before (Edmunds et al., 2023; Egenvall et al., 2005; Priester, 1979; Rodriguez et al., 2022). Dachshunds (breed group four) was the breed group with the highest risk of MT, while the spitz and primitive types (breed group five) had the lowest risk. Many factors can contribute to differences in observed breed predisposition and protection, such as regional and time trends in breed popularity. For example, a high-risk breed with a low number of individuals in a study population might not be recognised due to low statistical power. A sufficient number of individuals is also necessary to conclude that a breed is at low risk (i.e. that a low number of disease cases in a breed is due to an actual low disease occurrence and not just due to a low number of individuals within the breed). Other factors that might contribute are differences in study populations (insured dogs, dogs attending primary or referral veterinary care, or dogs with tumours sent for histopathological examination), international differences in breeding lines, and varying longevity and general disease burden in different breeds. For example, a breed with short longevity or a high general disease burden might not live long enough to develop MT. International differences in rates of neutering might also contribute, as early spaying is reported to completely or partially protect from the development of MT (Beauvais et al., 2012; Berthoud et al., 2011;

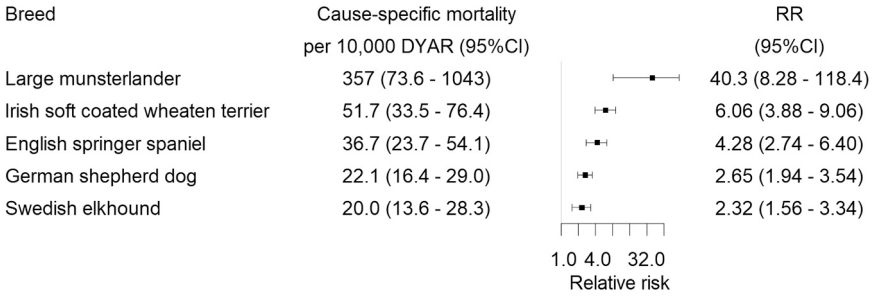

Fig. 3. Dog breeds with an increased risk of mammary tumour-related death (relative to the rest of the population with the breed excluded) in a cohort of bitches insured by Agria Djurförsäkring in Sweden (2011–2016). All relative risks (RR) presented in the figure were significantly different from one after the Bonferroni correction based on the number of breeds included in the comparison (n = 324). *CI* confidence interval, *DYAR* dog-years at risk.

Schneider et al., 1969; Stavisky and White, 2022). Further, genetics likely contributed to the observed breed predisposition and protection. For example, the human breast cancer genes *BRCA1* and *BRCA2* have been associated with significantly higher odds of MT in Springer spaniels, and the *CDK5RAP2* gene involved in cell cycle regulation has been associated with MT in the same breed (Melin et al., 2016; Rivera et al., 2009). In addition, MT-associated single nucleotide polymorphisms in the oestrogen receptor 1 gene, which is involved in both reproductive function and pathological processes such as breast cancer, have been found in several high-risk breeds including the English springer spaniel, Cocker spaniel, and Dachshund (Borge et al., 2013).

The roles of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) in canine mammary carcinogenesis have been explored in several studies (Mol et al., 1995; Ozmen, 2020; Queiroga et al., 2010). In humans, a positive association between increased levels of GH/IGF-1 and the risk of breast cancer has been reported (Subramani et al., 2017), and an increasing risk of MT has been observed after GH administration in GH deficient dwarf rats (Thordarson et al., 2004). Growth hormone and IGF-1 are expressed in both normal, benign and malignant canine mammary tissue, with higher levels in malignant tissues (Ozmen, 2020; Queiroga et al., 2010; Strage et al., 2014). Further, increased levels of IGF-1 and GH have been associated with a worse prognosis in dogs with MT, and IGF-1 has been suggested as a potential diagnostic marker for malignancy in canine MT (Ozmen, 2020; Queiroga et al., 2010). If and to what extent the association between breed and the development of MT is influenced by the expression of mammary GH and IGF-1 has yet to be explored. However, a general association between increasing bodyweight and IGF-1 levels have been observed (Greer et al., 2011). This contradicts the fact that the majority of the high-risk breeds in the current study were of small or medium size, but potentially contributed to an earlier diagnosis and higher mortality in large-sized breeds. This could be due to a higher incidence of malignant tumours in large dogs, which has been reported in previous studies (Itoh et al., 2005; Pastor et al., 2018)

The percentage of dogs affected by multiple events (13.2 %) is similar to the 12.0 % reported by Egenvall et al. (2005). It was not possible to evaluate if the multiple MT events were due to new tumours, recurrence of a surgically removed MT, or re-examination of an already present MT. As owners might send several receipts to the insurance company at the same time, it was not possible to verify that each claim with a diagnosis of MT corresponded to a separate veterinary examination, although each veterinary examination usually was registered as a separate insurance claim. Dogs with multiple MT events were younger at first diagnosis. However, having multiple MT events was not associated with a shorter lifespan compared to having one event. Thus, multiple MT events did not seem to affect the prognosis in the current study population. However, the association between multiple or recurrent mammary tumours and survival should be further explored in future studies, as it was not possible to verify if the multiple events in the current study were due to new tumours, recurrence or re-examination.

Bitches with gastrointestinal, integumentary, musculoskeletal, and urogenital diagnoses, as well as other general/unspecific diagnoses, had increased odds of a subsequent claim for MT, and dogs with MT had increased odds of subsequent diagnoses in all organ systems compared to controls. This could be due to an actual higher disease burden in bitches with MT, a higher chance of detecting other conditions at follow-up of MT treatment, or a higher tendency of bringing their dogs to a veterinarian in some owners. The percentage of cases and controls with diagnoses in each organ system and the magnitude of the OR should be considered when the results are interpreted. For example, 2.65 % of the cases had a subsequent cardiovascular diagnosis, compared to 2.00 % of the controls. Even though this difference is significant from a statistical perspective, it might not be clinically relevant.

Higher odds of MT were found in bitches with a history of pseudopregnancy (OR 2.10) and acute mastitis (OR 4.93), in line with the results from a previous study exploring risk factors for MT in dogs attending primary-care veterinary practices in the UK (Varney et al., 2023). The aetiology of pseudopregnancy is poorly understood, but a decline in plasma progesterone and high plasma levels and tissue sensitivity to prolactin has been shown in pseudopregnant bitches (Root et al., 2018; Tsutsui et al., 2007). In addition, increased serum prolactin levels have been reported in bitches with MT, and higher levels of tissue prolactin have been associated with tumour relapse and/or distant metastasis (Queiroga et al., 2014). If increased prolactin levels in the pseudopregnant bitches contributed to MT development could not be evaluated in the current study, and should be explored in further studies. Being intact is a potential confounder for the association between pseudopregnancy/acute mastitis and MT, as most bitches affected by pseudopregnancy and acute mastitis are intact (Kaszak et al., 2018; Root et al., 2018). Further, MT may cause mastitis, and it cannot be excluded that some cases of acute mastitis were caused by MT, although the MT was diagnosed at a later stage (Kaszak et al., 2018). Veterinarians could instruct owners of dogs with pseudopregnancy/acute mastitis to be extra observant of MT development, even though the causality of the association between these conditions is yet to be explored.

Mammary tumours are associated with the highest mortality of all tumours (Bonnett et al., 2005). In the current study, the cause-specific mortality of MT was 8.92 deaths per 10,000, compared to 6 deaths per 10,000 DYAR reported by Egenvall et al. (2005). Thus, the cause-specific mortality has increased slightly, which could be due to an increasing longevity of the dog population in general, and thus a higher risk of developing MT (Inoue et al., 2018). Of the bitches with veterinary care claims for MT and life insurance, 3.03 % died of MT-related causes during the study period. The MT-related deaths made up 28.3 % of the total deaths in these bitches. The corresponding percentage in the study by Egenvall et al. (2005) was 40.0 %. Hence, the percentage of bitches with MT that died of MT-related causes has decreased, possibly due to the development of better treatment protocols/guidelines or a changed owner attitude towards choosing treatment instead of euthanasia. The median time from the first MT claim during the study period to MT-related death was only 9.14 weeks, showing that bitches that died of MT-related causes generally died within 3 months from the first diagnosis. However, it should be noted that this is the median time to death in bitches with MT that were euthanised of MT-related causes, and not the median survival in bitches with MT in general. Death related to MT could be due to factors such as metastasis (indicating a poor prognosis (Hellmén et al., 1993; Moon et al., 2022; Santos et al., 2013)), limited dog owner economy precluding surgical treatment, malignancy of the tumour, concurrent comorbidities in combination with the MT, or age of the dog. Bitches that died of MT-related causes were older at death compared to bitches that died of other reasons (9.32 years vs. 7.57 years). As the median age at MT-related death approached the age at life insurance termination (8/10/12 years, depending on breed), the age is likely slightly underestimated. Five breeds had an increased risk of MT-related death: the Large Munsterlander (although the width of the confidence interval has to be considered), Irish soft coated wheaten terrier, English springer spaniel, German shepherd dog, and Swedish elkhound. These are all medium or large-sized breeds, even though no association between body weight and survival was found in a study evaluating prognostic factors in dogs with MT (Santos et al., 2013). However, longer survival has been reported in small breeds compared to larger breeds with MT (Itoh et al., 2005). The fact that the majority of the breeds with a high risk of MT-related death in the current study are used for hunting or as working dogs might have contributed to the increased risk, as a period of convalescence might be suboptimal in such breeds due to their high activity level. It could also be that owners of hunting/working dogs are less inclined to undertake expensive and/or demanding treatments and resort more easily to euthanasia if the dog develops disease and is no longer fit for purpose.

This study was performed on insurance data, and some important aspects should be considered when the results are interpreted. The included dogs likely represent the general dog with MT to a higher

extent than studies performed on histological data, as histopathological examination only is performed on a subset of MT cases. However, the insurance data depend on the veterinarians who examine the insured dogs and the dog owners who report the veterinary examinations to the insurance company. Further, the subset of dogs with MT that are brought for veterinary examination might be affected by factors such as the dogs' body condition score and fur coat (i.e. how easily the MT can be palpated by the dog owner) and if the owner has owned a dog with MT before (which might increase the chance of the owner detecting MT in their dog).

Information regarding neuter status was unavailable. As previously mentioned, a relatively low proportion of Swedish dogs are neutered (22.3 % ± 4.8 in 2012 (Statistics Sweden, 2012)), and neutering is often performed due to medical reasons (i.e. pyometra (Egenvall et al., 2001; Jitpean et al., 2012)). Thus, it can be assumed that the proportion of bitches neutered at a young age was low. It would also have been of interest to evaluate the risk of MT in bitches that had whelped or lactated, but that information was unavailable.

Each breed was compared to all other breeds in the analysis of breed as a risk factor for MT. It should be noted that the denominator population changed for each breed (i.e. included all dogs except for that breed). Therefore, the RRs are not directly comparable between breeds.

The Agria Djurförsäkring database was validated against practice records > 20 years ago, showing excellent agreement for sex and breed but a fair agreement for the birth date (Egenvall et al., 1998). There was a tendency for better agreement for clinics with computerised veterinary records. Since computerised veterinary records are used in the majority of Swedish clinics, the current agreement is most likely better. Validation of the diagnoses against veterinary records would have been desirable, but access to the veterinary records was not possible due to the GDPR (General Data Protection Regulation, which regulates the handling of personal information, in this case of the dog owners). The diagnosis of MT relied on the examining veterinarians, and there is a risk of misclassification bias if cutaneous tumours or other non-tumour mammary pathologies were classified as MT or vice versa. However, the diagnosis of MT is relatively straightforward, and clinical diagnosis of MT is fairly accurate; in a Swedish study by Hellmén et al. (1993), only 4 % of clinically diagnosed MT were considered non-MT on histological examination.

The cost associated with the claim needed to exceed the deductible of the insurance for the claim to be registered in the insurance database. Thus, the incidence of MT might be underestimated, as there is a risk that the costs for MT cases managed without surgical treatment were lower than the deductible. Finally, histopathological diagnoses would have been useful but were unavailable. Thus, it was not possible to differentiate malignant and benign lesions.

Conclusion

In total, 13,109 bitches had veterinary care claims for MT during the study period. The median age at first MT diagnosis was 8.94 years, and the incidence increased with age, peaking in dogs 10-< 11 years of age. In general, the breeds diagnosed at younger ages were large-sized, and the breeds diagnosed at higher ages were small-sized. This highlights the importance of regular mammary palpation in middle-aged and older bitches, but also in young bitches, especially of large breeds. Large breed-related differences in the risk of MT were found. Owners of high-risk breeds such as the Kerry blue terrier, English springer spaniel and Irish soft coated wheaten terrier should be extra observant of MT development. Of the bitches with MT, 13.2 % had multiple MT events (two claims at least six months apart). Thus, veterinarians should inform dog owners of bitches with MT about the risk of recurrent MT or the development of new tumours. In total, 486 bitches died of MT-related causes during the study period and the median age at MT-related death was 9.32 years. Of the 8127 bitches with veterinary care claims for MT and concurrent life insurance, 3.03 % died of MT-related causes during the study period. This indicates that although MT is a common disorder in bitches, it is associated with a relatively good prognosis and a low rate of death/euthanasia. In summary, the results can aid veterinarians advising dog owners regarding the risk of MT, hopefully resulting in an earlier diagnosis and better prognosis for the affected dogs.

Ethics approval and consent to participate

Not applicable.

Funding

This work was supported by the Agria and SKK Research Fund in Sweden. The research fund had no impact on the interpretation of the results. S.S. and H.R. were supported by the Johansson Family Swedish Boxer Club Cancer Donation. The funding sources were not involved in the planning of the study, data analysis and interpretation, or writing of the manuscript.

CRediT authorship contribution statement

Engdahl Karolina: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Hedhammar Åke:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Ström Holst Bodil:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Rönnberg Henrik:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Saellström Sara:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of Competing Interest

None

Acknowledgements

The data access and support from Agria Djurförsäkring and the financial support from the Agria and SKK Research Fund is gratefully acknowledged. We would like to thank Monica Dreijer and Lotta Möller for support with data processing, and Ulf Emanuelson and Pekka Olson for support and discussion.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tvjl.2025.106359.

Data availability

The data analysed in the current study are not publicly available due to a non-disclosure agreement with Agria Djurförsäkring.

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