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Epidemiology of mammary tumours in bitches under veterinary care in the UK in 2016

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Abstract

Background: There is limited information on the epidemiology of canine mammary tumours. This study aimed to estimate the incidence and risk factors for mammary tumours in UK bitches.

Methods: A nested case–control study was conducted within VetCompass to estimate the frequency and risk factors for clinically diagnosed mammary tumours during 2016 (VetCompass study). A second case–control study explored further breed associations for cases confirmed histopathologically compared to the VetCompass controls (laboratory study). Multivariable logistic regression was used to evaluate associations between risk factors and mammary tumours.

Results: The incidence of mammary tumours was 1340.7/100,000 per year (95% confidence interval: 1198.1–1483.3). A total of 222 clinical cases (VetCompass study) and 915 laboratory cases (laboratory study) were compared to 1515 VetCompass controls in the two analyses. In the VetCompass study, Springer and Cocker Spaniels, Boxers, Staffordshire Bull Terriers and Lhasa Apsos had increased odds of developing mammary tumours. Neutering was associated with reduced odds, while odds increased with increasing age and a history of pseudopregnancy. In the laboratory study, increasing age was associated with greater odds of mammary tumours, and the breeds most at risk were similar to those identified in the VetCompass study.

Limitations: The timing of neutering was not consistently available. Comparing laboratory cases to VetCompass controls provided only exploratory evidence for the breed associations identified.

Conclusions: The study provides an update on the frequency of canine mammary tumours.

INTRODUCTION

Mammary tumours have been reported as the most common neoplastic disease among bitches, representing over half of all tumour types diagnosed among entire bitches.[1,2] In addition to this, a previous study reported that approximately 50% of mammary tumours in bitches were malignant,[3] highlighting the potentially severe negative impact of the condition. However, few studies have evaluated the frequency of mammary tumours in bitches under primary veterinary care in the UK. An insurance-based study analysed a UK veterinary insurance database and reported a standardised incidence rate for mammary tumours of 205/100,000 bitches/year between 1 June 1997 and 31 May 1998.[4] The study by Dobson et al.[4] provides valuable evidence but included only insured bitches and is now over 20 years old.

Breed and other risk factors associated with the occurrence of mammary tumours in bitches have been reported in several studies. Age has been evaluated, and bitches older than 6 years had a higher risk of the disease when compared to those aged below 6 years.[5] Other risk factors, such as neuter status, time of neutering and breed, were also identified,[6] with entire bitches, bitches of an advanced age (i.e., greater than 12 years) at neutering and breeds such as Boston

Terrier, Cocker Spaniel, English Springer Spaniel, German Shorthaired Pointer, Labrador Retriever, Dachshund and Poodle showing increased risk of mammary tumours.[7–11] More recently, it has been reported that early ovariohysterectomy had a protective effect against mammary tumours.[12] However, there remains limited current evidence directly relevant to UK bitches.

This study therefore aimed to evaluate the epidemiology of mammary tumours in bitches attending UK primary-care practice. The objectives were to estimate the incidence, prevalence and risk factors associated with mammary tumours in bitches in the UK. It was hypothesised that increasing age and purebred compared to crossbred bitches were associated with an increased risk of mammary tumours.

METHODS

Two case–control studies were undertaken. A case–control study nested within the cohort of bitches attending participating VetCompass primary-care practices during 2016 was performed to estimate the incidence and prevalence of mammary tumours and evaluate animal risk factors for the diagnosis of mammary tumours (VetCompass study). A second case–control study of external laboratory-confirmed cases compared to VetCompass controls (laboratory study) was undertaken to allow further exploration of the breed associations in a group of histologically confirmed mammary tumours. Ethical approval was provided by the Social Science Research Ethical Review Board at the Royal Veterinary College for both the use of VetCompass data (SR2018-1652) and the use of external laboratory data (SR2020-0208).

VetCompass case–control study

In the VetCompass study, a sampling frame was prepared of all bitches under veterinary care at participating VetCompass UK practices during 2016. The case–control study included the subset of bitches that were female and aged at least 4 years old when diagnosed with mammary tumours between 1 January and 31 December 2016. Controls were aged at least 4 years on 30 June 2016. The decision to perform restricted sampling was based on assessment of the age distribution of cases and controls, which was skewed towards younger bitches in the controls and older bitches in the cases. This was done to ensure that the controls were selected from a more similar subsection of the veterinary attending population to the cases and reduce the potential data issue of separation of data.[13] Cases were defined as bitches with evidence of a clinical veterinary diagnosis of mammary tumours in their clinical records between 1 January and 31 December 2016 (incident cases in 2016). Pre-existing cases were also identified in order to calculate prevalence, where prevalent cases were defined as bitches diagnosed with mammary tumours both before and during 2016.

For the estimation of prevalence and incidence, mammary tumour cases of all ages were included based on the above case definition, while only incident cases aged 4 years and over were included in the risk factor analysis. Candidate mammary tumour cases were identified by searching in the clinical notes of the VetCompass database obtained during 2016 using both tumour terms (cancer, neopl*, tumour, tumor, tumur, mass, masses, lump) and mammary terms (mamm*). For an individual to be identified as a candidate case, both a tumour and mammary term were required in the clinical notes. The candidate cases were randomly ordered, and a random sample was examined in detail by reading the clinical notes to identify bitches meeting the case definition. The list of candidate cases was reviewed in detail until the required number of mammary tumour cases was achieved (see below for further details). Evidence of external laboratory confirmation of the diagnosis based on histopathology was additionally extracted. Candidate cases that did not meet the case definition were excluded from the analysis. All data collected from VetCompass were exported to a spreadsheet (Excel, Microsoft Corporation) where they were cleaned, and any discrepancies were double checked with the original electronic patient record (EPR) data.

The incident VetCompass cases were compared to a random sample of bitches aged 4 years and older without evidence of mammary tumours in their EPR, based on the search terms highlighted above, that were under veterinary care at a VetCompass practice during 2016 (VetCompass controls). The age for cases was defined as the age at first diagnosis of mammary tumours in 2016, while the age for controls was defined by their age on 30 June 2016. These were analysed as continuous data and then grouped into three age categories: 4 to less than 9 years, 9 to less than 12 years and 12 years or more. The neuter status of both cases and controls was extracted based on the evidence in the clinical records; all available records were read thoroughly to identify neuter status, where only bitches neutered before first diagnosis were considered as neutered. If neuter status was recorded as neutered in the clinical notes, the age at which they were neutered was also recorded and grouped into the following categories: less than 3 years, 3 to less than 6 years, 6 to less than 9 years and 9 years or more. Bitches were categorised into their individual breed, where there were five or more cases of that breed in the dataset, using the VeNom standardised breed terms.[14] All other purebreds were grouped into the category 'purebred other' and crossbreeds were categorised as 'crossbred'. A binary breed variable was also analysed, categorised as 'purebred' and 'crossbred'. The variables insurance status, history of pseudopregnancy and mastitis were all also extracted from the clinical notes and analysed as binary variables, based on previous work showing an association with insurance and pre-study hypotheses for pseudopregnancy and mastitis. Additionally, if a history of pseudopregnancy was recorded as 'yes', treatment with cabergoline (Galastop, Ceva) was extracted for analysis as a categorical variable, defined as 'no history of pseudopregnancy', 'history of pseudopregnancy and treated' and 'history of pseudopregnancy and not treated'. Lastly, the practice group, that is, the veterinary group to which the practices belonged, was categorised into five groups and included in the analysis to account for variation between practice groups.

Laboratory case–control study

In the laboratory study, cases were provided by an external private laboratory (Bridge Pathology) with controls being derived and defined as above from VetCompass bitches without evidence of mammary tumours under veterinary care in 2016 (VetCompass controls). Cases were bitches aged 4 years or above at the date of an external laboratory-confirmed diagnosis of mammary tumour between January 2009 and December 2019. Cases that were male, under 4 years of age or of unknown sex or age were excluded from the analysis.

For the analysis, laboratory-confirmed cases were compared to the VetCompass controls to further explore breed associations. Risk factors including breed, neuter status and age were analysed, where each variable was defined and categorised as described for the VetCompass study.

Statistical analysis

The annual prevalence and incidence risk for bitches of any age were calculated from the VetCompass study, where prevalent cases represented those diagnosed with mammary tumours both before and during 2016 and incident cases represented bitches newly diagnosed with mammary tumours during 2016. The risks and 95% confidence intervals (CIs) were calculated adjusting for the sampling approach as reported in previous work, such that as 5.79% of the 31,272 randomly ordered candidate cases were manually reviewed, the identified mammary cases related to 5.79% of the over 4 years of age 2016 female dog denominator.[15]

For the evaluation of risk factors, data checking and cleaning were performed in Microsoft Excel (2019), producing one record per dog, and the data were then imported into Stata 16 (StataCorp) for analysis. Categorical data were summarised as counts and percentages. Median, interquartile range (IQR) and range were calculated for continuous variables. Univariable analysis tested associations between risk factors and a diagnosis of mammary tumours using univariable logistic regression. Multivariable logistic regression analysis was conducted on the risk factors in both the VetCompass and the laboratory studies. Explanatory variables that showed a broad association with a diagnosis of mammary tumours in the univariable analysis [likelihood ratio test (LRT), $p < 0.2$] were carried forward for assessment in the multivariable model. Collinearity was assessed between all variables taken forward for multivariable consideration using the chi-square test and exploring cross-tabulation of the independent variables to assess for a statistical association between categorical variables.[13] Where variables were highly related, only one of the collinear variables was evaluated in the multivariable model at a time and the most statistically significant variable and/or the one with the fewest missing values was retained.[13] The multivariable models were constructed using a manual backward elimination approach with the removal of variables based on the LRT statistic.[13] The main explanatory variables of interest were breed, age and neuter status, while insurance status was evaluated in the VetCompass study as a confounder. In the VetCompass model, practice group was retained a priori to adjust for data clustering at the practice group level, and additionally, clinic ID was assessed as a random effect in both the univariable and multivariable analyses to further adjust for clustering at the individual practice level and was retained if statistically significant. For the laboratory study, only a fixed effects model was constructed. Final model variables were evaluated for pairwise interactions and the final model fit was evaluated with the area under the receiver operating characteristic (ROC) curve and the Hosmer–Lemeshow goodness-of-fit test.[13] A p-value less than 0.05 was used as the statistical significance level.

Sample size calculations, using OpenEpi[16] to evaluate the association of the main variables of interest with the diagnosis of mammary tumours, estimated that in order to detect an odds ratio of 1.50–2.00 or greater for both purebreds and bitches of increased age, assuming 48%–68% of controls were exposed to the risk factors of interest (purebred status and increased age), approximately 115–297 mammary tumour cases and 483–1778 controls aged 4 years and older would be needed based on an efficient 1:4 case-to-control ratio with an 80% power and 95% CI.[13,17]

RESULTS

VetCompass study

The study population comprised 431,708 bitches under veterinary care at participating veterinary practices in the UK during 2016. From the 31,272 candidate cases identified using the stated search terms, 1810 (5.79%) were examined in detail against the case definition and 475 cases were identified, consisting of 140 pre-existing cases and 335 incident cases. An annual prevalence risk of 1901.0/100,000 bitches per year (95% CI: 1731.7–2070.3) and an annual incidence risk of 1340.7/100,000 bitches per year (95% CI: 1198.1–1483.3) were estimated.

Of the 335 incident cases in 2016, 51 (22.5%) cases had evidence of confirmation with histopathology. Seventy-seven bitches (33.9%) underwent surgery to remove the tumours, of which 57 (25.1%) had local resection and 20 (8.8%) had either a complete bilateral mastectomy or unilateral mammary strip. Seven bitches (3.1%) showed later evidence of tumour recurrence. Eight (3.5%) cases showed evidence of metastases at diagnosis.

In the risk factor analysis, after excluding bitches less than 4 years, 222 incident cases were retained. There were 85 (38.3%) neutered bitches, with the remaining 137 incident cases being entire (61.7%). Nineteen cases (8.4%) had a history of pseudopregnancy prior to diagnosis and 10 cases (4.4%) were previously diagnosed with mastitis. Of the 222 incident cases, the median age at first diagnosis was 10.0 years, with the oldest being 19.0 years (IQR: 8.0–11.0). One hundred and eighty bitches (81.1%) were purebred and 22 (9.9%) had evidence of prior or current insurance. The most common breeds among the cases were the Labrador Retriever, English Cocker Spaniel, Jack Russell Terrier and Staffordshire Bull Terrier (Table 1).

The cases were compared to 1515 randomly selected controls aged 4 years and older. The median age of the controls was 7.0 years, with the oldest being 20.0 years (IQR: 5.0–9.0). There were 991 (65.4%) neutered bitches, and 1127 (74.5%) were purebreds. The most common breeds in the controls were the Labrador Retriever, Jack Russell Terrier, Staffordshire Bull Terrier, Yorkshire Terrier, English Cocker Spaniel and West Highland White Terrier. Of the controls, 14.4% (218) had evidence of insurance.

Univariable analysis identified all variables as broadly associated with mammary tumours ($p < 0.20$, see Table 1), and these were taken forward to the multivariable analysis. Both 'treatment with Galastop' and 'history of mastitis' were highly correlated with 'history of pseudopregnancy' and only the latter variable was retained in the final model, based on the LRT statistics when including one of these three collinear variables in the model. The variable 'age at neuter' was closely related to the variable 'neutered' and, given age at neuter had more unrecorded observations, it was excluded from the final model. In the multivariable analysis, all risk factor variables taken forward for multivariable evaluation, except insurance status and practice group, showed statistically significant associations with mammary tumour diagnosis (Table 2 and Figure 1). Practice group was not statistically significant but was retained in the final model to take account of potential clustering at the practice level. Evaluation of pairwise interactions between final model variables showed no statistically significant interactions between the variables in the multivariable model. Neutered bitches had 0.32 times the odds (95% CI: 0.23–0.44) of diagnosis of mammary tumours compared to entire bitches. Bitches aged both 9 to less than 12 years and 12 years or more showed increased odds compared to those aged 4 to less than 9 years, with odds ratios of 4.57 (95% CI: 3.22–6.49) and 4.68 (95% CI: 3.09–7.10), respectively. The Lhasa Apso, English Springer Spaniel, Boxer, English Cocker Spaniel and Staffordshire Bull terrier were all associated with increased odds of mammary tumours compared to crossbreeds. Including 'clinic ID' as a random effect variable did not significantly improve the model fit and was not retained in the final model ($\rho = 0.003$, $p = 0.495$). The Hosmer–Lemeshow test was not statistically significant ($p = 0.477$), suggesting no evidence of poor model fit, and the area under the ROC curve (0.775, 95% CI: 0.742–0.808) indicated an acceptable ability to differentiate mammary tumour cases from controls.

Laboratory study

In the external laboratory case–control study, there were 1017 dogs with laboratory submissions during the study period, of which five were excluded for being male, 51 of unknown sex, 28 under 4 years of age and 18 of unknown age, leaving 915 mammary tumour cases (90% of total). These 915 cases submitted to a commercial histopathology laboratory, aged 4 years and older, were compared to the 1515 VetCompass controls described above. Of the 915 laboratory-confirmed cases, 195 (21.3%) were mammary carcinomas and 720 (78.7%) were adenomas. There were 299 (32.7%) neutered bitches, with 477 (52.1%) having an unrecorded neuter status. The median age was found to be 8.0 years, with the oldest being 20 years (IQR: 6–10). Seven hundred and sixty-four laboratory-confirmed cases (83.5%) were identified as purebreds. Breed and age were statistically significant in the univariable analysis (Table 3) and were considered in the multivariable analysis. Neuter status was not taken forward due to missing data.

After adjusting for confounding in the multivariable analysis (Table 4 and Figure 1), breed and age were associated with mammary tumour diagnosis. Evaluation of pairwise interactions between all variables showed no significant interactions between the variables in the multivariable model. The English Setter, German Shorthaired Pointer, Dachshund, Greyhound, English Springer Spaniel, Doberman Pinscher, Pomeranian, Cocker Spaniel, Lurcher, German Shepherd Dog, Bichon Frise, Jack Russell Terrier, Yorkshire Terrier and Labrador Retriever had increased odds compared to the baseline crossbred bitches. The Staffordshire Bull Terrier appeared to be at reduced odds of mammary tumours. Bitches aged both between 9 and less than 12 years and 12 years or more showed increased odds compared to those aged 4 to less than 9 years, with odds ratios of 3.37 and 1.76, respectively. The Hosmer–Lemeshow test was not statistically significant ($p = 0.696$), suggesting no evidence of poor model fit, and the area under the ROC curve (0.712, 95% CI: 0.691–0.733) indicated acceptable ability to differentiate laboratory tumour cases from controls.

TABLE 1 Descriptive and univariable logistic regression analysis of risk factors in bitches 4 years and older with a diagnosis of mammary tumours (cases) compared to randomly selected controls attending UK VetCompass primary-care veterinary practices in 2016.

Variable	Number of cases (%)	Number of controls (%)	Odds ratio	95% confidence interval	Category *p*-value	LRT *p*-value
Neutered						
Entire	137 (61.7)	524 (34.6)	–			<0.001
Neutered	85 (38.3)	991 (65.4)	0.33	0.25–0.44	<0.001	
Age (years)						
4 to <9	72 (32.4)	987 (65.1)	–			<0.001
9 to <12	97 (43.7)	336 (22.2)	3.96	2.85–5.50	<0.001	
≥12	53 (23.9)	192 (12. 7)	3.78	2.57–5.57	<0.001	
Age at neuter (years)						
Not neutered	137 (61.7)	524 (34.6)	–			<0.001
0 to <3	2 (0.9)	178 (11.7)	0.04	0.01–0.18	<0.001	
3 to <6	4 (1.8)	91 (6.0)	0.17	0.06–0.47	<0.001	
6 to <9	10 (4.5)	43 (2.8)	0.89	0.44–1.82	0.748	
≥9	10 (4.5)	16 (1.1)	2.39	1.06–5.36	0.035	
Unrecorded	59 (26.6)	663 (43.8)	0.34	0.25–0.47	<0.001	
Breed group						
Crossbred	42 (18.9)	385 (25.5)	–			0.035
Purebred	180 (81.1)	1127 (74.5)	1.46	1.03–2.09	0.035	
Breed						
Crossbreed	42 (18.9)	385 (25.5)	–			0.002
Lhasa Apso	5 (2.3)	14 (0.9)	3.27	1.12–9.54	0.030	
Boxer	6 (2.7)	17 (1.1)	3.24	1.21–8.65	0.019	
English Springer Spaniel	9 (4.1)	27 (1.8)	3.06	1.35–6.93	0.008	
Yorkshire Terrier	13 (5.9)	48 (3.2)	2.48	1.24–4.95	0.010	
Staffordshire Bull Terrier	24 (10.8)	104 (6.9)	2.12	1.23–3.65	0.007	
English Cocker Spaniel	11 (5.0)	48 (3.2)	2.10	1.01–4.35	0.046	
Labrador Retriever	23 (10.4)	122 (8.1)	1.73	1.00–2.99	0.050	
Border Collie	7 (3.2)	39 (2.6)	1.64	0.69–3.91	0.259	
Jack Russell Terrier	15 (6.8)	106 (7.0)	1.30	0.69–2.43	0.416	
West Highland Terrier	5 (2.3)	46 (3.0)	1.00	0.38–2.65	0.994	
Purebred other	62 (27.9)	556 (36.8)	1.02	0.68–1.54	0.917	
Previous pseudopregnancy						
No	203 (91.4)	1467 (96.8)	–			<0.001
Yes	19 (8.6)	48 (3.2)	2.86	1.65–4.96	<0.001	
Pseudopregnancy treatment with cabergoline (Galastop)						
No history of pseudopregnancy	203 (91.4)	1467 (96.8)	–			<0.001
Pseudopregnancy and no treatment	15 (6.8)	24 (1.6)	4.41	2.27–8.54	<0.001	
Pseudopregnancy and treatment	4 (1.8)	24 (1.6)	1.18	0.40–3.42	0.767	
History of mastitis						
No	212 (95.5)	1512 (99.8)	–			<0.001
Yes	10 (4.5)	3 (0.2)	23.77	6.49–87.07	<0.001	
Insurance status						
Not insured	200 (90.1)	1297 (85.6)	–			0.073
Insured	22 (9.9)	218 (14.4)	0.65	0.42–1.04	0.071	
Practice group						
Group 1	32 (14.4)	331 (21.8)	–			0.108
Group 2	74 (33.3)	420 (27.7)	1.82	1.18–2.83	0.007	
Group 3	105 (47.3)	669 (44.2)	1.62	1.07–2.46	0.023	
Group 4	11 (5.0)	83 (5.5)	1.37	0.66–2.83	0.394	
Group 5	0 (0)	12 (0.8)				

Abbreviation: LRT, likelihood ratio test.

TABLE 2 Multivariable logistic regression analysis of risk factors for mammary tumours in bitches, 4 years and older, attending UK VetCompass primary-care veterinary practices in 2016.

Variable	Odds ratio	95% confidence interval	Category *p*-value	LRT *p*-value
Neutered				
No	–			<0.001
Yes	0.32	0.23–0.44	<0.001	
Breed				
Crossbred	–			0.003
Lhasa Apso	5.43	1.71–17.20	0.004	
English Springer Spaniel	3.50	1.42–8.59	0.006	
Boxer	3.19	1.08–9.44	0.036	
Staffordshire Bull Terrier	2.44	1.36–4.40	0.003	
English Cocker Spaniel	2.20	1.01–4.80	0.046	
Yorkshire Terrier	1.91	0.92–3.96	0.085	
Labrador	1.77	0.99–3.19	0.056	
Border Collie	1.31	0.52–3.30	0.561	
Jack Russell Terrier	1.11	0.57–2.15	0.763	
West Highland Terrier	0.86	0.31–2.41	0.777	
Purebred other	1.14	0.74–1.76	0.560	
Age (years)				
4 to <9	–			<0.001
9 to <12	4.57	3.22–6.49	<0.001	
≥12	4.68	3.09–7.10	<0.001	
Previous pseudopregnancy				
No	-			0.001
Yes	3.33	1.79–6.16	<0.001	
Practice group				
1	–			0.192
2	1.79	1.12–2.86	0.015	
3	1.57	1.01–2.44	0.047	
4	1.63	0.75–3.56	0.218	
5	–			

Abbreviation: LRT, likelihood ratio test.

DISCUSSION

This is the largest study to date to evaluate the frequency and risk factors for mammary tumours in bitches seen at primary-care veterinary practice in the UK and provides a baseline estimate of the frequency of the condition. Important breed predispositions were identified, with Springer and Cocker Spaniels in particular consistently showing increased odds of diagnosis of mammary tumours in both clinical and laboratory studies when compared to crossbreeds. Older bitches were associated with increased risk, based on both clinical and laboratory diagnoses, and neutered bitches were at two- to five-fold reduced odds of diagnosis, based on clinical diagnosis. A history of pseudopregnancy was also associated with increased odds of clinical diagnosis of mammary tumours.

The incidence risk (1304.7/100,000 bitches per year) and prevalence (1901.0/100,000 bitches per year) reported in this study provide new and valuable information on the frequency of mammary tumours in bitches attending primary-care veterinary practice in the UK. The incidence calculated was greater than the incidence reported by Dobson et al.,[4] although the latter was based on insurance data. The authors of the latter work acknowledged that the incidence reported was likely to be an underestimation due to exclusion of non-insured bitches. In contrast, in the current study, due to the inclusion of cases that were not confirmed by histology, it is possible that some of the cases reported may have been incorrectly diagnosed with mammary tumours and the incidence observed could have been overestimated. However, even the incidence of only histologically confirmed incident cases in the current study was higher than the previous estimate, suggesting that the true level of mammary tumours diagnosed in primary practice is likely to be greater than the previously reported insurance-based estimates.

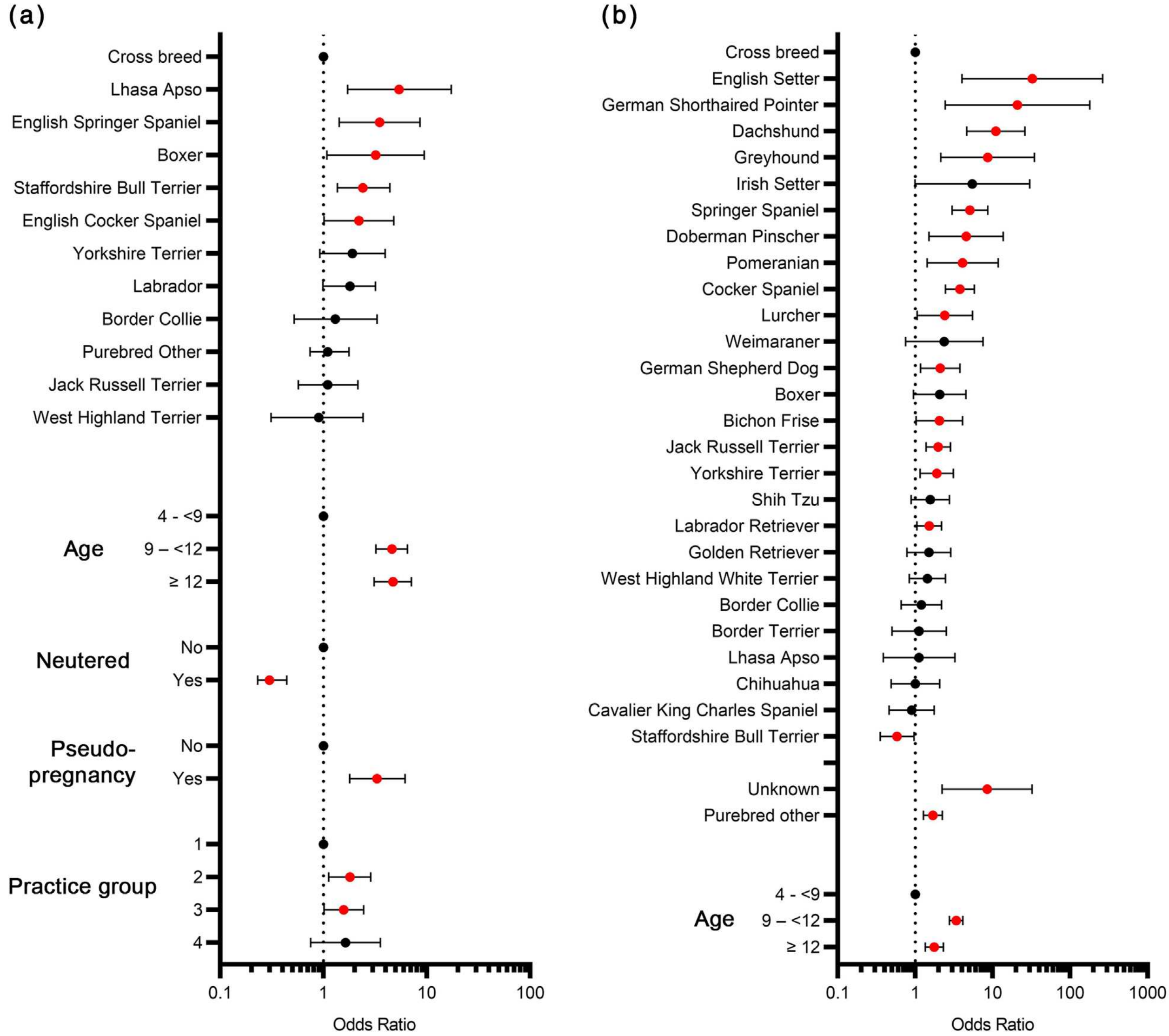

FIGURE 1 Forest plots showing the multivariable logistic regression results for risk factors for a diagnosis of mammary tumours in both (a) the VetCompass study and (b) the laboratory study. Black dots without error bars indicate reference categories, dots with error bars indicate odds ratios with 95% confidence intervals, and red dots indicate categories that differ significantly from the reference category.

Previous work has reported a reduced risk of mammary tumours in neutered bitches.[18] The findings of the VetCompass study align with these previous conclusions and highlight a two- to five-fold reduction in odds in neutered bitches suggestive of a substantial protective effect from neutering. In previous studies, increased age at the time of neutering was associated with an increased incidence of mammary tumours and early neutering has been recommended.[5,19,20] In a systematic review of the role of neutering on mammary tumours, the authors identified much of the earlier work on the topic as having some level of bias. However, they suggested that there was moderate evidence that neutering bitches at an early age, and in particular before the age of 2.5 years, was associated with a decrease in the risk of mammary tumours.[21] Since the age at neuter was unavailable for 27% of cases and 44% of controls in the VetCompass study and information regarding age at neuter was not available in the laboratory study, it was not possible to explore this in depth in the current study. Furthermore, in the laboratory study, it was difficult to assess the role of neutering per se, as this was not entered in over 50% of laboratory cases. Further work is merited to evaluate associations between age at neuter and mammary tumours.

Several breeds have been previously reported to have an increased risk of diagnosis with mammary tumours, including Boston Terrier, Cocker Spaniel, English Springer Spaniel, German Shorthaired Pointer, Labrador Retriever, Dachshund and Poodle.[7–11] A more recent study conducted in Sweden reported that Springer Spaniels, Cocker Spaniels, German Shepherds and Boxers were all predisposed to mammary tumours.[22] However, that report was conducted more than a decade ago, and it is therefore unclear whether the results of the study on dogs in Sweden can be generalised to the UK canine population, particularly given their reported far lower rate of neutering compared to the UK.[22] Nonetheless, the findings of the VetCompass and laboratory studies were generally consistent with this earlier work. Both the

TABLE 3 Descriptive and univariable logistic regression analysis of risk factors in bitches, 4 years and older, with an external laboratory diagnosis of mammary tumours (cases) compared to VetCompass controls attending UK primary-care veterinary practices in 2016.

Variable	Number of external laboratory cases (%)	Number of VetCompass controls (%)	Odds ratio	95% confidence interval	Category *p*-value	LRT *p*-value
Neutered						
No	139 (15.4)	524 (34.6)	–			0.540
Yes	299 (32.7)	991 (65.4)	1.14	0.91–1.43	0.267	
Unrecorded	477 (52.1)	0 (0.0)	–			
Breed group						
Crossbred	141 (15.4)	385 (25.4)	–			0.002
Purebred	764 (83.5)	1127 (74.4)	1.85	1.50–2.29	<0.001	
Unknown	10 (1.1)	3 (0.2)	9.10	2.47–33.55	<0.001	
Breed						
Crossbred	141 (15.4)	385 (25.4)	–			<0.001
English Setter	9 (1.0)	1 (0.1)	24.57	3.09–195.72	0.002	
German Shorthaired Pointer	6 (0.7)	1 (0.1)	16.38	1.96–137.28	0.010	
Dachshund	29 (3.2)	7 (0.4)	11.31	4.85–26.40	<0.001	
Irish Setter	5 (0.5)	2 (0.1)	6.83	1.31–35.58	0.023	
Greyhound	7 (0.8)	3 (0.2)	6.37	1.63–24.99	0.008	
English Springer Spaniel	45 (4.9)	27 (1.8)	4.55	2.72–7.61	<0.001	
Cocker Spaniel	70 (7.7)	48 (3.2)	3.98	2.63–6.03	<0.001	
Doberman Pinscher	8 (0.9)	6 (0.4)	3.64	1.24–10.68	0.019	
Weimaraner	7 (0.8)	6 (0.4)	3.19	1.05–9.64	0.040	
Pomeranian	8 (0.9)	7 (0.5)	3.12	1.11–8.76	0.031	
Lurcher	12 (1.3)	14 (0.9)	2.34	1.06–5.18	0.036	
Boxer	13 (1.4)	17 (1.1)	2.09	0.99–4.41	0.054	
Jack Russell Terrier	79 (8.6)	106 (7.0)	2.04	1.44–2.89	<0.001	
Yorkshire Terrier	35 (3.8)	48 (3.2)	1.99	1.24–3.21	0.005	
Bichon Frise	16 (1.7)	23 (1.5)	1.90	0.98–3.70	0.059	
German Shepherd Dog	23 (2.5)	34 (2.2)	1.85	1.05–3.24	0.033	
Golden Retriever	17 (1.9)	29 (1.9)	1.60	0.85–3.00	0.143	
Labrador Retriever	68 (7.4)	122 (8.1)	1.52	1.07–2.17	0.020	
West Highland White Terrier	25 (2.7)	46 (3.0)	1.48	0.88–2.51	0.140	
Shih Tzu	22 (2.4)	42 (2.8)	1.43	0.83–2.48	0.203	
Border Terrier	10 (1.1)	20 (1.3)	1.37	0.62–2.99	0.436	
Border Collie	19 (2.1)	39 (2.6)	1.33	0.74–2.38	0.336	
Lhasa Apso	5 (0.5)	14 (0.9)	0.98	0.35–2.76	0.962	
Cavalier King Charles Spaniel	13 (1.4)	41 (2.7)	0.89	0.45–1.66	0.665	
Chihuahua	11 (1.2)	36 (2.4)	0.83	0.41–1.68	0.613	
Staffordshire Bull Terrier	23 (2.5)	104 (6.9)	0.60	0.37–0.99	0.044	
Purebred other	167 (18.3)	284 (18.7)	1.61	1.22–2.11	<0.001	
Unknown	10 (1.1)	3 (0.2)	9.10	2.47–33.55	<0.001	
Samoyed	5 (0.5)	0 (0.0)	–			
Toy Poodle	7 (0.8)	0 (0.0)	–			
Age (years)						
4 to <9	376 (0.41)	987 (0.65)	–			<0.001
9 to <12	415 (0.45)	336 (0.22)	3.24	2.69–3.91	<0.001	
≥12	124 (0.14)	192 (0.13)	1.70	1.31–2.19	<0.001	

Abbreviation: LRT, likelihood ratio test.

TABLE 4 Multivariable logistic regression analysis of risk factors in bitches with an external laboratory diagnosis of mammary tumours (cases) compared to VetCompass controls attending UK primary-care veterinary practices in 2016.

Variable	Odds ratio	95% confidence interval	Category *p*-value	LRT *p*-value
Breed				
Crossbred	–			<0.001
English Setter	32.31	4.00–261.16	0.001	
German Shorthaired Pointer	20.85	2.43–179.34	0.006	
Dachshund	10.96	4.60–26.11	<0.001	
Greyhound	8.59	2.14–34.55	0.002	
Irish Setter	5.44	0.99–29.93	0.051	
English Springer Spaniel	5.06	2.98–8.60	<0.001	
Doberman Pinscher	4.53	1.50–13.67	0.007	
Pomeranian	4.08	1.42–11.72	0.009	
Cocker Spaniel	3.778	2.45–5.80	<0.001	
Lurcher	2.40	1.05–5.47	0.037	
Weimaraner	2.37	0.75–7.47	0.1432	
German Shepherd Dog	2.10	1.17–3.76	0.013	
Boxer	2.07	0.95–4.51	0.067	
Bichon Frise	2.04	1.02–4.08	0.043	
Jack Russell Terrier	1.98	1.38–2.84	<0.001	
Yorkshire Terrier	1.89	1.15–3.10	0.012	
Shih Tzu	1.56	0.88–2.76	0.126	
Labrador Retriever	1.51	1.05–2.19	0.027	
Golden Retriever	1.50	0.78–2.87	0.224	
West Highland White Terrier	1.43	0.83–2.46	0.194	
Border Collie	1.19	0.66–2.18	0.562	
Border Terrier	1.12	0.50–2.51	0.786	
Lhasa Apso	1.12	0.37–3.24	0.839	
Chihuahua	1.00	0.49–2.06	0.997	
Cavalier King Charles Spaniel	0.90	0.46–1.75	0.748	
Staffordshire Bull Terrier	0.58	0.35–0.95	0.032	
Purebred other	1.69	1.28–2.24	<0.001	
Unknown	8.45	2.21–32.29	0.002	
Samoyed	–			
Toy Poodle	–			
Age (years)				
4 to <9	–			<0.001
9 to <12	3.37	2.77–4.10	<0.001	
≥12	1.76	1.35–2.31	<0.001	

Abbreviation: LRT, likelihood ratio test.

VetCompass and laboratory studies identified Springer and Cocker Spaniels to have increased odds of diagnosis of mammary tumours. It has been previously reported that the risk alleles *BRCA1* and *BRCA2* were common among the Springer Spaniel breed and there was a strong association between both *BRCA1* and *BRCA2* and mammary tumours, with both genes showing a four-fold increased risk for mammary tumours.[23] Low BRCA1 levels are reported in most canine mammary tumours relative to normal tissue,[24,25] and in one study, the presence of low BRCA1 levels was associated with deletion of a single nucleotide in the *BRCA1* promoter.[24] A single nucleotide polymorphism in the *BRCA1* promoter is reported as significantly associated with canine mammary tumours,[26] and alterations in *BRCA1* splice variants have been found in mammary tumours relative to normal tissue,[27] although the functional consequences of this have not been determined. The presence of both the *BRCA1* and *BRCA2* genes in Springer Spaniels could give insight into why this breed appears predisposed to mammary tumours.

Staffordshire Bull Terriers and Lhasa Apsos also showed increased odds in the VetCompass study, despite no previous reports of predispositions for these breeds. In contrast, in the laboratory study, the Lhasa Apso was not associated with increased odds and the Staffordshire Bull Terrier appeared to be at reduced odds. This latter contradiction may be hypothesised to be due to potentially fewer of this breed type undergoing histological analysis relative to other purebreds and hence not being detected in the laboratory study; alternatively, differences between the VetCompass control population and the underlying veterinary population from which submissions to the private laboratory were derived could have explained these observations. Statistically significant associations with a diagnosis of mammary tumours were also found for a range of other breeds in the laboratory study, including English Setters, Doberman Pinschers, Pomeranians and Lurchers, which were consistent with the findings of Cohen et al.[7] and Mitchell et al.[9] The laboratory study had the advantage of having a greater number of cases with histological confirmation and it was primarily evaluated to further explore breed associations with mammary tumours by using triangulation to combine the findings of the two approaches to increase confidence in the results. However, it is acknowledged that the comparison of laboratory cases to a distinct set of VetCompass controls may have increased the risk of bias and it remained a secondary and exploratory analysis only. Evaluation of the risk of diagnosis of mammary tumours in other breeds identified in previous literature was limited in both current analyses due to these other breeds being represented in too low numbers in the study populations.

Analyses in the current study were restricted to bitches aged 4 years or above at the time of diagnosis. The development of mammary tumours before 5 years of age is uncommon.[28] Therefore, limiting the analysis to an older population allowed focus on the specific age subset of the population in which mammary tumours were of most relevance. Furthermore, it was found that in the VetCompass control population prior to age restriction, the age distribution was skewed with a relatively young median age. This is consistent with findings in previous literature, which found a median age of 4.5 years (IQR: 1.9–8.1, range: 0.0–20.5) for bitches presenting to veterinary practice.[29] Alenza et al.[28] suggested that bitches with a diagnosis of mammary tumours tend to have a mean age of 9–11 years. In the current work, increased age was consistently associated with increased odds compared to younger animals, confirming the findings in the previous literature. However, it should be noted that, given the restriction to bitches 4 years and older, the current findings are particularly relevant to a mature population and the risk factors identified may not be completely representative of those seen in animals under 4 years of age. Furthermore, it is acknowledged that, by representing age as a categorical variable, some information about the association with age may have been lost; however, it was considered that a categorical version of age facilitated the interpretation of the main association observed. Nonetheless, based on these findings, it could be recommended that owners of older bitches should be advised to monitor their bitches more carefully and veterinarians should prioritise mammary examinations in older bitches.

Varying associations between a history of pseudopregnancy and mammary tumours are reported in the literature. Several authors have previously observed that a history of pseudopregnancy was not associated with the development of mammary tumours.[30,31] However, a positive association between a history of pseudopregnancy and diagnosis with mammary tumours has previously been noted.[32] The results obtained in the current study support the latter findings; however, they are based on a relatively small number of bitches with reference to pseudopregnancy in their records. The pathogenesis of clinical pseudopregnancy is still not clearly understood[33]; however, pseudopregnancy has been previously reported to be linked to increased prolactin production.[34] Recent studies found that bitches with mammary tumours had increased serum prolactin levels compared to healthy animals[35,36]; thus, the association between a history of pseudopregnancy and mammary tumours is supported by the hormonal rationale reported in the previous findings. However, despite the statistical significance reported, the results in the current study should be interpreted with caution due to the small number of animals. Furthermore, for some of these animals, there was evidence that they were neutered subsequent to pseudopregnancy, suggesting that separating this condition from their neuter status was difficult and that further work is advisable.

The study had some limitations. Data were not collected primarily for research purposes. In this case, the ability to record and evaluate the risk factors of interest may have been limited, and missing data were particularly evident in the laboratory-derived data. Furthermore, for some data items coded, the assumption was made that the condition or entity was not present if it was not recorded in the clinical notes, for example, presence of pseudopregnancy. In the VetCompass study, approximately 20% of cases showed evidence of histological confirmation of mammary tumours, whereas the other 80% of cases were diagnosed clinically by a veterinarian. In this case, some of those determined to have mammary tumours by a veterinarian may have been misclassified and thus posed a limitation to the study due to possible false-positive diagnosis. However, due to financial and other considerations, the reality of first-opinion veterinary practice is that many diagnoses remain based on clinical criteria alone and the current study reflects this setting. On the other hand, the laboratory-confirmed cases were likely to be subject to selection bias related to the requirement of these cases to have a sample submitted for histology at an additional cost and anaesthetic risk. The use of triangulation to combine the inference from both approaches allowed the risk of both selection bias and misclassification to be reduced in the conclusions.[37] Nonetheless, in the context of the risk factors evaluated, the laboratory study, which benefited from a larger sample of cases that were all histologically confirmed, was broadly consistent with the VetCompass findings and increased the validity of the overall conclusions. The use of an external control group in the laboratory study could be considered a limitation since the cases and controls were not selected directly from the same study population.[13] Ideally, the controls should be representative of the population from which the cases were derived.[13] The preferred control group would consist of animals randomly selected from the primary-care practices submitting samples to the laboratory for canine mammary tumour cases during the same time period, rather than from a different population over a 1-year period (2016) as in the current study. However, this source population was not available, and the control group was randomly selected from bitches attending a large group of veterinary practices and as such was likely to provide a representation of the animal characteristics of bitches in UK practice to allow preliminary comparisons to the laboratory cases.[38,39] This secondary study was undertaken primarily to support the breed associations identified in the first study.

In conclusion, this study evaluated the risk of mammary tumours in primary-care veterinary practice in the UK and documents a current estimate for the occurrence of mammary tumours in primary-care practice. Several risk factors were identified. In particular, certain breeds, including the Springer Spaniels, had an increased risk of a diagnosis of mammary tumours, which coincides with the findings of previous literature. Intact and older bitches were also identified to have a strong association with the diagnosis of mammary tumours. These findings can help guide veterinarians in primary-care practice when advising their clients of the risks of mammary tumours.

AUTHOR CONTRIBUTIONS

The laboratory dataset was acquired by Sam Beck and Matthew J. Smalley. The laboratory dataset was cleaned and explored by Danielle Varney, David Brodbelt and Matthew J. Smalley. The VetCompass dataset was created and cleaned by Danielle Varney, Maeve O'Neill, Dan O'Neill and David Brodbelt. David Brodbelt and Dan O'Neill provided assistance with study design, model building, analysis and interpretation. The paper was initially prepared by Danielle Varney, with significant contributions from all co-authors.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Demographic data are available on request from the authors.

ETHICS STATEMENT

Ethical approval was provided by the Social Science Research Ethical Review Board at the Royal Veterinary College for both the use of VetCompass data (SR2018-1652) and the use of external laboratory data (SR2020-0208).

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