

The effect of neutering on the risk of mammary masses: a systematic review

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Aim

The primary aims of this project were:

➤ To evaluate the **strength of evidence** for an association between neutering, or age of neutering, and mammary masses of any histological type in bitches

➤ To estimate the **magnitude of the association**.



Method

A **systematic review** was conducted according to a pre-defined **protocol based on Cochrane guidelines**. PubMed^a, Cab Direct^b and ISI Web of Knowledge^c were searched according to terms shown in Box 1. Articles from peer-reviewed journals published in English were eligible, as shown in Box 2.

Eligible articles were reviewed independently by two epidemiologists, using a pre-defined data extraction form based on suggestions from the Cochrane Handbook^d. Risk of bias was assessed using the Cochrane^d (trials), Newcastle Ottawa^e (case control; cohort) and Downs and Black^f (cross-sectional) systems and classified according to SIGN^g recommendations.

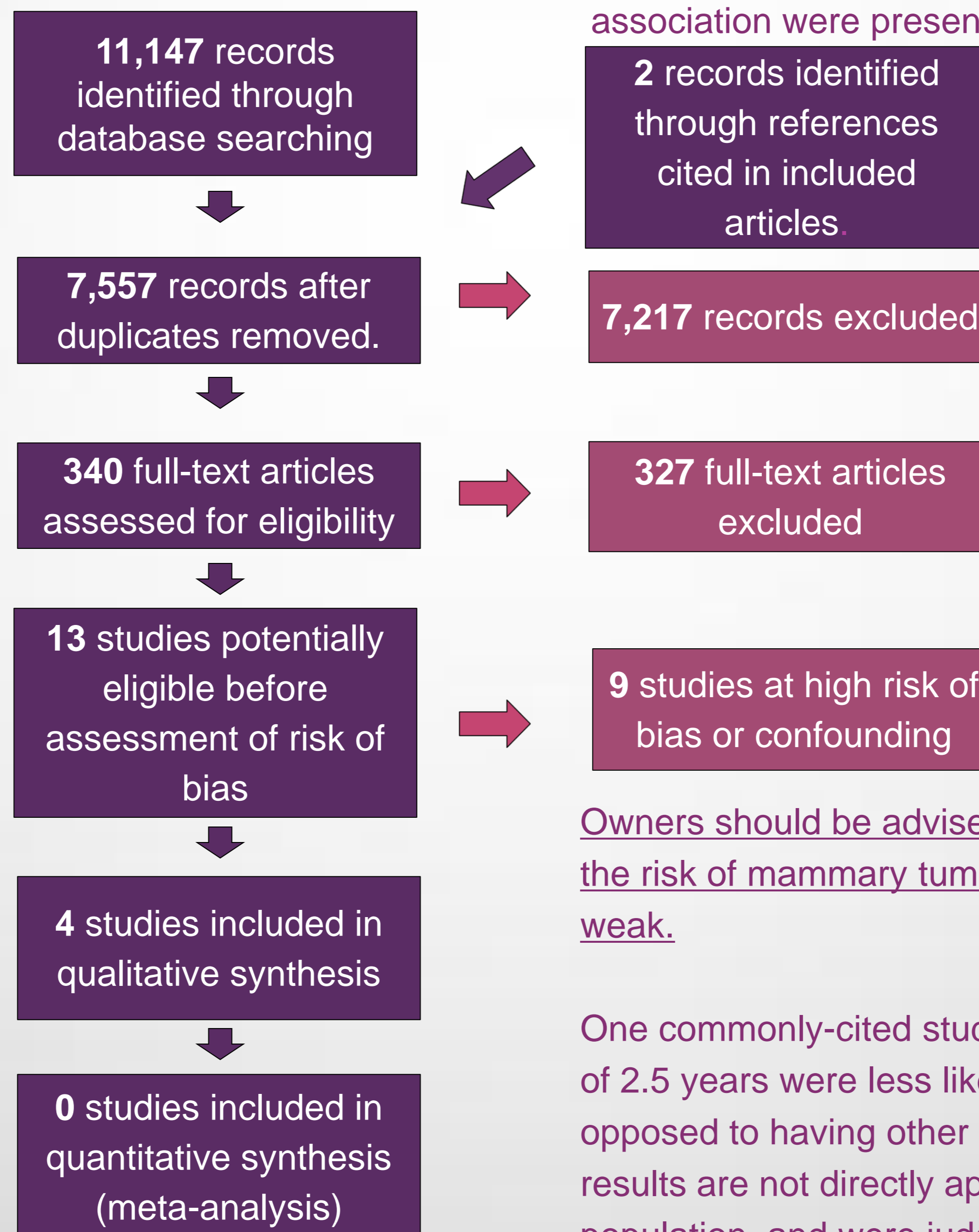
Box 1. Search Terms

1. Dog OR dogs OR bitch* OR canis* OR canine* OR canid* OR "Dogs"[MAJR]^h
2. Spay* OR neuter* OR ovariectomy* OR ovarioectomy* OR gonadect* OR gonad OR gonads OR spey* OR "Ovariectomy/veterinary"[MAJR]
3. mammar* OR breast* OR "Mammary Glands, Animal"[MAJR]
4. tumour* OR tumor* OR cancer* OR neoplas* OR mass OR masses OR lump* OR "Neoplasms/veterinary"[MAJR]

(#1 AND #2) OR (#1 AND #3 AND #4)

Box 2. Eligibility Criteria

1. **Either** the frequency of mammary masses was measured in both neutered and entire female dogs (or animals neutered at different ages); **or** the frequency of neutering (or neutering at different ages) was recorded in both female dogs with and without a history of mammary masses.
2. The results of Criterion 1 were reported.
3. The "neutered" dogs were neutered by ovariectomy or ovariohysterectomy.
4. The report was an original research article.ⁱ
5. The report was published in a peer-reviewed journal (according to the journal's current guidelines).ⁱ
6. The full text of the report was available in English.ⁱ



Results

Of 11,149 records initially identified by the search strategy, 13 articles satisfied the eligibility criteria, as shown in the flow-diagram. Nine of these were judged to have a high risk of bias; the remaining four^{1,2,3,4} were classified as having a moderate risk of bias. The table below summarises potential bias in included studies.



One study¹ of histopathology results (n=174 found a strong protective effect of neutering before 2.5 years of age (Relative Risk 0.06), particularly neutering before 1st oestrous (Relative Risk 0.005) on the risk of mammary malignancy, as opposed to other diagnoses. However, these results are not directly applicable to the general dog population because the study population consisted only of dogs from whom biopsies were submitted. Also, no confidence interval or p value was presented and there were other potential biases, summarized in the table below.

Two studies found no evidence of an association between neutering and the risk of developing any mammary mass² (n=144) or the risk of neoplasia amongst dogs with mammary masses³ (n=2270). One study⁴ (n=65) reported "some protective effect" of neutering on the risk of developing mammary tumours, but no measures of association were presented.

Source of Bias ⁱ		Bias in Included Studies						
		Confounding	Control Selection	Missing Data	Neuter Status Ascertainment	Case Selection	Miscellaneous	Loss to Follow Up
Case Control	Schneider 1969	High Risk	High Risk	High Risk	High Risk	High Risk	High Risk	High Risk
	Perez Alenza 1998	High Risk	High Risk	High Risk	High Risk	High Risk	High Risk	High Risk
	Richards 2001	High Risk	High Risk	High Risk	High Risk	High Risk	High Risk	High Risk
Cohort	Bruenger 1995	High Risk	High Risk	High Risk	High Risk	High Risk	High Risk	High Risk

Legend

High Risk of Bias	High Risk
Low Risk of Bias	Low Risk
Unclear Risk of Bias	Unclear Risk

j. The studies were at low risk of bias in the following categories:- case control: case definition, miscellaneous; cohort: length of follow up, classification of mammary tumour status and ensuring cohorts were disease-free at start of study. k. Two different control groups used.

Conclusions

Owners should be advised that the overall strength of evidence that neutering reduces the risk of mammary tumours—and that early neutering is more strongly protective—is weak.

One commonly-cited study of biopsy results found that bitches neutered before the age of 2.5 years were less likely to be diagnosed with malignant mammary tumours, as opposed to having other diagnoses (reduction approximately 20-fold). However the results are not directly applicable to the risk of developing tumours in the general population, and were judged to be at moderate risk of bias and confounding. Two studies, also at moderate risk of bias, found no evidence that neutering either reduces the risk that a dog will have a mammary mass, or reduces the risk of malignancy amongst dogs with mammary masses.

This information should be balanced with other available information on the risks and benefits of neutering in general, and in particular early versus late neutering.

Further research into the association between mammary masses and neutering should focus on recording:

- age, breed and exposure to synthetic Progesterones, as potential confounders.
- age at neutering and length of subsequent follow-up period.

Acknowledgements

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1. Schneider, R., Dorn, C., Taylor, D. (1969). Factors influencing canine mammary cancer development and postsurgical survival. *J Natl Cancer Inst* 43(6): 1249-1261.
 2. Perez Alenza, D., Rutteman, G., Pena, L., Beynen, A., Cuesta, P. (1998). Relation between habitual diet and canine mammary tumors in a case-control study. *Journal of Veterinary Internal Medicine* 12(3): 132-139.
 3. Richards, H., McNeil, P., Thompson, H., Reid, S. (2001). An epidemiological analysis of a canine-biopsies database compiled by a diagnostic histopathology service. *Prev Vet Med* 51(1-2): 125-136.
 4. Bruenger, F., Lloyd, R., Miller, S., Taylor, G., Angus, W., Huth, D. (1994). Occurrence of mammary-tumours in Beagles given RA-226. *Radiation Research* 138(3): 423-434.
 a. <http://www.ncbi.nlm.nih.gov/pubmed/> b. <http://cabdirect.org/> c. <http://www.isiknowledge.com> d. <http://www.cochrane-handbook.org/> e. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp f. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *Journal of Epidemiology and Community Health* 1998; 52: 377-384. g. Scottish Intercollegiate Guidelines Network. h. MeSH terms used in PubMed only. i. These criteria were added during the review process for logistical reasons.