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The Hunt Institute for Botanical Documentation, a research division of Carnegie Mellon University, specializes in the history of botany and all aspects of plant science and serves the international scientific community through research and documentation. To this end, the Institute acquires and maintains authoritative collections of books, plant images, manuscripts, portraits and data files, and provides publications and other modes of information service. The Institute meets the reference needs of botanists, biologists, historians, conservationists, librarians, bibliographers and the public at large, especially those concerned with any aspect of the North American flora.

Hunt Institute was dedicated in 1961 as the Rachel McMasters Miller Hunt Botanical Library, an international center for bibliographical research and service in the interests of botany and horticulture, as well as a center for the study of all aspects of the history of the plant sciences. By 1971 the Library's activities had so diversified that the name was changed to Hunt Institute for Botanical Documentation. Growth in collections and research projects led to the establishment of four programmatic departments: Archives, Art, Bibliography and the Library.

NEOPLASM CASE REPORT

LEAVE COLUMN BLANK

1. Name of Owner LAST FIRST MIDDLE

2. Address STREET CITY

3. Name of Animal	4. Species	5. Breed
6. Age ____YR. ____MO.	7. Weight ____LBS.	8. Color

9. Sex
☐ SPAYED FEMALE ☐ FEMALE ☐ CASTRATED MALE ☐ MALE

QUESTIONS *(ask owner)*

	YES	NO
10. If female, has animal ever given birth?	☐	☐
11. Is animal usually kept at owner's address	☐	☐
12. If dog, is it AKC registered?	☐	☐
13. Has animal had previous owner(s) since 1962? . . .	☐	☐

14. Has animal been kept since birth in either Alameda or Contra Costa County? ☐ Yes ☐ No ☐ Unknown
15. Is animal outdoors? ☐ Both day and night
☐ Only during the day ☐ Only at night ☐ Seldom outdoors
16. When was tumor or condition first noticed (by owner)?
_____19____ ☐ Not previously noticed

DIAGNOSIS

17. Date first observed or clinically diagnosed _____19____
18. Clinical diagnosis (type of neoplasm) _____
19. Primary site _____; ____x____x____cm.
20. Other sites _____ ☐ None
21. Believed to be: ☐ Benign ☐ Malignant ☐ Unknown
22. If Benign:
☐ Single neoplasm
☐ Multiple neoplasms of same type
23. If Malignant:
☐ Localized
☐ Metastasis, regional
☐ Metastasis, diffuse or remote
24. Autopsy performed? ☐ Yes ☐ No
25. Other disease(s) present (including other neoplasms)
_____
_____
_____
26. Comments
_____
_____
_____
_____

► Signature _____ Date _____

27. If specimen submitted, check appropriate box:
☐ Surgery ☐ Autopsy ☐ Biopsy ☐ Other _____
Name tissue(s) submitted: _____
_____
_____

GENERAL DIRECTIONS

A. Record any animal exhibiting a neoplasm.

B. Submit specimens for microscopic examination from as many cases as possible.

C. If animal has multiple neoplasms of the same type, record on one report form and submit representative specimens in one container.

D. If animal has neoplasms of more than one type, record each on a separate report form and submit each specimen in a separate container.

E. Enclose an original report with each specimen submission.

F. Record a case even though a specimen cannot be submitted; these reports will be periodically collected.

G. Record a case even though animal was previously diagnosed as having a neoplasm of a different type.

H. Record a case even though referred from or to another veterinarian.

I. Do not record a case in which there is recurrence of a neoplasm that has previously been reported.

J. If you have any questions about completion of this report form or submission of specimens, please telephone the Epizoology Section, California Cancer Field Research Program at 843-7900, Ext. 611, 2151 Berkeley Way, Berkeley.

SPECIFIC DIRECTIONS FOR SELECTED ITEMS

5. *Breed:* Record *name of breed* stated by owner, if animal closely resembles breed appearance. If animal does not closely resemble the breed stated by the owner, consider that animal crossbred unless both parents are known to have been purebred.

   Crossbred animals resembling one breed more than another, record *name of predominant breed component and the symbol X.* Example: Boxer X.

   Crossbred animals not resembling one breed more than another, record as *mixed breed.*

18. *Clinical Diagnosis:* If type of neoplasm is unrecognizable, record type as unknown.

19. *Primary Site:* Indicate type of tissue and part of body involved. Example: "skin of the neck."

21. *Malignancy:* Mark as malignant if neoplasm is known, or highly suspected to be malignant.

    Malignancy criteria: Sudden onset
    Rapid increase in size
    Invasion of neighboring tissue
    Metastasis
    Recurrence

(REV. 7-1-66)
FORM CCFRP-2670A
STATE OF CALIFORNIA, DEPARTMENT OF PUBLIC HEALTH
14050-430 6-66 12,500 Ⓒ OSP

STATE OF CALIFORNIA—HEALTH AND WELFARE AGENCY

RONALD REAGAN, Governor

DEPARTMENT OF PUBLIC HEALTH
2151 BERKELEY WAY
BERKELEY 94704

May 27, 1969

George Estabrook
Taximetrics Lab
University of Colorado
Boulder, Colorado 80302

Dear George:

I mentioned your letter to Dr. Schneider and he would be interested in knowing more about what the taximetrics lab has to offer. I am not really sure how you tie into data banks of this sort but I will explain our program and see if it interests you.

We are the Animal Neoplasm Registry and have collected information, slides, and the actual excised lesions of all suspected cancer cases from the veterinarians in Alameda and Contra Costa Counties (the East Bay area). I am enclosing the form submitted with each tumor. This, along with the specimens are sent to a hospital pathology lab for diagnosis. We have fairly accurate information on dogs, cats, birds, and all sorts of pets (even 1 gold fish) for almost 6 years and the first 5 have been printed out on the computer here. There are many areas to explore, digging through this information, but our staff consists presently of Dr. Schneider; D.V.M., M.S. in veterinary pathology and veterinary epidemiologist, a statistician, and myself. So our time is relatively limited.

There are a few 'hot' areas now in cancer research such as cat leukemia. This department has recently isolated what may be the virus involved and we have been funded by the National Cancer Institute to initiate a study on leukemia cases in the Registry. The Registry itself is supported by a large grant from the American Cancer Society.

Dr. Schneider has just finished a paper on mammary cancer in the bitch which will show you the type of work he does. There really isn't much more to it than that - a basically untapped animal tumor information depot. If that stimulates your interest let us know.

Factors Influencing Canine Mammary Cancer Development and Postsurgical Survival*

* Supported by Public Health Service research grant CA-05924 from the National Cancer Institute and research grant EP-6 from the American Cancer Society, Inc.

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From the

Viral and Rickettsial Disease Laboratory

California State Department of Public Health

Berkeley

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SUMMARY

A retrospective study was conducted using canine mammary cancer cases and age and breed matched controls. Only histologically confirmed malignant mammary cases were utilized of which 71 were diagnosed as adenocarcinomas and 22 as malignant mixed mammary tumors. There were 87 case-control matches. The factors studied were classified within the categories of neutering, estrus, pseudopregnancy, parity, fecundity and postsurgical survival.

Within the scope of the variables studied, no differences in effects were found on the occurrence of adenocarcinomas or malignant mixed mammary tumors. Among the variables, it was found that neutered bitches had 12% of the mammary cancer risk when compared to entire animals. Bitches neutered prior to any estrous cycles had approximately 0.5% of the mammary cancer risk; those experiencing only 1 estrous cycle prior to neutering had 8% and animals experiencing 2 or more estrous cycles prior to neutering, 26%.

Within the group having 2 or more estrous cycles prior to being neutered, it was found that for bitches neutered before $2\frac{1}{2}$ years of age, a marked sparing effect on mammary cancer risk was found. Animals neutered after $2\frac{1}{2}$ years of age did not exhibit this effect. Tests of various factors within the categories of pseudopregnancy, parity and fecundity indicated no significant effects on mammary cancer risk.

Survival data, based on observation for a minimum of 42 months after surgical removal of the cancer, indicated excess mortality due to mammary cancer was concentrated in the first year; $2\frac{1}{2}$ times more cases died than expected. It appeared that the younger an animal at the time of cancer surgery, the more apt it was to survive. Neutering at the time of cancer surgery was found to have no effect on either survival or cause of death.

The age distribution of mammary cancer in female dogs was compared to the age distribution of breast cancer in women. It appears that mammary cancer in the bitch mimics that of human breast cancer, except that the dog, after maturity, is biologically aging at 4 times the rate of humans. This age similarity and the common sparing effect of neutering in the 2 species, provides strong support for the use of canine mammary cancer as a research model for breast cancer in women.

FACTORS INFLUENCING CANINE MAMMARY CANCER DEVELOPMENT AND POSTSURGICAL SURVIVAL

INTRODUCTION

Mammary cancer is the most common malignant neoplasm in the bitch. Recently, it has been reported that the incidence rate for all malignant neoplasms was 453.4 per 100,000 female dogs; mammary cancers accounted for nearly ½ with a site specific incidence of 198.8 per 100,000 (1).

Many reports describe and analyze case series (2-6). However, epidemiologic studies of variables effecting the occurrence of mammary cancer in the bitch have been few. Reports by Frye et al. (7) and Dorn et al. (1) have shown neutered (ovariohysterectomized) female dogs had a significantly lower relative risk of developing mammary neoplasia than intact females. Brodey et al. (8) found no relationship of either estrous irregularity, pseudopregnancy or pregnancy with the occurrence of mammary tumors in 57 bitches. In an extension of that study to include more bitches, Fidler et al. (9) again found no association of mammary tumor development with either estrous cycle patterns or pregnancy histories. There was however, a significant difference concerning pseudopregnancy; mammary tumor cases had fewer episodes of pseudopregnancy. Uberreiter (10) on the other hand, reported that pseudopregnancy was associated with increased mammary cancer while pregnancy was associated with a decrease. Anderson (11) has indicated that in a beagle colony: " A comparable incidence (of mammary tumors) occurred in virgin bitches and those bred twice prior to 4 years old, but mammary tumors were not apparent in those bred on each successive estrous period throughout life."

The results of some of the above studies support different conclusions. This is particularly true for the effects of pseudopregnancy and of pregnancy. The causes of this disagreement may be many. This present study was undertaken to try to clarify some of the above results by measuring the effect on canine mammary cancer risk of various factors classified within the categories of neutering, estrus, pseudopregnancy, parity, fecundity and postsurgical survival. The study was limited to only histologically malignant neoplasms comprising the 2 major canine histologic types: adenocarcinomas and mixed mammary tumors.

METHODS

The retrospective approach utilizing case and control groups was used to test for an association of factors and the development of mammary cancer. The case group was composed of bitches with histologically confirmed adenocarcinomas or malignant mixed mammary tumors diagnosed among dogs from Alameda County in a morbidity survey (12). Ninety-three cases reported within the period, July, 1963 - June, 1965, were studied.

The controls were Alameda County resident bitches which had never had tumors of any type, drawn from submissions to the survey within the period, July, 1963 - March, 1966. The veterinary practitioners taking part had been instructed for completeness of the survey, to submit any lesion that could possibly have been neoplastic. Thus there was a large pool of dogs with lesions that were histologically non-neoplastic. These animals were suitable for controls since they were from veterinarian-using households and were predominantly older animals, as were the cancer cases. The majority of their lesions were of the skin, such as reactions to injury or irritation. Bitches with non-neoplastic mammary gland submissions were not included.

Cases and controls were preliminarily matched on breed and age. It was anticipated that some additional matching would be necessary since some controls might not be useable due to having tumors of any type which were either removed prior to the survey, or present at the time of owner interview; hence, all possible controls were chosen. There were 146 controls chosen of which 105 were useable.

Personal household interviews were conducted with owners of cases and controls during the spring and summer of 1966. In addition to general demographic information, the date of birth and the breed of the sire and the dam were also collected for each animal. Questions were asked about variables that were thought to have a possible effect on mammary cancer tumorigenesis, included within the categories of neutering, estrus, pseudopregnancy, parity and fecundity. For as complete and as accurate data as possible, veterinary hospital records of both cases and controls in all local practices mentioned in the interview were independently reviewed for the same data asked of the owners. The veterinary hospital data was used to supplement the data from the owner. For survival data, owners of living cases and controls were contacted through December, 1968.

After the interviews a tumor-free control was matched with a case based on the following criteria for the age and the breed variables. For the age variable, the age of the case at the time of first histologically confirmed index tumor diagnosis was matched within 3 years with the age of the control at the time of interview or death. Ages were calculated in years and months from the date of birth for most animals. When the month of birth was not available, the mid-point of the year of birth was used.

For the breed variable, there are a large number of dog breeds and there are differences in cancer risk between purebred and crossbred dogs (1) and between specific breeds (1,7,13,14). Hence designation of breed in both cases and controls was made utilizing the owner's breed classification of the sire and the dam in addition to the breed designation of the index case. An animal was considered purebred where the breed of the index case, sire and dam agreed. An animal was considered crossbred when the sire and dam designations indicated that the index case was the progeny of 2 different purebred breeds. For matching purposes, an animal was considered crossbred of either the breed of the sire or of the dam until matched. Animals were classified mixed if the evidence indicated that they were of 3 or more breeds. Final matching of the useable 93 mammary cancer cases and 105 controls resulted in 87 case-control matches within the breed designated categories as indicated in table 1.

Tests of statistical significance were obtained using the Mantel-Haenszel procedure (15). With this procedure it is possible to test the significance of relative risks (ie. sparing effect of a test variable). Misleading associations were minimized by matching and/or controlling on breed, neutered status and age. Estimates of relative mammary cancer risk were obtained by the formula $\Sigma(AD/T)/\Sigma(BC/T)$, where the summation is over all control factor categories. A and C represent the number of cases with and free of the test factor, respectively; B and D represent the number of controls with and free of the test factor, and T represents the total number of cases and controls.

In all tests, neutered status was controlled except when it was the test factor, and age was controlled using the following 3 year age categories: 1-3, 4-6, 7-9, 10-12, 13-15, and 16 and over. The age in years at the time of index cancer diagnosis was used for the cases and the age at the time of interview or death was used for the controls. Initial Mantel-Haenszel tests were on the adenocarcinoma and mixed mammary groups separately, hence the combined (table 3), also was controlled for cancer type.

Tests of the effect of neutering on survival (tables 8 & 9), were made using only the case group, but still controlling on age. In instances where means were compared, Student's "t" test was used.

RESULTS

Table 1 indicates the major breed components within the 87 matched cases and controls. There were 66 matches of purebred or crossbred of the same breed and of mixed; the remaining 21 matches were of purebred with purebred of another breed or crossbred with crossbred of another breed. The purebred/crossbred ratios were 56/31 for cases and 55/32 for the controls. No significant mean age difference was detected between cases and controls. The mean ages and standard deviations were: for the 87 cases, 10 years 7 months ± 2 years 10 months, and for the matched controls 10 years 4 months ± 3 years 1 month.

Table 2 indicates the histologic type of mammary cancer in the original 93 index cases and the histologic type of the first mammary tumor that occurred in these animals. The mean age at first veterinary diagnosis of mammary adenocarcinoma as the first cancer in 61 bitches was 10 years 5 months ± 2 years 7 months, and for 22 animals with malignant mixed mammary tumors, 10 years 8 months ± 3 years. The difference between the mean ages at diagnosis of the 2 cancer types was not significant ($p>0.50$).

The mean ages for the same groups when each cancer type was first observed (first noticed by the owner) of 10 years 1 month ± 2 years 9 months for adenocarcinomas also was not significantly different from the 9 years 8 months ± 3 years 3 months for the malignant mixed mammary tumors ($p>0.50$).

Effects of Neutering and Estrus

Table 3 indicates the effect of neutering on the occurrence of mammary cancer. Overall, neutered bitches experienced approximately 12% of the mammary cancer risk found in entire animals. The effect of neutering on both the adenocarcinoma and malignant mixed mammary tumor groups also was significant.

Data was available which could separate neutered animals into 3 estrous groups: Those which had no estrous cycles, 1 estrous cycle, or 2 or more cycles. Comparing the no and 1 estrous cycle groups with the multi-estrous group indicated a significant sparing effect on mammary cancer risk for the animals experiencing fewer estrous cycles (table 3). This effect was the same for bitches with adenocarcinoma or with malignant mixed mammary cancer. Testing those animals neutered prior to any estrous cycles, indicated that non-estrous animals had approximately 0.5% of the mammary cancer risk experienced by entire multi-estrous ones; animals with only 1 estrus prior to neutering had approximately 8% of the risk and animals with 2 or more estrous cycles prior to neutering, 26% (table 4).

Testing various age groups of neutered bitches which experienced 2 or more estrous cycles, indicated that animals neutered before $2\frac{1}{2}$ years of age exhibited a significant sparing effect on mammary cancer risk, while those neutered after $2\frac{1}{2}$ years of age did not exhibit a significant effect (table 5). Animals neutered by $2\frac{1}{2}$ years of age would be expected to have experienced a maximum of 4 estrous cycles.

Comparing multi-estrous bitches having owner stated abnormal estrous cycles with those having normal, indicated no significant risk for animals with abnormal cycles (table 3).

Effects of Pseudopregnancy, Parity and Fecundity

There was no effect on mammary cancer risk of an animal having one or more episodes of pseudopregnancy (table 3). Bitches that were neutered prior to their first estrus were excluded from this test. The effect of more than one pseudopregnancy was tested in the adenocarcinoma group and also was found not to be significant ($p>0.30$).

The difference in frequency of parous females in case and control groups, excluding animals neutered prior to their first estrus, was not significant (table 3). Testing the effect of the number of litters a parous female gave birth to, also was without significance.

Age at the time of birth of the first litter was found not to effect mammary cancer occurrence. Table 3 shows the result of testing animals who gave birth for the first time at 1 year of age or younger compared to animals who gave birth for the first time at 2 years of age or older. Tests of other age group comparisons were also negative.

Litter size and total number of offspring per female did not effect mammary cancer risk in this study. Eighty-one cases that experienced at least 1 estrous cycle each had given birth to a total of 345 puppies in 67 litters, and 57 controls to 158 puppies in 29 litters. There was no significant difference between the mean litter size of 5.1 for the cases and 5.4 for the controls ($p>0.10$). There also was no fecundity effect when the adenocarcinoma or malignant mixed mammary group was tested separately. Still births were not significantly different; there was an average of 0.15 dead puppies per litter in the case group and 0.14 dead puppies per litter in the controls. Total number of offspring per animal also was not significantly different in case and control groups ($p>0.10$).

Survival After Cancer Removal

Table 6 indicates the number and percent distribution of animals by cause of death for an observation period of 42 months after removal of the index cancer. The cause of death was determined from veterinary hospital records or from the owner. Death was attributed to either mammary cancer or other causes. There was no significant difference in postsurgical survival between the adenocarcinoma or malignant mixed mammary cancer groups, either for all causes of death ($p>0.70$) or for only mammary cancer deaths ($p>0.80$).

The mean survival period between mammary cancer surgery and natural death due to the mammary cancer for 14 animals was 8.8 months (median 4.5 months). The mean survival period between surgery and euthanasia due to mammary cancer of 38 animals was 11.3 months (median 7.5 months). Hence, for the 52 animals with mammary cancer as the cause of death, mean survival after cancer excision was 10.7 months (median 7.0 months); whereas 21 animals whose deaths were not attributed to mammary cancer had a mean survival period of 20.6 months (median 20.0 months).

Of the 93 cases, 62 or 66.7% were found to have experienced more than one mammary tumor. Several of the 31 animals not found to have a second mammary tumor, may have had one. The veterinary hospital records were not always clear when an animal died or was euthanized because of mammary neoplasia whether additional mammary tumors were present at that time. Assuming that all of the 52 bitches with death attributed to mammary cancer had additional tumors or evidence of metastasis, then 63 of 88 cases or 71.6% either experienced more than 1 mammary tumor or complications of their neoplastic condition.

Text-figure 1 indicates the percent survival of mammary cancer cases from date of cancer surgery as compared to the expected, calculated using the survival of the control population weighted for the age distribution difference between cases and controls. It would appear that excess death from mammary cancer only was present in the first year after cancer surgery. Expected percent of deaths for other than mammary cancer indicated 17.2%, 22.6% and 17.1% dying in the first, second and third years after surgery. Actual deaths for the case group were 43.8%, 20.2% and 16.7% for each of the 3 years, respectively. Thus only the first year was in excess for the case group, at approximately $2\frac{1}{2}$ times the expected death rate.

Text-Figure 1 - Postsurgical survival of canine mammary cancer cases compared to controls, weighted in proportion to the age distribution of the case group.

Two possible effects on survival were studied. Table 7 indicates the effect of age at the time of cancer surgery on survival. It is apparent that the younger the animal at the time of cancer removal, the more apt it was to survive. Part of this longevity may be due to decreased risk of additional mammary tumors or complications of the index cancer (table 7).

The second effect studied was the result on survival of neutering a bitch after the diagnosis of a mammary cancer. Animals neutered after mammary cancer diagnosis did not exhibit any significant increase in survival at 6 month intervals up to 42 months of observation (table 8). Testing cancer caused deaths for the group of animals neutered at the time of cancer surgery as compared to those not neutered, indicated that neutering also had no significant effect on mortality from the index cancer or deaths resulting from new mammary tumors (table 9). It appears that age was an important factor in the selection of which bitches would be neutered after the diagnosis of mammary cancer, since the group neutered after cancer diagnosis was on the average approximately 2 years younger at the time of cancer diagnosis than those not neutered (table 10).

DISCUSSION

Within the scope of variables studied, it would appear that there was no difference in the natural history of adenocarcinomas and of malignant mixed mammary tumors of the dog. A significant or non-significant effect with one was also present for the other. The mean age when either cancer type was first diagnosed was within 3 months of the other (table 2) with most of the cases of both groups expected within the ages of 4-17 years.

Additionally, in table 3, although some difference in numerical values of chi-square and relative risks were found, the direction of expected as compared to observed numbers for all 5 variables was the same for both cancer types. In other comparisons, including distribution of causes of death (table 6), there were also no differences between the two.

Because the subdivision of the cases into adenocarcinoma and malignant mixed mammary case groups resulted in small sample sizes, a possible subtle difference between types may not have been observed. However, since the metastisizing component of the malignant mixed tumors has generally been the carcinoma, an explanation for the occurrence of connective tissue involvement in mixed tumors, might be an incidental host-determined response to a cancer inciting stimulus.

In 1927, Cori (16) demonstrated that oophorectomy in mice at increasing age, had a decreasing sparing effect on mammary tumor occurrence. The data presented in this report indicates that this effect of neutering is also present in the dog. Neutering had an overall marked effect on canine mammary cancer risk in this study (table 3). Its effect decreased rapidly with the number of estrous cycles bitches experienced (table 4); by $2\frac{1}{2}$ years of age (a maximum of 4 estrous cycles), there was no detectable effect from neutering (table 5). Agreement with this is shown in that of the 21 neutered bitches in 161 mammary cases reported by Fidler et al. (9), none had been neutered prior to 2 years of age.

Thus the establishment of future mammary cancer risk in most bitches can be pinpointed to occur somewhere within the period of first estrus (approximately 6-18 months of age) and $2\frac{1}{2}$ years of age, although actual average first observation of the cancer does not occur until the animal is approximately 10 years of age.

Hyperplastic alveolar nodules, observed in mammary glands of mammary cancer susceptible mice, have been shown to be preneoplastic mammary tumor lesions (17). The effects of various hormonal milieus on the development and maintenance of such lesions in various mouse strains, have been described (18). Whether such nodules or other possible preneoplastic lesions are present in the bitch, should be investigated.

The greatest protective effect of neutering occurred if it was carried out prior to a bitch experiencing any estrous cycles. Neutering prior to any estrus reduced risk to 0.5%, while animals that were neutered after 1 to 4 estrous cycles, experienced 6-8% the risk of entire multi-estrous ones (tables 4 and 5). It is more likely, however, that animals experiencing increased numbers of estrous cycles between 1 and 4 cycles have decreased sparing effects, since after a bitch was $2\frac{1}{2}$ years of age, there was no effect of neutering on mammary cancer risk (table 5).

It should be realized that the numerical values of the sparing effects are estimates and that 1 animal more or less observed in a group where there are very few observed, would make a large difference in the numerical value of the relative risk. It is probable, however, that the sparing effect for animals neutered prior to any estrus is much greater than 0.5% (table 4). The one cancer case which was neutered prior to any estrous cycles may be a dubious report. Careful gathering of estrous histories for a large number of bitches that have developed mammary cancer would be necessary to clarify the relative sparing effects of various numbers of estrous cycles on mammary cancer risk.

In this study, the other variables of abnormal estrous cycles, pseudopregnancy, parity, age at birth of first litter, still birth experience and fecundity did not indicate any effect on mammary cancer risk. The effect of pseudopregnancy and parity will be discussed further.

In prior studies pseudopregnancy had been found: to have no effect on mammary tumorigenesis (8), to be significantly present in animals having mammary tumors (10), and to be significantly absent from animals having mammary tumors (9). In the present study, experiencing 1 or more pseudopregnancies was found to have no effect on mammary cancer occurrence (table 3). It was plausible to assume in reviewing the initial non-significant adenocarcinoma and mixed mammary tumor results that more than one pseudopregnancy might have an effect with the adenocarcinoma group that was not present when all cases with pseudopregnancy were combined. However, a comparison of bitches having mammary adenocarcinomas versus controls, limiting the analysis to those which had experienced 2 or more pseudopregnancies, also was not significant ($p > 0.30$).

The conflicting relationship of pseudopregnancy to mammary cancer described in previous studies listed above, needs clarification. Uberreiter's report (10) in which pseudopregnancy was significantly present in animals with mammary tumors, was impressive in that the study group comprised 888 bitches. It included animals from 2 different sources, 275 breeding or kennel bitches and 613 surgical and obstetrical patients. These were combined for testing. However, the occurrence of mammary tumors in both groups was different (4.4% in the breeding bitches vs. 40.8%). The difference in mammary cancer prevalence may be due to breeding bitches being a highly selected group.

Using only the 613 surgical and obstetrical patients, the pseudopregnancy effect was retested by the Mantel-Haenszel procedure (15). Testing the observation of 169 tumors in the 383 pseudopregnant bitches as compared to the 81 tumors in the 230 non-pseudopregnant ones in this manner, controlling on age in 1 year increments indicated that having at least one episode of pseudopregnancy did not have any significant effect on mammary tumor risk (table 11).

The other 2 studies cited above, Brody et al. (8) and Fidler et al. (9) were done by the same investigating team. The second paper was an extension of the first, utilizing 3 times as many cases, but the same control group. In the first paper no effect of pseudopregnancy on mammary cancer risk was reported. In the second, significantly more pseudopregnancy was found in the controls; however, the authors negated the biological significance of this latter observation. One possible reason for the result in the second paper could be decreased reporting of pseudopregnancy in the cases between study periods, in which case the significant finding would be a spurious one.

Thus, overall there does not appear to be any pseudopregnancy effect on mammary cancer risk. The most impressive result for this conclusion is the non-significance using Uberreiter's data on 613 bitches (table 11). Although not an unbiased group in that these were hospital cases, the number of animals and the frequency of pseudopregnancy in entire bitches, probably counteracted this bias. With that group, for animals experiencing pseudopregnancy, variation in cancer risk of the order of 2-fold should have been detected with high probability (19).

In previous studies, parity had been found not to be associated with mammary cancer by Brodey et al.(8) and Fidler et al.(9), and to be associated with a decrease by Uberreiter (10). In the present study, no significant parity effect was found on mammary cancer risk. In analyzing Uberreiter's data on parity for the 613 bitches, it was found that there was no parity effect when the Mantel-Haenszel procedure (15) was used, controlling on age in 1 year increments (table 11).

Attempts to test the effect on mammary cancer risk of having various numbers of litters also was negative in the present study. Further analysis of litter numbers with Uberreiter's data was not conclusive. However, from his data, for animals having many litters, a significant sparing effect possibly could be present. Although the magnitude of this possible effect may be small, it could be measured with a large enough sample and should be investigated further.

The excess mortality resulting from mammary cancer appeared to be concentrated in the first year after cancer removal (text-fig. 1) where the numbers dying were $2\frac{1}{2}$ times expectation, based on deaths among the control population. Since mammary cancer risk is predetermined by $2\frac{1}{2}$ years of age (table 5), with 8 - 10 mammary glands present on a bitch, it is logical to assume that many if not all glands will be effected during the initiating phase. Thus, once mammary tumors appear, a variable number of glands could develop tumors in a short period of time. Because of treatment costs and the age of these animals, euthanasia or death is likely if additional tumors or complications develop. Most of the animals with mammary cancer as the cause of death during the 42 month study period, were dead within 1 year of the index cancer surgery (table 6). It previously had been reported that average postsurgical survival for 100 bitches with mammary cancer was 8 months (20).

For years it has been assumed in veterinary medicine as in human medicine that oophrectomy at the time of mammary cancer removal increases the life expectancy of the host through a possible effect on cancer biology. This may not be true with dogs, since there was no significant increase in longevity for animals neutered after cancer diagnosis when compared to animals not neutered (table 8).

It appeared that age played a major part in selection of animals that were neutered as part of the cancer surgery. Table 10 compares mean ages in months at cancer surgery, at death and at the end of 42 months for 3 groups: bitches neutered before cancer diagnosis, bitches neutered after cancer diagnosis and bitches not neutered. Bitches neutered after cancer diagnosis were the youngest, averaging over 2 years less in age than bitches neutered prior to diagnosis and those not neutered. Since excess death due to mammary cancer only was present in the first post surgical year (text-fig. 1) and survival was better in the younger age groups (table 7), then a younger treatment group could give the impression that a given treatment was more successful than it actually was. For instance, after 42 months, 7 of 16 or 43.8% of animals neutered after cancer diagnosis were still alive; only 5 of 41 or 12.2% were alive in the not neutered group. Thus 44% vs. 12% were alive 42 months post surgery: Such a record of success for a treatment would be very good. However, when age at diagnosis was controlled, there was no significant difference in survival for animals neutered after cancer diagnosis compared to the not neutered ones (table 8).

Although neutering a bitch after cancer diagnosis may not have any effect on its survival, perhaps neutering does have an effect on cancer progression. If it does, then the effect would appear to be very transitory, since there was no significant difference found in the cause of death attributed to mammary cancer for animals neutered after cancer diagnosis (table 9), compared to animals not neutered. For the purpose of this test, bitches still alive after 42 months observation were considered to have died of causes other than mammary cancer. However, at least one of the 7 animals neutered after index cancer diagnosis, was known to have died of mammary cancer at 45 months following surgery. The others were still alive as of December, 1968.

Since most of the cancer cases neutered prior to the index cancer were neutered after 2½ years of age, it can also be seen in table 9 that these animals did not have significantly less deaths attributed to mammary cancer either. This would be expected since there was no measurable sparing effect from neutering after 2½ years of age.

In comparing mammary cancer in bitches to breast cancer in women, one is impressed by the biological similarities. Table 12 indicates the age distribution of the canine cases in which the index cancer was the first tumor, as compared to human breast cancer age distribution in Alameda County (21). Ages of dogs were converted to human equivalents using the conversion chart developed by Lebeau (22). It is seen that human and canine cancer shown in this manner have comparable distributions by age. The median age for human breast cancer in Alameda County was 58 years. This age is equivalent to 10 years 6 months of a dog's life according to Lebeau. The median age for first mammary cancer occurrence in this Alameda County dog sample was 10 years 2 months. Clearly, it would appear that distributions are similiar throughout life of breast cancer in women and mammary cancer in the bitch, except that the dog, after maturity, is biologically aging at 4 times the rate of humans.

In terms of factors possibly effecting breast cancer in women, the effect of neutering (artificial menopause) has been studied extensively. Feinleib (23) has recently reported that women neutered prior to 40 years of age had a .75 reduced risk of developing breast cancer. While .75 numerically does not compare to the .12 found in dogs in this study, it must be remembered that his control population did not contain women neutered with the frequency or at such young ages relative to sexual maturity as occurs in the dog. In addition, he found that artificial menopause in women after 40 years of age did not have a measurable effect on mammary cancer risk. Thus at some age prior to 40 years, there is most probably a cutoff above which there is no effect of neutering in women. Converting the $2\frac{1}{2}$ years of age found in this study as the cutoff age of a neutering effect for dogs, to human equivalents, would indicate an age of 26 years. Thus it is possible that the neutering effect in women is just as strong as in dogs. It is also interesting to note that first estrus in most dogs corresponds to 11-16 years of age of the human, the ages when puberty is usually achieved by women.

In conclusion, it appears that mammary cancer is predetermined by the time a bitch is approximately $2\frac{1}{2}$ years old. The predetermining factor is related to the number of estrous cycles experienced. Abnormal estrous cycles, pseudopregnancy, age at birth of first litter, still birth experience and fecundity, have no measurable effect on mammary cancer risk. Although not shown in this study, parity may have an effect in that having many litters possibly has some sparing effect. This latter effect needs to be tested further. In addition, neutering at the time of cancer surgery does not appear to have any effect on either animal survival or the ultimate cause of death. Since it appears canine mammary cancer mimics that of human breast cancer, further work should be done with the bitch toward elucidating the predisposing factors and/or specific etiology of canine mammary cancer for application to the human problem.

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Table 1 - Breed distribution and mean ages of canine mammary cancer cases and matched controls

Breed	Number of breed equivalents*	
	Mammary cancer cases	Controls
All breeds	87.0	87.0
Unknown breed+	18.5	19.5
Cocker Spaniel	12.5	11.5
Dachshund	8.0	5.0
Poodle	5.0	8.0
Boxer	7.5	4.5
Chihuahua	4.0	6.0
German Shepherd Dog	3.5	5.0
Boston Terrier	3.0	3.0
Labrador Retriever	2.0	3.0
Other breeds≠	23.0	21.5
Purebred/Crossbred ratio	56/31	55/32
Mean ages**	10 years 7 months	10 years 4 months

* Purebred of breed equaled 1.0; crossbred of breed equaled 0.5 for each breed component.

\+ Includes all animals of 3 or more breeds (mixed); and crossbred equivalence of 0.5 where breed of one parent was unknown.

≠ Includes all breeds where the total breed equivalent of cases and controls was 4.0 or less; the maximum breed difference between cases and controls was 2.0 for one breed only.

** s.d., Mammary cancer cases: 2 years 10 months: Controls: 3 years 1 month.

Table 2 - Comparison of histologic type for canine index and first mammary tumors

Histologic type: First mammary tumor	Total	Histologic type: Index mammary tumor	
		Adenocarcinoma	Malignant mixed mammary tumor
All cases	93	71	22
Adenocarcinoma	61*	61	--
Malignant mixed mammary tumor	22+	--	22
Benign tumors	2	2	--
Unknown type‡	8	8	--

* Mean age at diagnosis: 10 years 5 months ± 2 years 7 months.

\+ Mean age 10 years 8 months ± 3 years.

‡ These tumors were removed prior to diagnosis of the index tumor and tumor type was not histologically confirmed.

Table 3 - Effects of factors tested on canine mammary cancer risk for adenocarcinoma and malignant mixed mammary tumors

Factor	All cases				Histologic type: Adenocarcinoma				Histologic type: Malignant mixed mammary tumors			
	Observed	Expected*	Relative risk*	X^{2*}	Observed	Expected	Relative risk	X^2	Observed	Expected	Relative risk	X^2
Neutered vs. not neutered	24	43.41	.12	34.31	18	31.52	.14	22.21	6	11.88	.07	10.42
No or 1 estrus vs. 2 or more estrus	4	20.83	.05	29.39	4	14.69	.08	19.14	0	6.15	‡	6.80
Abnormal estrous cycles vs. normal estrous cycles+	8	8.41	**	.00	5	5.38	**	.01	3	3.03	**	.36
Pseudopregnancy vs. no pseudopregnancy+	21	17.53	**	1.99	15	11.50	**	2.63	6	6.03	**	.22
Parous vs. nulliparous+	41	36.81	**	2.08	30	27.98	**	.42	11	8.83	**	2.51
Age at first litter: 1 year vs. 2 years+	11	9.58	**	.37	8	6.58	**	.46	3	3.00	**	.56

* The expected, X^2 (df=1), and relative risk were computed using the Mantel-Haenszel procedure, controlling on age and testing each factor as indicated; $X^2 \geq 3.84$ is statistically significant at the 5% level or less.

\+ Controlled on neutered status in addition to age, animals never experiencing estrous cycles were excluded.

‡ Relative risk could not be computed, since no cases were observed.

** Relative risk was not computed if the X^2 value was < 3.84.

Table 4 - Effect of various numbers of estrous cycles prior to neutering on canine mammary cancer risk

Number of estrous cycles prior to neutering*	Number of mammary cases		Number of controls observed	X^{2+}	Relative risk+
	Observed	Expected+			
None	1	15.05	26	37.26	.005
1	3	9.34	11	12.85	.08
2 or more	20	28.69	25	10.06	.26

* Not neutered: 63 cases; 23 controls

\+ The expected, X^2 (df=1), and relative risk were computed using the Mantel-Haenszel procedure, controlling on age and testing the effect of various numbers of estrous cycles prior to neutering, separately, against bitches never neutered; $X^2 \geq 3.84$ is statistically significant at the 5 percent level or less.

Table 5 - Effect of age at neutering on mammary cancer risk in bitches that had experienced two or more estrous cycles

Age at neutering (months)*	Number of mammary cancer cases		Number of controls observed	X^{2+}	Relative risk+
	Observed	Expected+			
≤ 29	2	7.98	10	13.01	.06
≥ 30	18	22.47	15	3.21	.40

* Not neutered: 63 cases, 23 controls.

\+ The expected, X^2 (df=1), and relative risk were computed using the Mantel-Haenszel procedure, controlling on age and testing the effect of age at neutering for animals experiencing 2 or more estrous cycles against bitches never neutered; $X^2 \geq 3.84$ is statistically significant at the 5 percent level or less.

Table 6 - Canine postsurgical survival by cause of death for the adenocarcinoma and malignant mixed mammary tumor

Category	All cases			Histologic type					
				Adenocarcinoma			Malignant mixed mammary tumor		
	Number	Percent	Median in months after cancer surgery	Number	Percent	Median in months after cancer surgery	Number	Percent	Median in months after cancer surgery
All cases	93	100.1	14.0*+	71	100.1	14.0*+	22	100.0	11.5
Died, mammary cancer	15	16.1	4.5*	12	16.9	3.5*	3	13.6	5.0
Euthanized, mammary cancer	41	44.1	7.5+	31	43.7	9.5+	10	45.5	7.0
Died, other causes	9	9.7	18.0	7	9.9	19.0	2	9.1	4.0
Euthanized, other causes	12	12.9	27.5	10	14.1	28.0	2	9.1	15.0
Lost to followup before 42 months	2	2.2	33.0	1	1.4	38.0	1	4.5	28.0
Alive after 42 months	14	15.1	50.5	10	14.1	50.5	4	18.2	50.0

* 1 case that died during cancer surgery not included in calculations.

\+ 3 cases euthanized at the time of cancer diagnosis not included in calculations.

Table 7 - Postsurgical survival by age at the time of canine mammary cancer surgery, all causes of death

Age at cancer removal (years)	Number of cases	Months survived							Percent experiencing additional mammary cancer
		6	12	18	24	30	36	42	
All cases	89*	75.3	56.2	46.1	36.0	27.3+	19.3+	16.1+‡	71.6+
≤6	7	85.7	71.4	71.4	71.4	66.7+	66.7+	66.7+	50.0+
7-9	30	86.7	66.7	53.3	46.7	40.0	33.3	27.6‡	67.7
10-12	36	69.4	58.3	44.4	33.3	22.2	8.3	5.6	77.8
≥13	16	62.5	25.0	25.0	6.3	0	0	0	75.0

* 3 cases euthanized at the time of cancer diagnosis and 1 animal that died during surgery not included in calculations

\+ 1 case lost to follow-up at 28 months not included in calculation.

‡ 1 case lost to follow-up at 38 months not included in calculation.

Table 8 - Postsurgical survival of canine mammary cancer cases neutered after index cancer diagnosis

Survival (months)	Number of mammary cancer cases surviving		X^2*
	Observed	Expected*	
6	13	11.57	0.81
12	10	8.56	0.61
24	9	6.66	2.26
36	7	5.18	1.20
42	7	5.13	1.34

* The expected, and X^2 (df=1), were computed using the Mantel-Haenszel procedure, controlling on age and testing survival for various periods after cancer surgery between animals neutered after mammary cancer diagnosis and animals not neutered; $X^2 \geq 3.84$ is statistically significant at the 5 percent level or less.

Table 9 - Results of testing cancer as cause of death* for bitches neutered prior and after index cancer diagnosis

Neutered Category	Number of cancer deaths		
	Observed	Expected+	X^{2+}
Prior to index cancer	13	16.09	1.78
After index cancer	6	8.74	2.04

* Animals still alive after 42 months observation were presumed to die of other than mammary cancer.

+ The expected, and X^2 (df=1), were computed using the Mantel-Haenszel procedure; controlling on age, and testing cancer caused deaths in animals neutered prior or after index cancer diagnosis, as compared to animals not neutered; $X^2 \geq 3.84$ is statistically significant at the 5 percent level or less.

Table 10 - Comparison of canine mean ages at mammary cancer surgery and at death or survival (42 months), by neutered status*

Category (Mean age)	Mean age in months			
	Total	Neutered before mammary cancer diagnosis	Neutered after mammary cancer diagnosis	Not neutered
At tumor surgery	127 (77)+	131 (20)	105 (16)	133 (41)
At death or post-surgical survival for 42 months	145 (77)	145 (20)	134 (16)	150 (36)
At death before surviving 42 months	147 (64)	146 (19)	139 (9)	149 (36)
At post surgical survival for 42 months	139 (13)	132 (1)	128 (7)	155 (5)

* Excludes 10 cases in which the index cancer was not the first mammary cancer, 3 cases euthanized prior to surgery, 2 cases lost to follow-up prior to 42 months observation and 1 case that died at the time of surgery.

\+ Number of cases ( ).

Table 11 - Results of application of the Mantel-Haenszel procedure* to the data presented by Uberreiter+, illustrating the effect of pseudopregnancy and parity on mammary cancer risk in bitches

Test group	Comparison group	Effect measured on cancer occurrence‡	X^2§	Relative risk
383 S&O‖ pseudo-pregnancy	230 S&O no pseudo-pregnancy	Pseudopregnancy	2.09	.70
188 S&O litters	425 S&O no litters	Parity	2.57	.68

* Mantel, N. and Haenszel, W. (15).

\+ Data from Uberreiter, O. (10).

‡ In all tests age was controlled in 1 year increments.

§ $X^2 \geq 3.84$ is statistically significant at the 5 percent level or less.

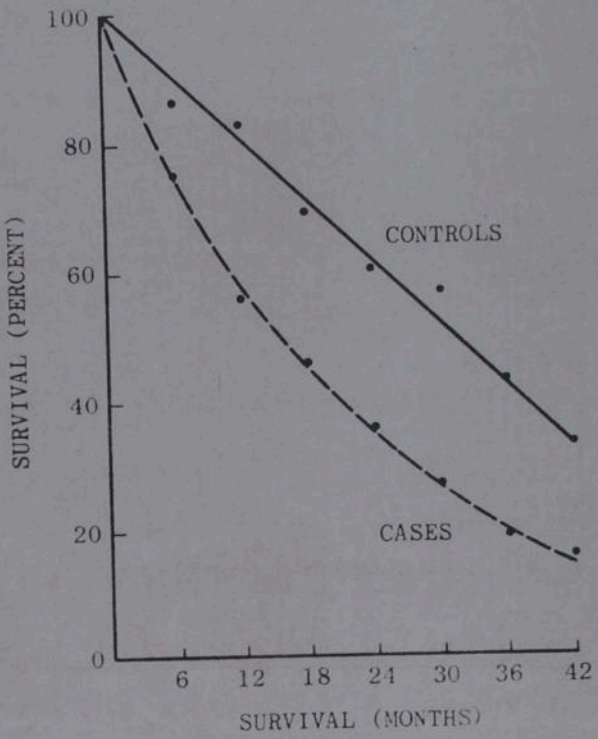
‖ S&O = Surgical and obstetrical cases.

Table 12 - Comparison of canine mammary cancer and human breast cancer by age equivalents for Alameda County, California

Range human age (years)	Range dog age equivalent (years/months)*	Human cases percent distribution+ (N=1771)	Canine first cancer cases percent distribution (N=83)
15-24	1/0-2/2	.28	--
25-34	2/3-4/8	2.71	2.41
35-44	4/9-7/2	16.15	7.23
45-54	7/3-9/8	24.56	32.53
55-64	9/9-12/2	20.50	28.92
65-74	12/3-14/8	18.58	21.69
75-84	14/9-17/2	14.12	6.02
>84	>17/2	3.11	1.20

* From Lebeau, A. (22).

\+ Data from Linden, G., Arellano, M., Hom, P., and Dunn, J. E., Jr. (21).



Text Figure 1 - Postsurgical survival of canine mammary cancer cases compared to controls, weighted in proportion to the age distribution of the case group.