Mammary Neoplasia in a Closed Beagle Colony

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SUMMARY

The incidence rate of mammary neoplasia in a large colony of beagles and the relationship to internal skeletal and/or liver radiation, age, relatively late ovariectomy (4 years and older), endometritis, parity status, and adrenal weight were examined. Of these various factors, age was the only condition that was clearly correlated with changes in the mammary tumor incidence. The rate became significant at approximately eight years of age and increased progressively throughout the older age classes. Among the female dogs, the incidence of mammary cancer was higher than that of any other form of spontaneous malignancy.

INTRODUCTION

Mammary neoplasia has been the most frequently observed spontaneous tumor type in the female dogs of the University of Utah beagle colony (1). The incidence increased progressively with age, and would have been a very important mortality factor in the older animals if early excision had not been performed.

It is the purpose of this report to present the incidence of breast tumors within this purebred dog colony up to March 31, 1973, and to examine the relationship of mammary neoplasia to internal skeletal radiation, age, ovariectomy, endometritis, parity status, and adrenal gland weight.

MATERIALS AND METHODS

All of the dogs summarized in this study were purebred beagles which, with very few exceptions, were born and reared at the Radiobiology Laboratory, University of Utah. Housing, diet, and animal care factors were nearly identical and remained virtually unchanged throughout the life of each animal (10). A high percentage of the dogs received carcinogenic radiation doses from internally deposited radioactivity in the skeleton ($^{90}$Sr, $^{226}$Ra, or $^{228}$Ra) or in the skeleton plus the liver ($^{239}$Pu, $^{226}$Th) (10). However, direct irradiation of the breast tissue was negligible (3, 10) and intercomparison of the irradiated and control groups, using the Kaplan and Meier (14) method, which continually corrects for the decrease in subjects at risk at increasing ages, did not indicate any direct or indirect radiation effect on mammary tumor incidence (Chart 1) (17). For this reason, the mammary tumor incidence data from the irradiated and control dogs were combined.

The duration of estrous was determined by twice-weekly examination of each dog throughout life. The stages of the estrous cycle were based on swelling of the vulva, genital discharge, and, occasionally, vaginal smears.

The years at risk, used in establishing the age-specific incidence curves, included only the female dogs, and the year designating a given age class was the mid-point of the class. For example, the 5-year age class includes dogs that were older than 4.49 years but less than 5.50 years. The dog years at risk within each class are given in Chart 2.

Most of the tumors in this study were surgical specimens that were removed relatively early in an attempt to reduce deaths from this type of disease. Thus, the data indicate morbidity and not mortality. In those animals that developed tumors at successively older ages during their life-span, as was frequently the case, only the first benign and/or malignant tumor was included in the incidence tabulation. Thus, the incidence data depict only the initial event of what was frequently a recurring disease. The malignant or benign status of the tumors was based on histological criteria.

RESULTS

Age-specific Incidence Rate. Mammary neoplasia was clearly a disease of adult animals. The incidence rate remained low through 7 years of age, and only 1 tumor was observed below the 5-year age class, a benign adenoma that appeared at 1.6 years of age. A sharp increase in the incidence rate occurred at approximately 8 years and remained high thereafter (Chart 2). The earliest cancer occurred at 7 years of age, and the incidence rate of both the benign and malignant tumors rose continuously in the successively older age classes.

Mammary tumors were not seen in the male population, consisting of over 500 dogs.

Anatomical Distribution. The number of mammary tumors was highest in the 2 posterior mammae, and diminished successively in the more proximal glands (Table 1) (17). This distribution pattern was directly correlated with the size of the glands. In 63% of the cases, more than 1 mammary tumor was present at diagnosis either in the same or in different glands.

Effect of Ovariectomy and Endometritis. Thirty-eight dogs, which were neutered at ages varying from 4 to 17 years, were available for study. In most instances, the reason for ovariectomy was endometritis; thus, these data present the influence of both ovariectomy and endometritis-inducing factors, or a combination of the 2 factors.
The earliest mammary tumor in the endometritis cases appeared at approximately 8 years of age, and the incidence rate extending up to the time of ovariohysterectomy was similar or slightly less than that observed in dogs that did not develop endometritis.

Relatively late ovarioectomy (4 years of age or older) likewise did not have any effect on the incidence rate of mammary neoplasia. The average incidence rate was similar to that observed in intact animals. Also, in several advanced, metastatic mammary cancers, ovarioectomy was performed as a therapeutic measure, without any apparent effect. Beyond 4 years of age, the presence or absence of the ovaries did not modify the tumor incidence rate or the biological behavior of an established mammary tumor.

Effect of Pregnancy. The incidence rate of mammary neoplasia in parous versus nulliparous beagles is compared in Chart 3. It is based on long-term observations in 45 dogs experiencing one or more pregnancies. Fifty-six % of the animals were bred on the 1st estrous cycle, and their 1st litter was born prior to 15 months of age. Most of the remainder had their 1st litter prior to 2 years of age. These data did not indicate any modification of the spontaneous tumor incidence as a result of pregnancy or any sparing effect related to early pregnancy, as reported in humans (International Collaborative Study of Breast Cancer, Department of Epidemiology, Harvard School of Public Health, unpublished data) (16).

Relationship of Mammary Neoplasia to Length of Estrous Cycle. Based on duration, the estrous cycles of dogs in this colony could be grouped into 3 general age classes: (a) under 8 years of age in which the average length was approximately 220 days; (b) 9 to 12 years of age, during which the average cycle increased to approximately 260 days; and (c) 13 years and older, in which the estrous pattern frequently became erratic, with both short and long cycles (Table 2). Corpora lutea were observed as late as 16 years age, but an apparent menopause occurred in some senile dogs, on the basis of the absence of corpora lutea. Pregnancy did not affect the length of the cycle.

Changes in the duration of the estrous cycle (Table 2) occurred in both the tumorous and nontumorous categories, and a specific relationship between mammary neoplasia and variations in the estrous interval was not apparent. The absence of any specific relationship was further

### Table 1
Anatomical distribution of 466 mammary tumors in beagles

<table>
<thead>
<tr>
<th>Gland</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axillary</td>
<td>3</td>
</tr>
<tr>
<td>Thoracic</td>
<td>14</td>
</tr>
<tr>
<td>Central</td>
<td>20</td>
</tr>
<tr>
<td>Abdominal</td>
<td>32</td>
</tr>
<tr>
<td>Inguinal</td>
<td>31</td>
</tr>
</tbody>
</table>

### Chart 1
Mammary tumor corrected cumulative incidence of internally irradiated plus control female beagles.
Relationship of length of estrous cycle to age (beagles)

Average age at first estrous, 314 days; earliest estrous observed, 232 days.

<table>
<thead>
<tr>
<th>Parous</th>
<th>Nulliparous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) in each age class</td>
<td>Length of estrous cycle (days)</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>39</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
</tr>
<tr>
<td>5</td>
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<tr>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>15</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 2. Relationship of length of estrous cycle to age (beagles)

Average age at first estrous, 314 days; earliest estrous observed, 232 days.

Although an increase in adrenal weight occurred at about the time at which the breast tumor incidence began to increase significantly, at least 4 factors tended to lessen the likelihood of a causal relationship: (a) the age-specific increase in adrenal weights was similar in animals with and without mammary tumors; (b) mammary tumors occurred, in some instances, without any evidence of adrenal cortical hyperplasia; (c) adrenal hyperplasia occurred with approximately equal frequency in both male and female dogs; and (d) the tumor incidence increased moderately prior to any marked changes in the gross appearance of the adrenals. These data did not support the observations of at least 1 other study in which mammary gland neoplasia was observed to be always associated with "tumors" of the adrenal cortex (12).

DISCUSSION

The true incidence of various types of tumors within dogs, especially those animals living in uncontrolled conditions, suggested by the moderate tumor incidence rate that existed prior to any significant change in the average length of estrous (Chart 2).

Relationship of Adrenal Gland Weight to Mammary Neoplasia. It was frequently not possible to determine adrenal weights at the time of mammary neoplasia, since most of the animals observed in this study were part of a life-span experiment and lived for at least several years after surgical removal of the tumor. However, some of the mammary tumors were obtained at autopsy, permitting an immediate correlation with the condition of the adrenals.

The weights of the adrenal glands remained relatively constant from approximately 1.5 years through 8 years of age, but increased at approximately 9 to 10 years age (Chart 4). The enlargement was principally the result of either nodular or diffuse cortical hyperplasia. True adrenal cortical neoplasms were uncommon and were not included in these adrenal weight data (23).

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such as private households, etc., is difficult to determine accurately, because of (a) poorly defined populations at risk, (b) a very low percentage of histological examinations, (c) incomplete reporting systems, and (d) very few animal tumor registries. Incidence studies are further complicated by variable environmental conditions, unknown breed differences, and cross-breeding. These and other factors probably account for much of the wide variation in the reported incidence of canine mammary neoplasms (1, 6). Incidence discrepancies also may account for much of the disagreement regarding the relationship of canine breast neoplasia to endometritis, pregnancy, pseudopregnancy, and irregularities in the estrous cycle.

In spite of the differences among the various reports of canine mammary neoplasia incidence, there are at least 3 factors in which there is general agreement: (a) the incidence does not become significant until approximately 5 to 7 years of age (2, 5-7, 9, 11, 13, 15, 18-20, 22); (b) a marked sparing effect is achieved when ovarioectomy is performed prior to 2.5 years of age (4, 7, 8, 21); and (c) the highest incidence rate occurs at about 10 to 12 years of age (2, 5, 6, 9, 11, 13, 15, 18, 19, 21, 22). Data from the Utah closed beagle colony, in which many of the variables described above have been eliminated, are in agreement with 2 of these 3 generally accepted features. There was concurrence on the age at which neoplasia first becomes significant, at approximately 7 years, and in the absence of a sparing effect produced by ovarioectomy of animals beyond young adulthood.

Relative to the influence of ovarioectomy, only a partial comparison with outside studies could be made, since the earliest any of the dogs in this colony were neutered was approximately 4 years age. Ovarioectomy at this and older ages did not modify the incidence of breast tumors. This is in agreement with most other investigations which have reported that ovarioectomy produced a mammary tumor sparing effect only in animals spayed prior to approximately 2.5 years of age (9, 11, 21). The effect of neutering at young ages may be related, at least in part, to the resultant underdevelopment of the breasts and, thus, to a much smaller amount of susceptible tissue at risk to various etiological factors. Certainly, the anatomical distribution suggests a relationship between mammary neoplasia and the size of glands. The relatively small amount of susceptible tissue at risk may also be a factor in the low incidence of breast tumors in male animals.

The age of highest mammary tumor incidence rate was not in agreement with other studies. The rate determined in this beagle colony increased progressively throughout life, such that the peak incidence rate occurred in the oldest age class and not at 10 to 12 years age (Chart 2). The incidence of mammary neoplasia was more closely correlated with length of life-span than any other factor examined, and increased progressively with age, although the rate of increase diminished after approximately 10 years. A similar age-tumor relationship was also observed in incidence data related to several neoplasms involving other organ systems (23).

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REFERENCES

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