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Feline Lymphoma in the Post–Feline Leukemia Virus Era

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Lymphoma (lymphosarcoma or malignant lymphoma) is the most common neoplasm of the hematopoietic system of cats and reportedly the cat has the highest incidence for lymphoma of any species. A 21-year retrospective survey of feline lymphoma covering the period 1983–2003 was conducted with the patient database at the Veterinary Medicine Teaching Hospital (VMTH) at the University of California, Davis, School of Veterinary Medicine. This period comprises the post–feline leukemia virus (FeLV) era. Feline lymphoma historically has been highly associated with retrovirus infection. Mass testing and elimination and quarantine programs beginning in the 1970s and vaccination programs in the 1980s dramatically reduced the subsequent FeLV infection rate among pet cats. The results of this survey confirm a significant decrease in the importance of FeLV-associated types of lymphoma in cats. In spite of this decrease in FeLV infection, the incidence of lymphoma in cats treated at the VMTH actually increased from 1982 to 2003. This increase was due largely to a rise in the incidence of intestinal lymphoma, and to a lesser degree, of atypical lymphoma. A high incidence of mediastinal lymphomas in young Siamese or Oriental breeds also was observed, supporting previous studies. Associations of intestinal lymphoma and inflammatory bowel disease and diet should be further considered.

Key words: Cat; Lymphosarcoma; Malignant lymphoma.

Lymphoma is the most common neoplasm of the hematopoietic system of cats, with an estimated incidence in 1968 of 200 per 100,000.[1–3] This incidence was reportedly the highest of any species.[4,5] Two basic types of feline lymphoma currently are recognized—those that are retrovirus-associated, and those that are nonviral in origin.[5] Feline leukemia virus (FeLV) is the most lymphomagenic of the retroviruses, with carrier cats having a 60-fold or greater relative risk of the cancer.[6] Before control of FeLV in the 1980s, FeLV accounted for as many as 70% of the cases of feline lymphoma.[5] Feline immunodeficiency virus (FIV) also is a cause, either directly or indirectly, of lymphomas in cats[7,8] and increases the relative risk of lymphoma in infected cats 5- to 6-fold.[6] FeLV-associated lymphomas tend to be of T-cell lineage and relatively unique in form, including generalized (multicentric or nodal) lymphoma, thymic (mediastinal) lymphoma, neurolymphoma, and ocular lymphoma.[5] FIV-associated lymphomas are more likely to be of B-cell lineage and less unique in type, with the exception of nasopharyngeal lymphoma, which may be overrepresented.[8,9] The incidence of FIV-associated lymphomas does not appear to have changed, because the prevalence of this infection has not been drastically affected by the testing of household cats. FIV is enzootic in the outdoor feral or semiferal cat population, and most FIV-infected household pet cats come from this population.[8,9]

Non–retroviral-associated lymphomas constitute the largest group of lymphocytic cancers observed in cats at the present time. These lymphomas are of B- or T-cell lineage, and tend to be more organ specific and solitary. Renal lymphoma[10] and intestinal lymphoma,[11–13] both subcategories of abdominal lymphoma, are the most common non–retrovirus-associated tumors, with lymphomas of the head and neck,[14,15] other internal organs, eyes, and central nervous system (CNS)[16] being collectively less common.

The underlying cause of non–retroviral-induced feline lymphomas is not completely understood. A link is thought to exist between chronic cigarette smoke exposure and development of feline lymphoma.[17] Feline lymphomas frequently arise in organs or sites affected by chronic inflammation. Chronic inflammatory bowel disease is common in cats, and a linkage to alimentary lymphoma has been suggested.[13,18] The role of chronic inflammation from vaccine adjuvants in inducing fibrosarcomas has been well documented.[19] Interestingly, cats developing vaccine-site sarcomas have a much higher subsequent risk of developing lymphoma.[20] This observation suggests that lymphoma in cats, like many cancers, requires both a predisposition and additional triggers, such as chronic inflammation.

Dogs, which have no known retroviruses, also have a high incidence of lymphoma, although the incidence is lower than that observed in cats. Lymphoma is the most common hematopoietic tumor of the dog, representing 83% of all cases. The incidence of lymphoma is particularly high or low in certain breeds, suggesting strong negative and positive genetic influences.[21] Genetic factors also may play a role in lymphoma in cats. Siamese cats appear to have a predilection for lymphoma, mainly of the mediastinal type, with a potentially recessive pattern of inheritance.[5,22–26] Early-onset mediastinal lymphoma has been documented in Siamese-type breeds of cats in Australia and Europe.[23,24,27,28] Twelve additional cases of FeLV-negative Oriental Shorthair cats with lymphoma from the United States have been presented to 1 of the authors (LAL) by clinicians or private breeders. These cats all received treatment for mediastinal lymphoma by the age of 2 years. The breed specificity, absence of retroviruses, early onset, and consistent clinical presentation suggest a heritable form of lymphoma in Siamese-type breeds.

The present survey of feline lymphoma was conducted from 1983 to 2000 with the patient database of the Veterinary Medicine Teaching Hospital (VMTH), School of Vet-

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erinary Medicine, at the University of California, Davis. The goal of the survey was to gain background information on lymphoma incidence, and non–FeLV-related mediastinal lymphoma in particular. This survey covered a period during which FeLV infection dramatically decreased because of the implementation of mass testing, elimination and quarantine programs,[29,30] and vaccination.[5]

Methods

The VMTH is a referral clinic that serves the Northern California area and surrounding states. The electronic database of the VMTH consists of all patient records from 1987 until 2003. This study represents a retrospective analysis of patient cases. No animals were used in this study. The database was searched by using the terms feline, lymphoma, lymphosarcoma, and malignant lymphoma. The FeLV status of cats in the study was accurate, given routine testing of cats for this disease by referring veterinarians and VMTH clinicians during this period. FIV testing was not routine, especially before 1990, and was based on records and not verified by polymerase chain reaction (PCR) assay. Therefore, the actual FIV status of cats with lymphoma was less certain. Cats that were positive for FeLV, FIV, or both were excluded from the detailed analyses of tumor incidence. All cases were reviewed for clarity and categorized by signalment, gender, reproductive status, and anatomical location of the tumor. Malignancy had been confirmed by biopsies that were obtained by endoscopy, laparotomy, or at postmortem examination. Information from physical examination, radiography, ultrasonography, laparotomy, biopsy, and postmortem examination was used to assist clarification and anatomic classification. The classifications suggested by Gabor et al[24] were used to make a direct comparison with the reported incidence of feline lymphoma in Australia and Europe.[23,24,28] Lymphoma categories were defined as mediastinal for tumors located in the mediastinum; atypical for CNS and nasopharyngeal tumors; nodal for lymphoma with only lymph node involvement; abdominal for tumors located in the intestine and abdominal organs including spleen, liver, and kidneys; and mixed when tumors could be defined by multiple categories.

All cats admitted from 1987 to 2003 were compared as controls. A given patient was considered only once to prevent bias due to follow-up visitations in control and lymphoma cases. A 2-tailed Fisher exact test estimated the significance of the breed incidence of lymphoma. The data comparisons were considered significant at $P < .05$.

Results

Patient Characteristics

Five hundred forty-six cases of feline lymphoma were identified from the VMTH patient population between the years 1983 and 2003. Seventy-nine (14.5%) of the 546 cases were confirmed as FeLV-positive, FIV-positive, or both by the referring clinic, the VMTH, or both. Forty-four (56%) of the cases occurred from 1984 to 1990. Approximately 1.25 cases of FeLV-positive, FIV-positive, or both, lymphoma were presented in each of the years 1991–2003, except for 1995, in which 7 FeLV-positive cases were identified. Cats with retrovirus-associated lymphomas were excluded from the remainder of the study.

The age distribution of the 477 cats with retroviral-negative lymphoma is presented by anatomic form in Table 1. The age of the VMTH feline patient population ranged from 0.1 to 28.8 years, with a median age of 6.25 years. Ages for cats with lymphoma ranged from 0.6 to 20 years, with the median age of all cats with any particular type of lymphoma of approximately 11 years. Only mediastinal lymphoma had a significantly different median age of presentation of 2 years.

Table 1. Age distribution of primary anatomic presentation for cats with lymphoma.

Age (years)	Abdominal	Atypical	Mediastinal	Mixed	Nodal
1	2	2	4	3	0
2	6	0	7	5	3
3	2	3	0	5	0
4	2	1	1	3	0
5	5	4	0	3	0
6	8	6	2	1	2
7	14	6	0	4	4
8	10	9	0	4	0
9	15	9	0	8	1
10	27	9	2	9	3
11	26	11	1	4	2
12	24	9	1	4	3
13	30	5	0	4	2
14	26	11	0	5	2
15	22	5	0	3	1
16	14	5	0	6	0
17	6	2	0	2	0
18	1	1	0	2	0
19	4	0	1	0	0
20	2	0	0	0	0
Adult	5	1	0	1	0
Unknown	6	1	0	2	0
Total cats	257	100	19	78	23
Median age (years)	12	11	2	10	10

The breed distribution of the total VMTH cat population and lymphoma cases was considered in the survey. The breed origin of 10 cats was unknown. Approximately 15% of the VMTH patient population was represented by purebred cats. Several breeds were pooled based on their common genetic origins. The Persian family consisted of Persians, Exotic Shorthairs, and Himalayans. The Oriental family consisted of Oriental Shorthair, Siamese, Colorpoint Shorthair, and Javanese. These 2 breed families represented approximately 4.5% of the total patient population each, and approximately 30% of the pedigreed population each. For lymphoma cases, 394 (82.6%) of the 477 cats were domestic shorthaired or domestic longhaired random-bred cats; 39 (8.2%) of the cats were from the Oriental group; 8 (1.7%) of the cats were from the Persian group; and the remaining 26 (5.5%) of the cats were other purebred cats, including Abyssinian, Burmese, Maine Coon, and Manx. The occurrence of lymphoma in the Siamese was the only statistically significant ($P < .05$) breed association. The sex of the cats or the effects of neutering or spaying were not significantly associated with lymphoma incidence (data not shown).

Viral-negative lymphoma was identified in approximately 18 cats per year from 1984 to 1994. Lymphoma increased to an average of 32.4 cases per year in the period 1994–2003, nearly doubling the incidence observed in the previous decade (Fig 1; Table 1). During this period of rapid increase in lymphoma, the feline patient load increased from 1,881 cats in 1993 to 2,324 cats in 2003, an

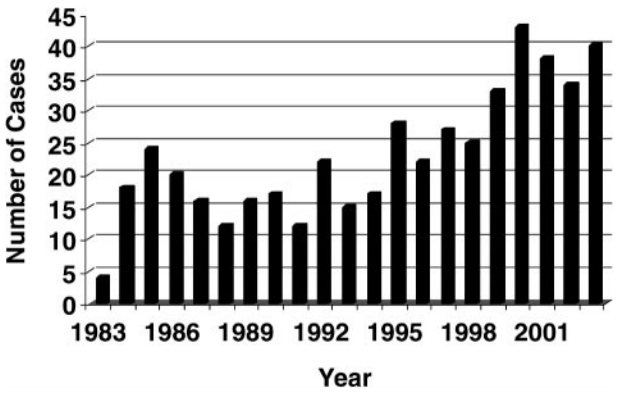

Fig 1. Increase in feline lymphoma incidence from 1983 to 2003. All cases of feline lymphoma presented each year to the University of California, Davis, Veterinary Medicine Teaching Hospital from 1983 to 2003 are shown.

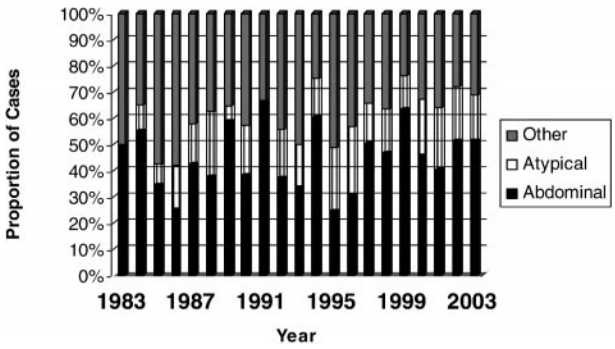

Fig 3. Proportion of feline lymphoma type from 1983 to 2003. The yearly proportion of abdominal, atypical, and all other forms of lymphoma combined per total lymphoma cases is shown.

increase of only 29%. The highest increases were identified in the abdominal and atypical (nasopharyngeal) forms (Fig 2), with the incidence of mixed, nodal, and mediastinal presentations consistent over the 21-year period.

Anatomical Classification of Cases

Abdominal lymphoma, 257 (53.9%) of 477 cases, was the most common form of lymphoma, 2-fold more frequent than atypical cases (100 [21%] of 477 cases) and the 3 other forms combined (120 [25.1%] of 477 cases; Fig 3). The intestine was classified as the primary tumor site for a majority of abdominal lymphomas (186 [72.4%] of 257 cases). Proportionally, abdominal lymphoma represented approximately 50% of total lymphoma cases over the study period; however, the incidence of intestinal-specific lymphoma increased during the survey period (Fig 4) to >80% of cats with abdominal involvement (Figs 1, 2). The increase of intestinal lymphoma was not consistent throughout the study but was caused by a surge over the past 10 years. The incidence of intestinal lymphoma remained constant at approximately 5–10 cases per year between 1983 and 1995, and then increased steadily thereafter to 15–25 cases per year (Fig 2). This increase of 5–15 cases per year was re-

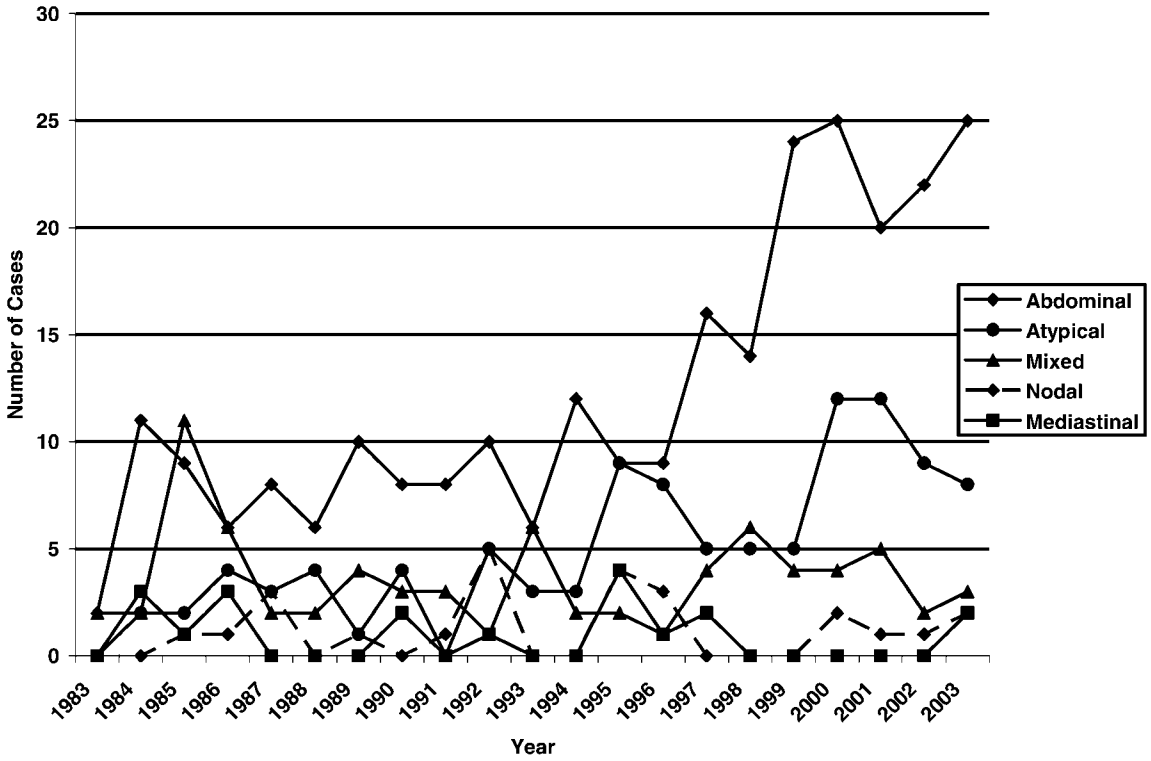

Fig 2. Lymphoma incidence by category from 1983 to 2003. The number of cases for each lymphoma category presented to the University of California, Davis, Veterinary Medicine Teaching Hospital from 1983 to 2003 is shown.

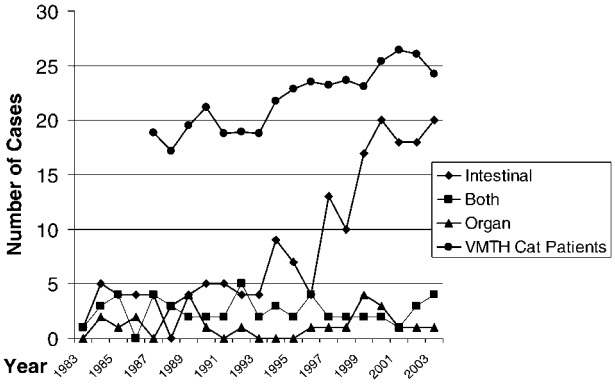

Fig 4. Increase of intestinal form of abdominal lymphoma from 1983 to 2003. The increase in intestinal lymphoma cases over the survey period as compared to the constant frequency of cases for lymphoma that involved other abdominal organs, such as liver, kidney, spleen, and mixed cases is shown.

flected in a similar upswing in total lymphoma cases from 1995 onward (Fig 1). Lymphoma was restricted to other abdominal organs (eg, spleen, liver, pancreas, and kidney) in 53 (20.6%) of 257 abdominal cases. Fifteen of the 53 organ cases were restricted to the kidneys. The primary abdominal site could not be determined in 24 of 257 cases because tumors were present in the alimentary tract and abdominal organs. The incidence of organ-restricted or mixed cases did not increase during the survey period (Fig 4).

Atypical lymphoma was present in 100 (21%) of the 477 lymphoma cases, increasing to approximately 20% of all lymphoma cases during the survey period (Fig 3). Nasal tumors had the highest incidence (30 [30%] of the cases) and involvement of the CNS occurred in 23 (23%) of the cases. Mammary, vulvular, and vascular occurrences were rare, each represented by a single case. Remaining cases comprised lymphomas localized to the epidermis, the bronchi, or larynx, and various other tissues that are not represented in other categories.

Tumors were restricted only to lymph nodes in 23 (4.8%) of 477 cases but 115 (24%) of the 477 cases had lymphoma-positive lymph nodes as a component of the disease. Eight (34.5%) of the 23 node-restricted cases were multinodal lymphoma, 5 (21.7%) of the cats presented with several positive regional lymph nodes, and 10 (43.5%) of the cats had a solitary affected lymph node.

Twenty-seven (5.7%) of 477 lymphoma cases had mediastinal involvement; 19 (70.4%) of these 27 cases were restricted to the mediastinum. Eleven (57.9%) of 19 cats with thymus-restricted tumors were 2 years of age or younger. The median age of affected cats over the age of 2 years was the same as that for all other forms of lymphoma (ie, approximately 10 years).

Lymphoma cases were identified as the mixed category when tumors were in more than 1 category location and the primary versus secondary tumor could not be distinguished. Approximately 78 (16.4%) of 477 lymphoma cases were classified as mixed. A majority of these cases had abdominal, atypical, and nonregional lymph node involvement. Six cases (1.25%) of secondary leukemia were identified within the 477 lymphoma cases, all in cases with widespread lymphoma.

Discussion

The present survey of feline lymphoma covered the admitted VMTH patient population from 1983 to 2003. This period was relevant for being in the post-FeLV era. FeLV infection was common in cats from the 1950s through the 1970s, but was unknown as an entity until 1964 when researchers discovered FeLV from studies of multicat households suffering from numerous cases of lymphoma.[31] The 1st diagnostic test for infected cats, an indirect immunofluorescence assay on blood smears, was reported in 1973,[32] and rapidly became integrated into a test and elimination regimen.[5] This regimen alone was responsible for the rapid disappearance of FeLV from large, indoor, multicat populations[30,33] and a marked decline in the infection in the population as a whole.[34] The 1st report of a commercial FeLV vaccine was made in 1986,[35] and vaccines may have contributed further to the control of the infection after that time.[5]

Several important findings regarding the prevalence and etiology of lymphoma came from our study. The 1st involved the decrease in the incidence of FeLV-associated tumors presented to the VMTH. Some of this decrease may have been due to the use of rapid commerical and in-house FeLV tests by practitioners, hence few FeLV cases were referred to the VMTH. However, the opposite is more likely true. FeLV testing has dramatically reduced FeLV infection among pet cats and in turn decreased FeLV-associated diseases.[30] Before control of FeLV by test and vaccination in the early 1980s, more than 70% of all cats with lymphoma were infected with the virus.[5] From 1983 to 2003, 546 cases of feline lymphoma were presented to the VMTH in California, and only 79 (14.5%) were retrovirus (mainly FeLV)-associated. A majority of these cases (56%) were seen before 1991 at the VMTH, with only 1 or 2 cases of FeLV-associated lymphoma presented per year since 1991. These findings confirmed that FeLV-induced tumors were relatively uncommon compared to their peak in the 1960s and 1970s. The 467 virus-negative cases were not subjected to PCR to detect proviral DNA; thus, a portion of these cases may have had occult retroviral exposure.[9]

Second, in spite of a dramatic decrease in FeLV infection, lymphoma in cats appears to be increasing in prevalence. The incidence of viral-negative lymphomas has nearly doubled, increasing from approximately 18 cases per year before 1994 to approximately 32.4 cases per year over the past decade. This change cannot be attributed to better care of pet cats and longer lifespan because the median age of cats with lymphoma (11 years) was not significantly different from the general cat patient population seen at the VMTH and was not changed from that of the past decade (1983–1993). However, more clients may be considering treatment and this factor may be reflected in the increase in feline case load at the VMTH. With the 29% increase in cats, lymphoma incidence still increased by approximately 20%.

The 3rd finding was the relatively high incidence of me-

diastinal lymphoma in Siamese-type breeds. The age at diagnosis also was considerably younger for cats with mediastinal lymphoma (2 years of age). Lymphoma generally is a disease of older cats, with a median age of 11 years. The bimodal distribution of age seen in this study has been reported in other studies, in which thymic, mediastinal, or both forms of lymphomas also were documented in young cats.[3,23,24,28] The high incidence of mediastinal lymphoma in younger Siamese and Siamese-related breeds (eg, Oriental Shorthair) suggests a genetic predisposition. Furthermore, mediastinal lymphoma was not seen in Persian and related breeds. This observation tends to rule out most environmentally predisposing factors, which should affect all purebred cats more or less equally. How this putative genetic predisposition relates to other cancers in Siamese-type cats is unknown. Siamese cats have an 8-fold increase in the risk of intestinal adenocarcinoma as compared to other breeds, but this cancer tends to occur in older cats and may involve a different genetic predisposition.[36]

The 4th finding concerned a change in the predominant types of non–retroviral-associated lymphomas. Marked increases were observed in the abdominal (particularly intestinal only) and atypical (mainly nasopharyngeal) forms of lymphoma. More cats with the abdominal form have been brought to the VMTH, which is consistent with a similar survey of Australian cats.[37] Lymphocytic-plasmacytic enterocolitis has been suggested as a precursor to feline intestinal lymphoma,[38,39] but this suggestion has not been supported by other studies.[40] Dietary allergies and chronic inflammatory bowel disease have been postulated as precursors to intestinal lymphoma but associations have not been documented. Cat foods have changed in response to health issues, particularly urinary tract disease (reviewed by Markwell et al[41]) and diet has been a postulated cause of the increase in inflammatory bowel disease. Approximately 71% of cats with chronic diarrhea are improved when changed from commercial diets that are relatively high in carbohydrate to high–animal protein, low-carbohydrate diets.[42] Additionally, meat meal has been suggested as a better protein source for cats than corn gluten meal with respect to its higher digestibility.[43] Hence, chronic inflammation may be a contributing factor in an individual cat predisposed to development of intestinal lymphoma.

The present study had some limitations. This survey classified lymphoma as proposed by several investigators,[23,24,28] but not all surveys use the same classification scheme. The mediastinal category is the least dissimilar among surveys, whereas the atypical classification often is used synonymously with unclassified. Thus, these 2 categories should be highly consistent across studies. The mixed category used in this survey has been reserved for lymphomas involving multiple sites and with no primary site categorization. Thus, the inclusion of this mixed category in the present study would underestimate the incidence of primary site tumors reported in other studies. The multicentric classification is represented in this survey by the more commonly used nodal category, although spleen and liver involvement, which is sometimes classified as multicentric, was not included. The abdominal classification is the most inconsistent, with renal, spleen, and liver resulting in disparate classifications. Thus, multicentric disease may be underrepresented in this survey, whereas abdominal disease could be overrepresented by the inclusion of renal, hepatic, and splenic disease. Regardless of between-study comparisons, lymphoma consistently was classified for this survey and the identified changes in incidence represent the VMTH population. The noted increase in abdominal lymphoma is highly influenced by the increase of the intestinal form and the increase in abdominal lymphoma should not be greatly influenced by misclassifications of renal, hepatic, and splenic forms of the disease.

Additionally, this study did not completely address the issue of non-FeLV, retroviral-induced lymphomas, such as those associated with FIV. FIV-infected cats were removed from the non–retroviral-induced group of lymphomas whenever positive test results were available. However, testing for FIV was not routine until after 1990. Therefore, it is possible that some of the earlier non–FeLV-infected cats were FIV infected, but this number would be small.

The relative importance of certain types of lymphoma in this study may have been affected by technology. For example, the number of cats with nasopharyngeal (atypical category) lymphoma was relatively high. This finding may have reflected the difficulty that field veterinarians have in diagnosing this form of disease, but this difficulty has been consistent in the private practice setting; hence, it is unlikely that referrals have increased substantially. Signs of this cancer are similar to those of nasal adenocarcinoma and chronic rhinosinusitis, and differentiation often requires specialized endoscopic and biopsy equipment and magnet resonance imaging (MRI) and computed tomography (CT) scans not routinely used in most private veterinary practices. At the VMTH, endoscopic biopsies are the standard for diagnosis, as has been true for the past 20 years. Hence, improvements in MRI and CT should not have had a large influence in the diagnosis of nasopharyngeal lymphoma. Additionally, this increase in nasopharyngeal lymphoma of 20% could have been a result of the 29% increase in the feline caseload.

A skewing effect also may have applied to intestinal lymphoma. The impression from the VMTH population is that intestinal lymphoma is increasing in incidence, whereas other abdominal forms of lymphoma are remaining constant. However, dramatic improvements also have been made in premortem diagnostic techniques for intestinal lymphoma during the last 20 years. Laparotomy with full-thickness biopsy, fine-needle aspiration, ultrasound-guided biopsy, and endoscopy have made the diagnosis of lymphoma easier for practitioners. There also is a growing appreciation that the disorder exists in at least 2 forms. The 1st form is considered a lower-grade disease similar to chronic lymphocytic-plasmacytic enteritis. This disease often responds well to therapy with oral chemotherapeutic agents and survival times often are 1–2 years or longer. The 2nd (lymphoblastic) form is more likely to present with discrete intestinal masses, perforating intestinal ulcers, inappetence with weight loss, and a rapid course. The median survival time for this form of the disease is only approximately 6 months. Given the fact that low-grade disease is readily amenable to conservative therapy, cats with this form of lymphoma may not be referred as often to the

VMTH as cats with the more aggressive, lymphoblastic form of the disease.

Although effective eradication of FeLV has influenced the predominant clinical forms of lymphoma, lymphosarcoma remains a persistent, and based on VMTH data, an increasingly common disease in the cat population. This study supports the genetic influence of early-onset, mediastinal lymphoma in Siamese-type cats. Chronic inflammation may be a secondary trigger contributing to the higher incidence of abdominal and possibly other forms of lymphoma. Many forms of feline lymphoma occur in sites in which chronic lymphocytic inflammation occur frequently (eg, mouth, nasal passages, intestines, and kidneys). Chronic inflammatory bowel disease may be a precursor event to intestinal lymphoma; thus, correlations with history of inflammatory bowel disease and detailed delineation of the primary sites for intestinal lymphoma should be considered. Although 1 cause of lymphoma (ie, FeLV) has been nearly eliminated for the cat, it is clear that additional factors contribute to the development of this disease, especially with respect to intestinal lymphoma. Therefore, further investigations into the potential role of inflammatory bowel disease, diet, and environmental influences should be undertaken.

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