Epidemiologic study of relationships between consumption of commercial canned food and risk of hyperthyroidism in cats

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Objective—To determine whether the increasing prevalence of feline hyperthyroidism is the result of aging of the cat population and whether consumption of canned foods at various times throughout life is associated with increased risk of hyperthyroidism.

Design—Retrospective and case-control studies.

Study Population—Medical records of 169,576 cats, including 3,570 cats with hyperthyroidism, evaluated at 9 veterinary school hospitals during a 20-year period, and 109 cats with hyperthyroidism (cases) and 173 cats without hyperthyroidism (controls).

Procedure—Age-adjusted hospital prevalence of hyperthyroidism was calculated by use of Veterinary Medical Database records. On the basis of owners' questionnaire responses, logistic regression was used to evaluate associations between consumption of canned food and development of hyperthyroidism.

Results—Age-specific hospital prevalence of feline hyperthyroidism increased significantly from 1978 to 1997. Overall, consumption of pop-top canned (vs dry) food at various times throughout life and each additional year of age were associated with greater risk of developing hyperthyroidism. In female cats, increased risk was associated with consumption of food packaged in pop-top cans or in combinations of pop-top and non-pop-top cans. In male cats, increased risk was associated with consumption of food packaged in pop-top cans and age.

Conclusions and Clinical Relevance—These findings suggest that the increasing prevalence of feline hyperthyroidism is not solely the result of aging of the cat population and that canned foods may play a role. (*J Am Vet Med Assoc* 2004;224:879–886)

Hyperthyroidism is a commonly diagnosed disease of cats older than 6 years of age.[1] Feline hyperthyroidism was first described in 1979, and since that time its occurrence has reached epidemic proportions. The etiology of hyperthyroidism is unknown; however, it is likely multifactorial.[2] Clinically, hyperthyroidism of cats resembles toxic nodular goiter of humans,[3] a disease of the elderly that is more common in iodine-deficient areas.[4] The first epidemiologic study[5] of feline hyperthyroidism found associations between hyperthyroidism and consumption of canned cat food in the 5 years prior to diagnosis, partial or complete indoor housing, non-Siamese breed, and regular exposure to lawn and flea control products. A subsequent study[6] found that consumption of canned commercial cat food presently or in the past and use of cat litter were associated with greater risk of hyperthyroidism. Both studies found that the greater risk of hyperthyroidism associated with consumption of canned food was statistically independent of other variables examined. Another study[7] found that increasing age and preference for certain flavors of commercial canned cat food in the present diet were associated with greater risk of hyperthyroidism.

Food with a high iodine content may be a possible cause of feline hyperthyroidism.[8] Iodine content of commercial cat food varies widely, and the greatest variations occur in canned foods.[8-10] Human thyrotoxicosis has been linked to excess iodine consumption (via food, water, or milk) after a period of iodine deficiency, especially when a concurrent thyroid disorder, such as toxic nodular goiter, is present.[11] In toxic nodular goiter, affected thyroid follicles act autonomously without regulation by the hypothalamic-pituitary-thyroid feedback mechanism, so that increased availability of iodine as substrate permits increased production of thyroid hormones beyond the metabolic requirement.[11]

Many goitrogens have been associated with development of human toxic nodular goiter, including those found in cruciferous vegetables (cabbage family), onions, and garlic.[12] Minerals in hard water and water contaminated with bacteria, runoff from coal and shale deposits, hydrocarbons, phthalates (plasticizers), and perchlorate are also goitrogenic.[12] Goitrogenic chemicals identified by the **Environmental Protection Agency (EPA)** as endocrine disrupters include certain insecticides, pesticides, heavy metals, components of cigarette smoke, disinfectants, deodorizers, and manufacturing compounds and by-products of manufacturing (eg, phthalates, polycyclic aromatic compounds, phenols, and dioxins).[13] Endocrine disrupters such as heavy metals (eg, mercury) and chlorinated hydrocarbons (eg, polychlorinated biphenyls) contaminate commercial canned cat and dog foods.[14,15]

The purpose of the study reported here was to determine whether the increasing prevalence of feline

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Supported by a fellowship in Epidemiology and Animal Welfare from the Kenneth Scott Charitable Trust (Edinboro).

The authors thank Patty Bonney, Yun Shen, Kristin Cake Kennedy, Tana Lee, and Dr. Daniel Cher for technical assistance.

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hyperthyroidism is the result of aging of the cat population and whether consumption of canned foods at various times throughout life is associated with increased risk of hyperthyroidism. We wished to confirm and expand on findings of 2 previous epidemiologic studies[5,6] that suggested an association between consumption of canned foods and increased risk of hyperthyroidism in cats.

Criteria for Selection of Cases

To determine hospital prevalence of hyperthyroidism in cats, the **Veterinary Medical Database (VMDB)** was searched electronically for records of the first hospital visit of cats with hyperthyroidism from 1978 to 1997. Only records from 9 institutions that contributed continuously to the VMDB were used (Michigan State University, Iowa State University, Purdue University, University of Georgia, University of Illinois, Colorado State University, Texas A&M University, University of Minnesota, and University of Missouri).

Procedures

Medical records—Medical records in the VMDB from 1978 to 1997 were retrieved electronically. Age in the records was available only in broad categories (including 4 to 7 years, 7 to 10 years, 10 to 15 years, and ≥ 15 years). The exact age of individual cats was not available, and cats listed as 10 years old, for example, might have been placed in the 7- to 10-year-old or 10- to 15-year-old category at the discretion of participating institutions. To compare hospital prevalence of feline hyperthyroidism with that of other common diseases of cats during this 20-year period, VMDB records from the first hospital visit of cats with a diagnosis of renal insufficiency and diabetes mellitus were also reviewed.

Data analyses—Data were analyzed by use of a spreadsheet[a] and statistical[b] software. The 20 years for which data were retrieved were divided into four 5-year periods. The ages of cats in each 5-year period were compared by use of the extended **Mantel-Haenszel test** (χ^2_{MH}).[16] The hospital prevalence and 95% **confidence interval (CI)** of feline hyperthyroidism were calculated and expressed as the frequency/1,000 visits in each 5-year period. The age-specific hospital prevalence and 95% CI of feline hyperthyroidism in each 5-year period were calculated (by dividing the number of cats with hyperthyroidism in each age category by the total number of cats in that age category in that 5-year period) and compared by use of χ^2_{MH}. Direct age-adjustment techniques[17] were used to control for changes in the age of the cat population over time; all cats for which records were retrieved over the 20-year period were considered the standard population, and age-adjusted hospital prevalence (95% CI) for each 5-year period was calculated by multiplying age-specific prevalence in each age category by the total number of cats in that age category, summing the resultant standardized prevalences, and dividing by the total number of cats. The hospital prevalence and 95% CI of renal insufficiency and diabetes mellitus were calculated for the 20-year period as well as for each calendar year, and trends for changes in prevalence were evaluated by use of χ^2_{MH}. Linear regression was used to estimate the slopes of the prevalence of these 3 diseases over the 20-year period, and these were compared. A value of $P < 0.05$ was considered significant.

Case-control Study

Subject recruitment—Medical records of cats assessed at the **Purdue University Veterinary Teaching Hospital (PUVTH)** from January 1, 1998 to August 15, 2000, that had serum **thyroxine (T_4)** concentration measured by the PUVTH Clinical Pathology Laboratory were reviewed. Of these cats, cats ≥ 6 years of age that did not have a previous diagnosis of hyperthyroidism (eligible cats) were evaluated. The medical history and physical examination findings of eligible cats were recorded. If a serum T_4 concentration determination had been made more than once, the maximum serum T_4 concentration was recorded.

Letters were sent to owners of eligible cats inviting them to participate in a study of feline nutrition and health. A questionnaire developed by the authors on the basis of an extensive literature review of dietary goitrogens was sent to owners who agreed to participate. Cats whose owners did not return questionnaires and did not respond to 6 follow-up telephone calls were excluded from the study. The research protocol was approved by the Committee on the Use of Human Research Subjects at Purdue University.

Questionnaire—The questionnaire focused on each cat's lifetime diet and medical history. Diet information from the time that the cat was acquired to 1 year before the date of the hospital visit was requested. Diet information was not collected for the 1-year period prior to the visit because clinical signs of hyperthyroidism or other diseases may have led to a change in the diet during this time.

Diet information from four 3-month periods in the first year of life and from 1-year periods thereafter was requested. Owners were asked to estimate the proportions of all food types fed by volume (ie, the percentage of the total volume of food fed). Food type categories included commercial canned, dry, and semimoist cat and dog foods identified by brand name, variety, and flavor, as well as home-cooked foods that were part of a regular diet (ie, foods fed at least once weekly for at least 3 months during the first year of life and at least 6 mo/y thereafter). Food labels sent to the authors by owners, a published reference,[18] and commercial cat food manufacturers' data were used to identify specific foods.

Serum T_4 assay—Serum T_4 concentration was measured by use of a chemiluminescent enzyme immunoassay[c] validated by the PUVTH Clinical Pathology Laboratory. Intra-assay **coefficients of variation (CV)** were 14.5% (at mean T_4 concentration, 1.3 µg/dL), 8.2% (at mean T_4 concentration, 5.2 µg/dL), and 4.5% (at mean T_4 concentration, 11.9 µg/dL). Interassay CVs were 14.9% (at mean T_4 concentration, 1.3 µg/dL), 9.0% (at mean T_4 concentration, 5.2 µg/dL), and 7.0% (at mean T_4 concentration, 11.9 µg/dL). Sensitivity was 0.3 µg/dL. There was excellent correlation with a commer-

cial canine T_4 assay[d] (r^2 = 0.92). The T_4 reference range established by use of serum from 30 healthy pet cats was 2.4 to 4.6 µg/dL.

Definition of cases and controls—Cases were cats ≥ 6 years of age with a diagnosis of hyperthyroidism made on the basis of serum T_4 concentration ≥ 5.0 µg/dL and a report from the medical record or the questionnaire of 1 or more clinical signs, including weight loss, polyphagia, vomiting, polyuria and polydipsia, agitation, sleeping less than usual, patchy alopecia, unkempt hair coat, seeking cool areas to sit or sleep, and increased vocalization. Cats ≥ 6 years of age with a serum T_4 concentration ≤ 3.5 µg/dL served as controls.

Data analyses—Data obtained from the questionnaire were entered into databases[a,e,f] and analyzed by use of statistical software.[g] Characteristics of case cats were compared with those of control cats by use of the χ^2 statistic, *t* statistic for normally distributed continuous data, or Mann-Whitney *U* test for non-normally distributed continuous data. Continuous variables were compared by use of the Pearson correlation coefficient.

Food consumption patterns for 3 life stages (kitten [birth to 1 year of age]; young adult [> 1 to 7 years of age]; and older adult [> 7 years of age]) were evaluated. Categoric variables were constructed by use of the proportions of each cat's life and its entire lifetime, during which its diet was composed of > 75%, > 50% to ≤ 75%, > 25% to ≤ 50%, > 0% to ≤ 25% canned food, or all dry food by volume. Food can types for each life stage were identified by use of manufacturers' literature or Web sites. Food packaged only in cans with easy-open lids was classified as being from "definite pop-top cans," whereas food sold both in cans with easy-open lids and cans requiring openers was classified as being from "possible pop-top cans." For cats that ate combinations of food from definite pop-top cans and possible pop-top cans, the can type was designated as definite pop-top because the cats had known exposures to at least some food supplied in definite pop-top cans. A summary "lifetime" food can variable indicated consumption in any life stage of canned food packaged in definite pop-top, possible pop-top, or no cans.

Odds ratios (ORs), 95% CIs, and *P* values were determined for each potential risk factor by use of univariate logistic regression. Risk factors with values of $P < 0.20$ were also assessed by multivariate logistic regression. Risk factors that changed ORs for other factors in logistic models by ≥ 10% were considered potential confounders and retained in multivariate models. Values of $P < 0.05$ were considered significant. Trends in frequency of exposure for ordinal categoric risk factors in case cats were compared with those for control cats by use of the extended χ^2_{MH}.[16,e]

Results

Hospital prevalence—Medical records of 169,576 cats for 249,526 visits from 1978 to 1997 were retrieved from the VMDB. In each successive 5-year period, the age at first hospital visit increased ($P < 0.001$).

The hospital prevalence of feline hyperthyroidism ranged from 0.61/1,000 visits (95% CI, 0.41 to 0.81/1,000 visits) for the period of 1978 to 1982 to 29.64/1,000 visits (95% CI, 28.23 to 31.05/1,000 visits) for the period of 1993 to 1997 ($P < 0.001$). The age-adjusted hospital prevalence of feline hyperthyroidism ranged from 1.15/1,000 visits (95% CI, 0.87 to 1.43/1,000 visits) in the period of 1978 to 1982 to 20.24/1,000 visits (95% CI, 19.07 to 21.41/1,000 visits) in the period of 1993 to 1997 ($P < 0.001$; **Fig 1**).

In each age category, the hospital prevalence of feline hyperthyroidism increased from the period of 1978 to 1982 to the period of 1993 to 1997 ($P < 0.001$). In each 5-year period, the hospital prevalence of feline hyperthyroidism also increased with increasing age group ($P < 0.001$).

Over the 20-year period, 3,570 diagnoses of hyperthyroidism, 1,241 diagnoses of diabetes mellitus, and 426 diagnoses of renal insufficiency were made at the 9 veterinary school hospitals. The hospital prevalence of feline hyperthyroidism over 20 years was 21.05/1,000 visits (95% CI, 20.37 to 21.74/1,000 visits), whereas the hospital prevalence of diabetes mellitus was 7.32/1,000 visits (95% CI, 6.91 to 7.72/1,000 visits), and the hospital prevalence of renal insufficiency was 2.51/1,000 visits (95% CI, 2.27 to 2.75/1,000 visits). There was a significant ($P < 0.001$) trend in increasing hospital prevalence for each disease over the 20-year period (**Fig 2**). The rate of increase in the prevalence of hyperthyroidism was significantly ($P < 0.001$) greater than the increases in prevalence of the other 2 diseases.

Case-control study—Medical records of 642 cats assessed at the PUVTH between January 1, 1998, and August 15, 2000, that had serum T_4 concentration measured were reviewed. Of these, 535 (83.3%) cats ≥ 6 years of age that did not have a previous diagnosis of hyperthyroidism (eligible cats) were evaluated. Owners

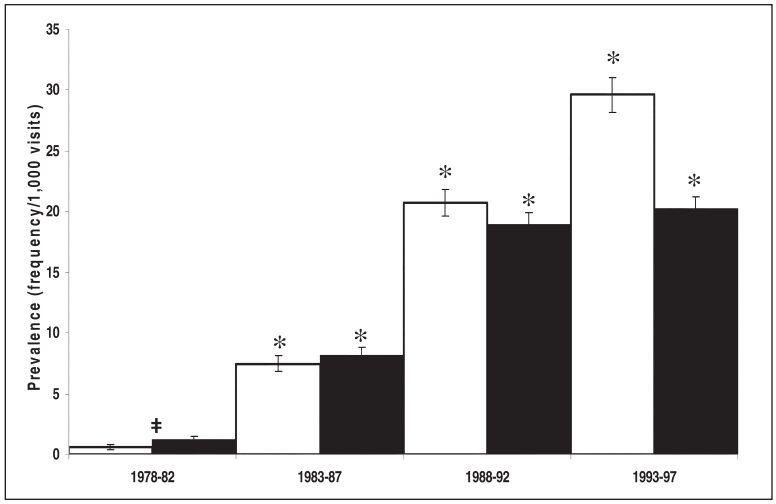

Figure 1—Hospital prevalence (open bars) and age-adjusted hospital prevalence (solid bars) of feline hyperthyroidism at 9 veterinary teaching hospitals from 1978 to 1997. Vertical lines indicate 95% confidence intervals. Trends are significant ($P < 0.001$). *Significantly ($P < 0.05$) different from reference category (‡).

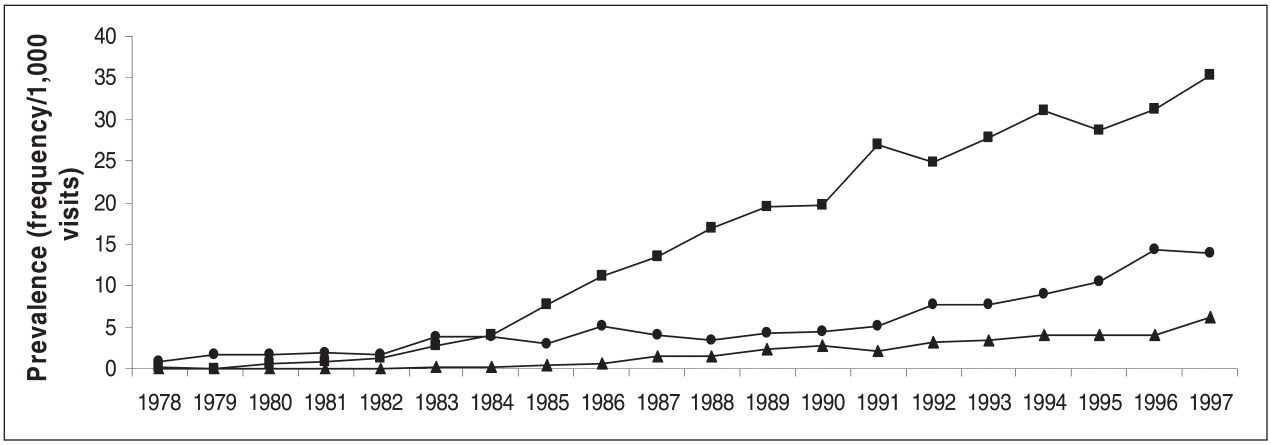

Figure 2—Hospital prevalence of hyperthyroidism (squares), diabetes mellitus (circles), and renal insufficiency (triangles) at 9 veterinary teaching hospitals from 1978 to 1997. Trends are significant ($P < 0.001$).

of 313 eligible cats completed questionnaires. On the basis of study criteria, 109 cats were cases and 173 were controls. The response rate was 34.8% (109/313) and 55.3% (173/313) for cases and controls, respectively ($P = 0.27$). Control cats had various clinical diagnoses, including cancer (n = 34 cats), renal or urinary tract disease (27), and gastrointestinal or hepatic disease (19). Ten control cats were identified as being in good health at the conclusion of the visit. The proportion of cases that were female (62.4%) was significantly ($P = 0.005$) different from that of controls (45.1%). All except 1 female cat had been spayed or neutered, and there was no significant difference in median age at the time of spay or neuter between case and control cats. There were no significant differences in breed distribution (mixed breed, purebreed cross, or purebreed), body condition (underweight, average, or overweight), or median weight as healthy adults between case and control cats. The median age at acquisition for case and control cats was 3.0 months. Mean ± SD age at the hospital visit of case (13.1 ± 2.6 years) and control cats (11.4 ± 3.1 years) was significantly ($P < 0.001$) different. Mean ± SD time owned of case (12.3 ± 2.9 years) and control cats (10.5 ± 3.6 years) was significantly ($P < 0.001$) different. Age and time owned were highly correlated ($r = 0.89$; $P < 0.001$). Case cats consumed a mean of 3.5 ± 1.7 diets over their lifetimes, whereas control cats consumed a mean of 3.1 ± 1.4 diets.

***Univariate analysis*—**The relative risk of hyperthyroidism for female cats was twice that for male cats (OR, 2.02; 95% CI, 1.24 to 3.30). Compared with purebreed cats, mixed-breed cats were nearly 3 times as likely to be hyperthyroid (OR, 2.91; 95% CI, 1.15 to 7.36). Each year of age increased the relative risk of hyperthyroidism by 21% (OR, 1.21; 95% CI, 1.11 to 1.32).

In each life stage, a diet that included canned food was associated with a higher relative risk of hyperthyroidism, compared with a diet that did not include canned food (**Table 1**). For cats that consumed > 50% to ≤ 75% canned food in their diet in the kitten or young adult stages, increased risk of hyperthyroidism was not significant, although few cats had this diet pattern. Because many owners reported that they fed their cats diets containing 50% canned and 50% dry food, the canned food categories were collapsed to include no canned food and < 50%, 50%, and > 50% canned food. Cats in each life stage had the highest ORs for developing hyperthyroidism when they consumed 50% canned food in their diets. Cats that consumed > 50% canned food over a lifetime had more than 3 times the relative risk of hyperthyroidism as did cats that ate only dry food. The relative risk for cats that consumed 50% canned food over a lifetime was more than 3.5 times higher than for cats that consumed only dry food, and cats that consumed < 50% canned food over a lifetime had nearly 3 times the relative risk of hyperthyroidism as cats that ate only dry food. In cats that consumed ≥ 50% canned food, compared with no canned food, the relative risk of hyperthyroidism increased with increasing length of time on this diet ($P < 0.001$).

Cats that consumed food from definite pop-top cans had significantly increased relative risk of hyperthyroidism (Table 1). Cats that ate food from definite pop-top cans at any time during life had nearly 5 times the relative risk of hyperthyroidism as cats that ate no canned food, whereas cats that ate food from cans with possible pop-tops had nearly 2.5 times the relative risk of hyperthyroidism. Cats had significantly increased relative risk of hyperthyroidism with each life stage in which they ate food from definite pop-top cans ($P = 0.01$) or from possible pop-top cans ($P = 0.001$). Each year of food consumed from cans with possible pop-tops was associated with a significantly increased relative risk. In cats that consumed food from definite pop-top cans, the relative risk of hyperthyroidism remained significantly ($P < 0.001$) increased with increasing length of time on this diet. All cats that consumed canned food ate food known to be packaged in pop-top cans only (definite pop-top cans) or ate food packaged in both pop-top cans and cans requiring openers (possible pop-top cans). Therefore, the ORs for hyperthyroidism associated with consumption of food from cans requiring openers only could not be calculated.

Cats that ate baby food when they were kittens or were fed baby food as a treat were nearly 5 times as likely to develop hyperthyroidism, compared with cats

Table 1—Univariate comparison of case and control cats for potential risk factors for hyperthyroidism

Variable	Odds ratio	No. (cases, controls)	95% Confidence interval	*P* value
Diet-related factors				
Kitten				
No canned food	1.00	35, 86	—	—
≤ 50% canned food	2.02	14, 17	0.90, 4.55	0.09
50% canned food	2.95	12, 10	1.17, 7.45	0.02
> 50% canned food	2.29	14, 15	1.00, 5.25	0.05
χ^2 test for trend				0.01
Young adult				
No canned food	1.00	30, 72	—	—
≤ 50% canned food	1.60	30, 45	0.85, 3.00	0.14
50% canned food	3.51	19, 13	1.54, 8.00	0.003
> 50% canned food	1.82	19, 25	0.88, 3.80	0.11
χ^2 test for trend				0.02
Older adult				
No canned food	1.00	22, 60	—	—
≤ 50% canned food	2.59	39, 41	1.35, 5.00	0.004
50% canned food	3.82	14, 10	1.48, 9.85	0.01
> 50% canned food	3.38	26, 21	1.59, 7.18	0.002
χ^2 test for trend				0.001
% Canned food fed over lifetime				
No canned food	1.00	19, 63	—	—
≤ 50% canned food	2.74	43, 52	1.43, 5.27	0.002
50% canned food	3.52	17, 16	1.50, 8.28	0.004
> 50% canned food	3.32	25, 25	1.56, 7.06	0.002
χ^2 test for trend				0.001
Years of ≥ 50% canned food consumption (categoric)				
No canned food	1.00	19, 63	—	—
> 0–3.75 y	3.32	15, 15	1.38, 8.00	0.01
> 3.75–8.0 y	3.11	15, 16	1.30, 7.43	0.01
> 8.0–12.5 y	3.11	15, 16	1.30, 7.43	0.01
> 12.5 y	5.64	17, 10	2.21, 14.35	< 0.001
χ^2 test for trend				< 0.001
Can-related factors				
Kitten				
No cans	1.00	35, 86	—	—
Possible pop-top cans	2.14	34, 39	1.12, 4.11	0.02
Definite pop-top cans	3.69	9, 6	1.09, 12.77	0.03
Young adult				
No cans	1.00	30, 72	—	—
Possible pop-top cans	1.97	55, 67	1.13, 3.43	0.02
Definite pop-top cans	2.67	20, 18	1.24, 5.74	0.01
Older adult				
No cans	1.00	22, 60	—	—
Possible pop-top cans	2.56	55, 58	1.40, 4.77	0.002
Definite pop-top cans	4.01	25, 17	1.83, 8.80	0.001
Lifetime* can type				
No cans	1.00	19, 63	—	—
Possible pop-top cans	2.46	52, 70	1.32, 4.61	0.005
Definite pop-top cans	4.76	33, 23	2.27, 9.96	< 0.001
No. of life stages on definite pop-top cans	1.57	105, 158	1.13, 2.18	0.01
No. of life stages on possible pop-top cans	1.43	105, 158	1.16, 1.77	0.001
Years on possible pop-top cans	1.12	105, 157	1.04, 1.22	0.003
Years on definite pop-top cans (categoric)				
No canned food	1.00	19, 65	—	—
> 0– 0.75 y	5.56	13, 8	2.01, 15.39	0.001
> 0.75–2.25 y	4.70	11, 8	1.66, 13.37	0.004
> 2.25 y	5.13	9, 6	1.62, 16.25	0.01
χ^2 test for trend				< 0.001

*Can type in any stage of cat's life.
— = Referent category.

Table 2—Multivariate model of risk factors for clinical hyperthyroidism in cats

Variable (No. of cases, controls)	Odds ratio	95% Confidence interval	*P* value
All cats (83, 134)			
Sex (female vs male)	1.33	0.73, 2.45	0.35
Age	1.21	1.08, 1.35	0.001
Lifetime* can type (vs no cans)			
Possible pop-top cans	1.56	0.74, 3.33	0.24
Definite pop-top cans	3.18	1.34, 7.56	0.01
Baby food fed when a kitten or as treat	4.44	1.05, 18.77	0.04
Female cats (64, 71†)			
Age	1.09	0.96, 1.24	0 . 1 9
Lifetime* can type (vs no cans)			
Possible pop-top cans	3.04	1.18, 7.81	0.02
Definite pop-top cans	4.38	1.49, 12.84	0.01
Male cats (40, 85)			
Age	1.28	1.09, 1.50	0.003
Lifetime* can type (vs no cans)			
Possible pop-top cans	1.21	0.47, 3.12	0.70
Definite pop-top cans	3.28	1.08, 9.95	0.04

*Can type in any stage of cat's life. †Baby food fed when a kitten or as a treat was removed from the stratified model because no female control cats ate baby food.

not fed baby food (OR, 4.71; 95% CI, 1.22 to 18.28). Dietary factors that had ORs that were not significant (ie, $P \geq 0.05$), yet met the criterion for inclusion in the multivariate analysis ($P < 0.20$), included eating cheese when a kitten (OR, 1.93; 95% CI, 0.75 to 4.98), salt added to cat food (OR, 2.72; 95% CI, 0.64 to 11.64), taking vitamins (OR, 1.83; 95% CI, 0.75 to 4.47), eating noncommercial foods (ie, home-cooked foods; OR, 1.52; 95% CI, 0.86 to 2.71), and having 4 or more diets over a lifetime (OR, 1.53; 95% CI, 0.90 to 2.57). Dietary factors that were not associated with risk of hyperthyroidism included eating most dairy products; dry kelp, onion, garlic, or other seasonings added to the cat's food; consumption of treats of canned fish or commercial treats; and hairball treatment.

Multivariate model—Retention of univariate risk factors with $P < 0.20$ in a logistic regression model revealed that consumption of food from cans with definite pop-tops, each additional year of age, and eating baby food when a kitten or as a treat were significantly associated with increased relative risk of hyperthyroidism, whereas increased risk associated with consumption of food from cans with possible pop-tops and female sex were not significant (**Table 2**). Because sex was a significant univariate risk factor and its OR changed by > 10% in the multivariate model, the multivariate model was stratified on the basis of sex. No female controls ate baby food, so this variable was removed from the stratified multivariate model. The risk of hyperthyroidism in females was significantly associated with consumption of canned food in possible pop-top cans and definite pop-top cans. In male cats, the risk of hyperthyroidism was significantly associated with age and consumption of canned food packaged in definite pop-top cans.

Discussion

The prevalence of feline hyperthyroidism in veterinary teaching hospitals increased significantly from

1978 to 1997 and at a faster rate than the prevalence of diabetes mellitus and renal insufficiency. The increase was not solely the result of aging of the cat population. The increase in prevalence was also not likely the result of increased laboratory testing for hyperthyroidism because most cats with hyperthyroidism have 1 or more easily recognized clinical signs and the diagnosis is seldom made on the basis of laboratory tests alone.[19] Feline hyperthyroidism was first reported in 1979; since that time, its prevalence has continued to increase. Initially, the high rate of diagnosis of hyperthyroidism may have been the result of increased awareness of the disease and subsequent diagnostic testing. Diagnostic tests for occult feline hyperthyroidism were described in the early 1990s.[20] The prevalence of feline hyperthyroidism has, however, continued to increase over a period during which no substantial advances in diagnostic testing or treatments for hyperthyroidism in cats were made. The 3 primary treatment modalities for hyperthyroidism (ie, antithyroidal medication,[21] surgery,[22] and radioactive iodine[23]) have been available since the mid 1980s.

To the authors' knowledge, this is the first study to examine the association between lifetime consumption of canned foods and risk of hyperthyroidism in cats. A significant association was found between hyperthyroidism and consumption of food from cans, particularly pop-top cans, and the risk was greater for female than male cats.

Although an association between diets with > 50% canned food and feline hyperthyroidism was reported in 2 earlier case-control studies,[5,6] lifetime diets were not evaluated. The first study examined the diets fed during the 5 years preceding a diagnosis of hyperthyroidism or other condition.[5] The second study obtained descriptions of the present diet and 1 previous diet.[6] In our study, owners were asked to describe their cats' diets from birth or time of acquisition to 1 year before their visit to Purdue University. With mean time owned > 10 years for case and control cats and a mean of 3.24 diets/cat, our study provided a more complete representation of a cat's lifetime diet.

The association of canned food consumption with development of hyperthyroidism suggests that possible causative agents may be found in food or can linings. At least 25 types of lacquers are used to line steel cans.[24] Can linings include epoxy resins, polyvinyl chloride organosols, and polyester; epoxy resins are most commonly used in cans that require openers, and organosol coatings are typically used in pop-top cans because they are more flexible.[25,26] **Bisphenol-A-diglycidyl ether (BADGE)** is used in an intermediate step in the epoxy-coating manufacturing process and is also used during heat treatment in the organosol-coating process.[26] Bisphenol-F-diglycidyl ether and novolac glycidyl ether are related compounds used during heat stabilization.[27] Migration of these compounds into foods, particularly foods with a high fat or oil content, has been detected.[25] Higher concentrations of migrated chlorhydroxy compounds of BADGE and bisphenol-F-diglycidyl ether have been found in high-fat foods from pop-top cans than in high-fat foods from other types of cans.[25,27]

Bisphenol-A-diglycidyl ether is cytotoxic and genotoxic in vitro[28]; it is a constituent of **bisphenol-A (BPA)** epoxy and organosol resins and is formed by the condensation of BPA and epichlorhydrin.[29] Bisphenol A has been detected in a variety of canned foods[30] and is classified as a weakly estrogenic endocrine disrupter[31] by the EPA. In rats, ingested BPA is eliminated primarily via glucuronidation; the percentage of BPA eliminated via this step is greater in female than male rats.[32] The glucuronidation step is slower in cats than in other species.[33,34] Bisphenol A reduces triiodothyronine binding to thyroid receptors in rat liver[35] and inhibits thyroid receptor-mediated transcription in a dose-dependent manner in vitro.[35] Interference with triiodothyronine binding may lead to increased TSH secretion and resultant increased thyroid hormone production, eventually leading to formation of goiter. Bisphenol A has been associated with many other effects,[36-41] including increased concentration of **vascular endothelial growth factor (VEGF)** in the uterus, vagina, and pituitary gland of rats.[42] The VEGF concentrations in thyroid glands of rats and mice that consumed iodine-deficient diets or were treated with antithyroidal drugs were higher than VEGF concentrations in thyroid glands of control animals.[43,44] Thyroid nodules in humans contain higher concentrations of VEGF than normal thyroid tissue.[45]

It is not known whether BADGE is present in canned cat foods; however, BPA has been detected in 15 canned cat foods.[46] Of 3 brands of canned cat food produced in the United States, 2 had the highest concentrations of BPA reported in that study.[46]

Commercial cat food cans typically require an opener or are pop-top cans with an easy-open lid; these cans have different interior coatings because pop-top cans are more flexible. Canned cat foods,[47] particularly those in pop-top cans, have a higher fat content than dry foods. At least 1 manufacturer marketed cat food in pop-top cans beginning in the early 1980s. Since then, the packaging of cat foods in smaller pop-top cans has increased. As can size decreases, the surface area per weight of food in contact with interior can surfaces increases. It is possible, therefore, that cats today are being exposed to higher amounts of fat-soluble contaminants in food than in the past.

In our study, 19 hyperthyroid cats (22.9%) were reportedly always fed dry food. Several explanations for this finding may be offered. It is possible that the diet history was inaccurate. A multifactorial etiology of hyperthyroidism may be implicated in which some factors, such as consumption of foods from pop-top cans, may be sufficient but not necessary for development of disease. It is also possible that chemicals in the linings of some dry cat food bags migrated into foods in a similar fashion to that described for canned foods. Bisphenol-A-diglycidyl ether and a related chemical migrated into fish products for human consumption that were packaged in cans and pouches.[48] The pouches were made of multiple layers of plastic and aluminum film, and the chemicals were believed to have originated in the glue used to laminate the films.[48] However, even if chemicals such as BADGE are found in the linings of dry cat food bags, these chemicals are less likely to migrate into dry foods because dry

foods have a lower fat content than canned foods. The lower water content of dry food would also not favor migration of bag lining chemicals into dry food.

The significant epidemiologic association found between female sex and hyperthyroidism in cats (univariate analysis only) has not been previously reported. Two other epidemiologic studies[5,6] matched case and control cats on the basis of sex. In an unmatched study,[7] there was a 30% increased risk of hyperthyroidism for female cats that was not significant. The risk of hyperthyroidism in female cats may be similar to the risk of toxic nodular goiter in women; older women have been reported to have 3 to 5 times greater risk for developing toxic nodular goiter, compared with men.[49] Because glucuronidation is a slow process in cats[33,34] and if ingested BADGE or other contaminants are eliminated via glucuronidation to a greater extent in female than male cats, as is the case for BPA in female rats,[32] female cats consuming canned foods may be at greater risk of hyperthyroidism.

Limitations of this case-control study include potential inaccuracy of owner recall of diet history and failure of some owners to provide food labels. However, such errors should be nondifferential between cases and controls and, if anything, bias ORs toward the null. Systematic bias may have occurred if owners suspected that they were participating in a study designed specifically to determine an association between diet and hyperthyroidism. To avoid this type of potential bias, the questionnaire indicated that the purpose of the study was to examine lifetime nutrition and feline health. Another potential concern was the fact that pop-top cans may have been a surrogate for other, as yet unknown, risk factors. For example, feeding food from pop-top cans could have been related to an owner's socioeconomic status and, therefore, other owner management practices that were not measured. Because feline hyperthyroidism appears to be a disease associated with host, environmental, and diet-related risk factors, it would be nearly impossible to be certain that all potential confounding factors were included in 1 multivariate logistic model.

Results of our study suggest that consumption of canned foods increases the risk of developing hyperthyroidism in cats and are consistent with results of previous studies. Until this association is verified, we suggest that cat owners limit the feeding of foods packaged in pop-top cans when possible. If owners follow these recommendations, however, a reduction in the incidence of hyperthyroidism in cats may not be seen for many years because cats presently consuming foods in pop-top cans may have already developed irreversible thyroid damage.

[a]Microsoft Excel 97 SR-2, Microsoft Corp, Redmond, Wash.
[b]SAS release 8.01, SAS Institute Inc, Cary, NC.
[c]Immulite total T4, Diagnostics Products Corp, Los Angeles, Calif.
[d]Canine T4 Coat-A-Count, Diagnostics Products Corp, Los Angeles, Calif.
[e]Epi Info, version 6.04b, Centers for Disease Control, Atlanta, Ga.
[f]Microsoft Access 97 SR-2, Microsoft Corp, Redmond, Wash.
[g]SPSS release 9.0.0, SPSS Inc, Chicago, Ill.

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