# Evaluation of euthyroid senior cats with and without palpable thyroid nodules for the development of hyperthyroidism

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### Abstract

**Aims:** To find the prevalence of palpable thyroid gland nodules and their association with the development of hyperthyroidism in cats near 10 years and older. To determine whether euthyroid cats with thyroid nodules are subsequently diagnosed with hyperthyroidism within one year of detection of the nodule by palpation.

Methods: Cats 10 years of age or older that had undergone cervical palpation and had total serum total thyroxine (TT<sub>4</sub>) concentrations measured were identified by a retrospective search of hospital and laboratory patient databases. In addition, during a six-year period cats 10 years and older examined at the Massey University Veterinary Teaching Hospital were prospectively enrolled in the study to have scheduled re-examinations after their first visit. The study comprised; a patient history, clinical examination, thyroid gland palpation and measurement of the TT<sub>4</sub> concentration. Cats were included in the study until they died, were diagnosed with hyperthyroidism or until conclusion of the study. Kaplan-Meier survival curves were generated to calculate the median time to detection of hyperthyroidism, the median time to detection of thyroid nodules, the proportion of cats developing hyperthyroidism within one year. Differences in the survival time between cats with and without thyroid nodules were compared using the logrank test.

**Results:** Data were collected from 170 cats between 10 to 21.1 years of age. A 48% prevalence of palpable thyroid nodules was documented at the first examination. Ten of 25 (40%) euthyroid cats with a thyroid nodule on the first examination, eventually developed hyperthyroidism. Cats with a palpable thyroid nodule were 3.1 times more likely to be diagnosed with hyperthyroidism than cats without a palpable nodule. Euthyroid senior (10 years of age and older) cats with palpable thyroid nodules were diagnosed with hyperthyroidism significantly earlier (median 460 days vs. 1095 days, p=0.001) than those without a palpable thyroid nodule. The probability of a euthyroid cat with a palpable thyroid nodule developing hyperthyroidism within one year was 0.22 (95% CI 0.05-0.40). Only 13% (6/47) of senior cats without a detectable thyroid nodule subsequently developed hyperthyroidism but at least one year elapsed before the diagnosis was made. Senior female cats were significantly (p=0.008) more likely to be diagnosed with hyperthyroidism than male cats.

**Conclusions:** Euthyroid cats with thyroid nodules were significantly more likely to be diagnosed with

hyperthyroidism and clinical signs of hyperthyroidism and laboratory confirmation occurred sooner in this group than in cats without thyroid nodules. Senior female cats were more likely to be diagnosed with hyperthyroidism than senior male cats.

**Clinical Relevance:** These findings provide a guide as to when veterinarians can reasonably expect to make a diagnosis of hyperthyroidism after a thyroid nodule is palpated and support the American Association of Feline Practitioner's current guidelines for how often senior cats with thyroid nodules should be reevaluated for hyperthyroidism. It is rare for a senior cat without a thyroid nodule to be diagnosed with hyperthyroidism within one year of measurement of a TT<sub>4</sub> concentration in the reference range for healthy cats. Such euthyroid cats without palpable thyroid nodules should be re-evaluated for hyperthyroidism at yearly intervals. Overt hyperthyroidism may not occur despite the presence of a thyroid nodule. In New Zealand senior female cats are more likely to develop hyperthyroidism than senior male cats.

**Key Words:** Feline hyperthyroidism, cervical nodule, senior monitoring

### Introduction

Hyperthyroidism is the most common endocrinopathy diagnosed in senior cats with 95% of cases documented in cats over 10 years of age (Peterson 2000). The majority of cats have thyroid hyperplasia or benign nodular adenoma(ata), autonomously secreting thyroid hormones independently of the normal homeostatic mechanisms. The excess thyroid hormone concentration results in widespread multisystemic signs of disease (Peterson *et al.* 1979; Holzworth *et al.* 1980). While several risk factors have been identified for the development of hyperthyroidism, the underlying cause for the primary thyroid pathology is not known (Gerber *et al.* 1994; Kass *et al.* 1999; Martin *et al.* 2000; Olczak *et al.* 2004).

At least 80% of cats diagnosed with hyperthyroidism have an enlarged thyroid gland resulting in a palpable ventral cervical nodule (Broussard *et al.* 1995). While the normal feline thyroid gland usually cannot be palpated, a population of euthyroid cats with palpable nodules of the thyroid gland has been identified. Up to 59% of euthyroid cats have palpable thyroid nodules (Norsworthy *et al.* 2002b). This group may represent early subclinical hyperthyroidism (Wakeling *et al.* 2007). Such cases are considered at risk for developing hyperthyroidism. Careful and regular monitoring for hyperthyroidism and possible preemptive thyroidectomy has been suggested for this group of cats (Graves and Peterson 1990; Norsworthy

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*et al.* 2002a). Little is known regarding how long before a diagnosis of hyperthyroidism is made in this group of cats after the detection of the nodule or if progression to hyperthyroidism is inevitable. More information is required to help determine the intervals required between each successive evaluation for hyperthyroidism and if pre-emptive treatment such as surgery is required for these cats.

The aims of this study were to determine the prevalence of palpable thyroid nodules in geriatric cats examined at the Massey University Veterinary Teaching Hospital and the association of the presence of a nodule with the future diagnosis of hyperthyroidism. Our goal was to determine if the majority of euthyroid senior cats with palpable thyroid nodules were diagnosed with hyperthyroidism within one year of the examination where the nodule was first detected. If the majority of euthyroid senior cats with palpable thyroid nodules were diagnosed with hyperthyroidism within one year of the initial examination where the nodule was detected then cats with thyroid nodules could require veterinary evaluation for hyperthyroidism more often than the current guidelines of the American Association of Feline Practitioners which recommends clinical evaluation for hyperthyroidism every six months and measurement of the serum total thyroxine every six to 12 months (Pittari et al. 2008).

#### **Materials and methods**

#### **Experimental design**

The study utilised both retrospective data and data from a prospective study. The Massey University VeterinaryTeachingHospital and laboratory databases were searched for cats 10 years and older that had undergone cervical palpation and determination of  $TT_4$  concentrations performed from March 1996 until December 2008. From July 2003 to June 2009, cats examined at the Massey University Veterinary Teaching Hospital aged 10 years of age and older were enrolled in the study to have scheduled examinations including cervical palpation at 6-monthly intervals.

Each examination included a detailed patient history, clinical examination including cervical palpation conducted according to the method described by Peterson (2000) and a blood sample for measurement of serum TT<sub>4</sub><sup>3</sup> concentration. Ten veterinarians, each of whom had at least five years experience in veterinary practice, were involved in collecting the patient history and performing the physical examinations. Cats were diagnosed as hyperthyroid based on a combination of history, clinical signs and a measured TT<sub>4</sub> concentration above the upper limit of the laboratory reference range of 20-40nmol/L, and a response to treatment. If required multiple measurements of  $TT_4$ were performed two or more weeks later if there was doubt regarding the thyroid status of a cat, such as cats with  $TT_4$  concentrations between 40–65 nmol/L. Alternative tests for hyperthyroidism were left to the discretion of the individual clinicians.

Cats diagnosed with hyperthyroidism were excluded from any further involvement in this study and owners were offered staging and treatment options. Cats that were euthyroid were scheduled for a repeat evaluation and measurement of a TT<sub>4</sub> concentration every six months or sooner if the veterinarian or owner felt the cat was developing signs of hyperthyroidism. Owners were reminded of the required examination date by phone or mail. Cats with severe or rapidly progressive disease that were not expected to live more than six months were excluded from the study. Cats strongly suspected to be hyperthyroid at enrolment or were diagnosed as hyperthyroid within one month were excluded from long-term follow up. Cats were re-examined until they died, were diagnosed with hyperthyroidism, lost to follow up or were still fit and well at conclusion of the study. Post mortem examination was requested from the owners of all cats that died during the study and a post mortem completed if they agreed.

#### Ethical approval

All components of this study were approved by the Massey University Animal Ethics Committee and conformed to 'The code of ethical conduct for the use of live animals for teaching and research' as approved under the New Zealand 'Animal Welfare Act 1999'. Owners provided informed written consent and voluntary withdrawal at any time was possible. To encourage participation and compliance the owners were not charged for participating in the study.

#### Statistical analysis

All data were tabulated in Excel 2007 (Microsoft, Redmond, WA, USA). Statistical comparisons were made using PASW Statistics 18 (IBM Corporation, Armonk, New York, USA). Kaplan-Meier survival curves were generated to calculate the median time to detection of hyperthyroidism and the median time to detection of a thyroid nodule, one-year survival times and confidence limits. Differences in survival between cats with and without thyroid nodules were compared using the log-rank test. A Chi-squared test was used to compare the gender distribution of cats that developed hyperthyroidism with those that did not develop hyperthyroidism. A p value of < 0.05 was considered significant.

## Results

During the study, data were collected from 170 cats. Of these, 98 were recruited from the retrospective examination of case records and 72 were prospectively enrolled.

Overall there were 95 females (89 neutered, 6 entire) and 75 males (71 castrated, 4 entire). The study population was composed of 160 domestic shorthair cats, 3 Siamese, 2 Burmese and a single Abyssinian, American Shorthair, Birman, Oriental and a Tonkinese.

At study enrolment the mean age of cats was 13.4 years (SD 2.6 years, range 10–21.1 years). A palpable thyroid nodule was present in 82 of 170 (48%) cats at enrolment. A diagnosis of hyperthyroidism was made concurrently in 32 of the 82 (39%) cats with palpable nodules. Only four of the 88 (4.5%) cats without palpable thyroid nodules were diagnosed with hyperthyroidism at this time.

<sup>&</sup>lt;sup>3</sup> Chemiluminescent immunoassay T<sub>4</sub> assay (reference range 20-40 nmol/l). Reference range establish by manufacturer. New Zealand Veterinary Pathology, Institute of Veterinary, Animal and Biomedical Sciences, First floor, Massey University, Tennent Drive, PO Box 325, Palmerston North, 4440, New Zealand.

Of the 134 euthyroid cats, 62 cats were lost to follow up and 72 cats were recruited into the study for a total of 118 re-evaluations. Forty (56%) were male and 32 were female. Of these 72 cats, 25 (35%) had a thyroid nodule palpated at the time of enrolment. The median re-evaluation interval for these 72 cats was 282 days (range two – 1780 days, SD 355), this re-evaluation interval was 99 days over the planned re-evaluation interval of every 6 months. Of the 118 re-evaluations, 40 (34%) were conducted before six months, because clinical signs of hyperthyroidism were suspected by the primary care veterinarian or the cats' owners. Sixteen evaluations (14%) occurred between six to nine months and 62 (53%) evaluations occurred more than nine months after the last examination.

Of the 25 euthyroid cats with a thyroid nodule at the time of enrolment, 10 neutered female cats (40%) developed hyperthyroidism over a median time of 460 days (95% CI 606–1054, range seven to 845 days). One of these 10 cats presented earlier than their next scheduled six monthly evaluation due to clinical signs consistent with hyperthyroidism, 100 days after the last re-evaluation. The 25 cats with a thyroid nodule detected at the first visit presented for 40 re-evaluations ranging from two to 1780 days apart. Fourteen of these cats were reevaluated once, eight cats were re-evaluated twice, two cats were re-evaluated three times and one cat was reevaluated four times. Twelve re-evaluations occurred within the study plan for a six-month period, four reevaluations occurred between six to nine months, and 24 re-evaluations occurred at varying intervals over nine months. Nearly half (16 of 40) re-evaluations occurred no more than three months over the due date. The median re-evaluation interval for these 25 cats was 141 days over the planned revaluation interval of 6 months. Fifteen cats with thyroid nodules remained euthyroid during the study period, with 10 of the 15 dying from unrelated causes. Two cats remained euthyroid for 811 and 1295 days. Their palpated thyroid nodule was palpated over 523 and 727 days before resolving over 288 and 565 days respectively. The remaining 13 cats with thyroid nodules were studied for two to 2829 days (median 489 days) and did not become hyperthyroid. The probability of a euthyroid cat with a palpable nodule developing hyperthyroidism within one year was 0.22 (95% CI 0.05-0.40).

Forty-seven cats without a thyroid nodule at enrolment were studied for a median period of 549 days (SD 492 days), with 78 re-evaluations ranging from two to 1639 days apart. Twenty-five cats had one re-evaluation, 16 cats had two re-evaluations, five cats had three reevaluations and one cat had six re-evaluations. Twentyeight of the re-evaluations occurred earlier than the planned six months, 12 re-evaluations occurred between six and nine months, and 38 re-evaluations occurred after nine months. Six cats without nodules (13%) developed hyperthyroidism over a median time of 1095 days (range 407-1639 days) which was significantly longer than cats with detected nodules (p=0.001). Confidence intervals around the median could not be calculated because the median survival time was not reached. No cat without a thyroid nodule was diagnosed with hyperthyroidism within one year of the first examination. Three of these six cats were

euthyroid six months or less prior to the diagnosis of hyperthyroidism. The other three cats were euthyroid nine months or more before the diagnosis of hyperthyroidism. Four of the six cats without nodules that developed hyperthyroidism were neutered females, all with a thyroid nodule detected before or at the time of the diagnosis of hyperthyroidism.

Amongst the 47 cats that were investigated in which no nodule was palpated at enrolment, 12 cats had a nodule palpated at a later examination. The median time to palpation of a thyroid nodule was 636 days (95% CI 958–1790) (range 51–1300 days). Two of the 12 were diagnosed with hyperthyroidism at the time the nodule was palpated at 407 and 1300 days after enrolment. Another two of the 12 cats, in which nodules were palpated 648 and 719 days after enrolment were diagnosed with hyperthyroidism 14 and 602 days respectively after the nodules were palpated. Amongst the 34 cats in which a nodule was never palpated two were diagnosed with hyperthyroidism 889 and 1639 days after enrolment.

Median time to diagnosis of hyperthyroidism in euthyroid cats with thyroid nodules was significantly earlier than euthyroid cats without a thyroid nodule (460vs. 1095 days, p = 0.001, Figure 1). Euthyroid senior cats with thyroid nodules were 3.1 times more likely to develop hyperthyroidism than cats without thyroid nodules. In 75% of the euthyroid cats with thyroid nodules that subsequent developed hyperthyroidism, the period from enrolment until diagnosis exceeded 459 days (95% CI 246–671 days).

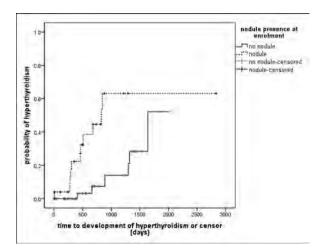
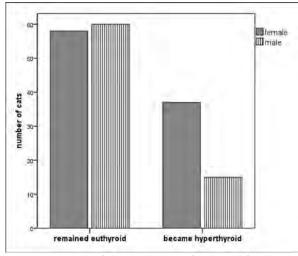


Figure 1. Kaplan-Meier analysis showing the probability of being diagnosed with hyperthyroidism over time for cats over 10 years of age according to the presence (dotted) or absence (solid) of a palpable thyroid nodule. Cats with thyroid nodules were significantly more likely to develop hyperthyroidism (p=0.001). In 75% of euthyroid cats with thyroid nodules, the period from enrollment until diagnosis with hyperthyroidism exceeded 459 days (95% CI 246–671). The probability of a cat with a thyroid nodule being diagnosed with hyperthyroidism within one year was 0.22 (95% CI 0.05–0.40). No cat without a thyroid nodule was diagnosed with hyperthyroidism within one year.

Within the group of 72 cats that were studied prospectively, female cats were diagnosed with hyperthyroidism significantly more frequently than expected if hyperthyroidism were equally likely in both sexes (p=0.003). Fourteen of the 16 (88%) cats

that became hyperthyroid were female compared with 28 of 56 that did not develop hyperthyroidism. Female cats were also significantly more frequently diagnosed with hyperthyroidism than expected (p=0.008) within the entire group of 170 cats studied. In this group 37 of the 52 (71%) cats that were or became hyperthyroid were female compared with 58 of 118 that were euthyroid (Figure 2).



**Figure 2.** Graph of the distribution of male and female cats amongst 118 cats that were euthyroid during the study and 52 cats that were or became hyperthyroid during the study. Female cats were significantly more frequently diagnosed with hyperthyroidism than expected (p=0.008).

Post mortem data were available on 27 of 103 (26%) cats that were dead at conclusion of the study. Five of these 27 (19%) cats were hyperthyroid. Fifteen of these 27 (56%) cats had gross thyroid enlargement at post mortem. On histologic examination, all 15 cats were diagnosed with thyroid adenomas. Seven of these 27 (26%) cats had parathyroid gland enlargement all due to renal secondary hyperparathyroidism which was clinically and biochemically evident before death. All seven cats had concurrent thyroid and parathyroid nodules. The results of the last known clinical thyroid palpation correlated to gross pathology findings in 85.2% (23 of 27) of cases. The 4 discordant results were in cats recorded to have no palpable thyroid nodule at the last check, however a thyroid nodule was found at post mortem. The difference was likely due to the long time (median 785 days, range 775-1070) between the last clinical examination and post mortem and the likely development of a thyroid nodule in the interim.

#### Discussion

This study determined a lower prevalence of thyroid nodules (48%) compared to a 65% prevalence in a study of 155 cats between five and 21 years of age followed for up to five years by Norsworthy *et al.* (2002b). This finding was surprising as geriatric cats usually have a higher prevalence of thyroid nodules than younger cats. Unless the thyroid nodules were very small it is unlikely that thyroid nodules were missed as all examiners were experienced and adept at palpation. Bias was introduced into this study by recruiting cats where the results of thyroid palpation and  $TT_4$  concentrations known. The true hospital prevalence

of thyroid nodules is likely to be overestimated for these reasons.

A recent study (Norsworthy et al. 2002a) followed 40 euthyroid cats with and without thyroid nodules with sequential examinations days to months to years apart and diagnosed six (15%) with overt hyperthyroidism 11 to 31 (median 15) months later. All six hyperthyroid cats lost at least one kilogram and three had an elevated thyroxine concentrations. The present study identified a 40% likelihood that a euthyroid cat with a thyroid nodule would become hyperthyroid. This difference is best explained by the study population of cats being older, all having thyroid nodules, and were examined for up to 7.8 years. Increasing age and thyroid size are known risk factor for hyperthyroidism (Broussard et al. 1995, Norsworth et al. 2002b, Boretti et al. 2009). Bias was also introduced into the present study by recruiting cats that had laboratory determination of total TT<sub>4</sub> and results of cervical palpation record. The TT<sub>4</sub> reference range used in this study was lower than the 13-67 nmol/L reference range used by Norsworthy et al. 2002a. The basal  $TT_4$  concentration is above the 65 nmol/L reference range in 90-98% of hyperthyroid cats (Feldman and Nelson 1996). The 40 nmol/L  $TT_4$ upper cut-off is relatively low compared to the more traditional values of 55 to 65 nmol/L in other studies using a comparable assay. The reference range used in this study was determined by the manufacturer of the TT<sub>4</sub> assay. The use of this lower upper limit in the present study likely resulted in a higher sensitivity, but lower specificity and potentially more false positives. The exact sensitivity and specificity of lower  $TT_4$  cut-offs are not well reported. It is generally recommended that veterinarians use the TT<sub>4</sub> reference range independently established via their laboratory for each individual assay, rather than rely on results in the literature (Feldman and Nelson 1996).

For these reasons it is very likely that the 40% likelihood that a euthyroid cat with a thyroid nodule will become hyperthyroid is an overestimation of the true hospital population risk.

While other non- $TT_4$  tests (such as  $T_3$  suppression testing and thyroid scintigraphy) were allowed for the diagnosis of hyperthyroidism in this study, none were performed. A validated free  $T_4$  was not readily available in New Zealand at the time of this study. It is possible that early mild cases of hyperthyroidism were missed for these reasons, however this is less likely given the low upper cut-off for  $TT_4$  used.

Progression to hyperthyroidism is not inevitable despite the presence of a palpable thyroid nodule. We documented 15 euthyroid cats with thyroid nodules that did not develop hyperthyroidism for up to 2829 days after examination. While 40% of euthyroid cats with thyroid nodules eventually developed hyperthyroidism, these cases were not typically diagnosed in the short term (median 460 days). From this study a palpable thyroid nodule alone in a euthyroid senior cat is an insufficient criterion to warrant pre-emptive thyroidectomy.

It is interesting that all 10 euthyroid cats with thyroid nodules that developed hyperthyroidism and all four euthyroid cats that developed a nodule followed by clinical signs of hyperthyroidism were neutered females. While most studies have shown no gender predisposition to develop hyperthyroidism (Broussard *et al.* 1995; Kass *et al.* 1999; Peterson 2000), a recent study in New Zealand showed female cats were 3.3 (95% CI 1.2–9) times more likely to be diagnosed with hyperthyroidism (Olczak *et al.* 2004). Our data showed a similar bias, with female cats two times more likely than male cats to develop hyperthyroidism. Our findings support a predisposition for senior female cats in New Zealand to be diagnosed with hyperthyroidism.

The size of the thyroid gland was not measured in this study. The likelihood of hyperthyroidism increases with increasing thyroid size (Norsworth *et al.* 2002b; Boretti *et al.* 2009). All cervical masses were assumed to be thyroid, however parathyroid enlargement, or other masses can cause false positives (Feldman and Nelson 1996). We assumed that once a cat developed hyperthyroidism that the cat remained hyperthyroid. Hence, if a cat was euthyroid it was assumed that that individual had always been euthyroid regardless of the interval between evaluations for hyperthyroidism. However, the authors acknowledge that fluctuations of a hyperthyroid cat's  $TT_4$  concentration into and above the reference range over time can occur (Peterson *et al.* 2001).

The cause of resolution of the palpable cervical nodule in two cats is unknown. Histology was not performed in these cases, thus no firm conclusions about the nature of the cervical mass palpated were possible. Possible reasons include an error in interpretation of enlargement of the thyroid due to parathyroid changes or an error in interpretation by the examiner (Feldman and Nelson 1996). Each cats was re-evaluated by the same veterinarian. The majority of cervical nodules identified in the cats at post mortem examination were due to thyroid gland enlargement rather than parathyroid gland enlargement. There was generally good agreement between the last clinical thyroid palpation status and the gross findings at post-mortem. All cats with parathyroid gland enlargement had overt biochemical evidence of renal disease, allowing secondary renal hyperparathyroidism to be a putative cause for a cervical nodule. While we assumed each cervical nodule to be thyroid in origin, parathyroid or other causes are possible. Parathyroid enlargement is likely to be reasonably common given the senior population of cats and the high prevalence of renal disease in this group.

We also assumed that cats involved in this study would be brought in for veterinary evaluation including assessment for hyperthyroidism sooner than 6 months if their owners noticed any signs of disease. Veterinarians participating in this study were actively encouraged to re-evaluate participating cats for hyperthyroidism sooner than six months if required. While efforts were made to encourage owners to bring their cats back for the six-monthly evaluations, cats that went longer than the planned re-examination date were assumed to be healthy during the "overdue" period. They may or may not have been healthy. The authors concluded that acceptable adherence to the study design was obtained when each reevaluation was no more than three months overdue. Overall, there was poor compliance with the study design with 62 of 118 (53%) evaluations occurring more than three months overdue, and 11 of 16 (69%) of cats that developed hyperthyroidism having their final evaluation were more than three months beyond the due date. Hence, it was likely that many cats may have developed hyperthyroidism well before the diagnosis was made. However, since monitoring intervals were similar between cats with and without thyroid nodules, we were confident that cats with thyroid nodules developed hyperthyroidism more frequently and sooner than cats without thyroid nodules. The progression from euthyroidism to hyperthyroidism is likely a gradual one, and this study was not able to determine exactly the first day signs of hyperthyroidism occurred. The results provide a guide as to when veterinarians might reasonably expect to make a diagnosis of hyperthyroidism in practice and are a guide for future studies.

Given the study duration and age of the cats involved, a large number of cases were lost to follow up or died during the study. There was difficulty in encouraging owners to bring their cats back for evaluations despite reminders and incentives. There was poor owner compliance which resulted in the wide confidence intervals and this result is a recognised weakness of this study. Repeating this study in senior cats housed in a colony would be an ideal way to guarantee that all examinations and evaluations are conducted on time.

The study population was not a random sample of the feline population. This is because the study only included cats belonging to owners who would bring their cat to the community practice of a veterinary teaching hospital. Many clients only use the hospital when their cats are severely ill and use other practices for routine health care examinations. The measures of prevalence in this study are likely to be overestimates of the true prevalence in the overall feline population because of the study population examined.

Euthyroid cats with palpable thyroid nodules are predisposed to develop hyperthyroidism which occurs earlier in cats without palpable thyroid nodules. It is rare for euthyroid senior cats without palpable thyroid nodules to be diagnosed with hyperthyroidism within one year of measurement of serum TT<sub>4</sub> concentration in the reference range. Progression to hyperthyroidism may not occur therefore pre-emptive thyroidectomy of euthyroid senior cats with a thyroid nodule is not indicated. The authors agree clinicians should use the American Association of Feline Practitioner's Senior Cat Guidelines euthyroid cats with thyroid nodules. Such cats should have clinical evaluation for hyperthyroidism every six months and measurement of serum total thyroxine every six-12 months (Pittari et al. 2008). However yearly clinical and laboratory evaluation is indicated for euthyroid senior cats without a palpable thyroid nodule.

#### **Acknowledgements**

The authors gratefully thank the New Zealand Companion Animal Society and the New Zealand Companion Animal Health Foundation for funding this study, Boyd Jones and Linda Abraham for their help with presentation of the manuscript, Neil Marshall, Cathy Dyer, Helen Orbel, Ros Carslake, Nick Cave, Angus Fechney and Dawn Kingsbury for their assistance, Janice Bridges for data entry, the staff of Massey University Veterinary Teaching Hospital, and the owners of the cats.

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