Acta Oncologica 29 (1990) Fasc. 1

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INCIDENCE OF SPORADIC AND FAMILIAL MEDULLARY THYROID CARCINOMA IN SWEDEN 1959 THROUGH 1981

A nationwide study in 126 patients

U. BERGHOLM, H.-O. ADAMI, M. TELENIUS-BERG, H. JOHANSSON, E. WILANDER, and the Swedish MCT study group

Abstract

Medullary thyroid carcinoma (MTC) was identified in 276 patients (in 27 diagnosed at autopsy) by a review of virtually all 6513 notifications of primary thyroid cancer ot the National Cancer Registry in Sweden 1959 through 1981. The diagnosis was confirmed in 268 of the 276 cases by histophatological and histochemical reexamination. Anamnestic data and morphological characteristics indicated that 208 (75%) patients had sporadic and 68 (25%) familial MTC. The mean ages at diagnosis of these two groups were 57.0 and 42.6 years respectively. The age-standardized incidence rate per 10^5 inhabitants was 0.18 for males and 0.23 for females. The age-specific incidence of sporadic MTC increased markedly with age, whereas no unequivocal rise was found after the age of 20 for familial disease. Standardized morbidity ratios (SMR), calculated separately for each of the six Swedish health care regions, revealed a roughly two-fold and mostly non-significant geographical variation in the occurrence of sporadic MTC. SMR for familial disease varied, however, between 0 and 306 and deviated highly significantly from the national average in four of the six regions. Regional differences in diagnostic intensity were considered unlikely as the sole explanation of this finding.

Key words: Medullary thyroid carcinoma, sporadic type, familial type, incidence.

Medullary thyroid carcinoma (MTC) was first described as a clinico-pathological entity by Hazard in et al. in 1959 (1). In 1961 Sipple (2) reported on an association between the occurrence of phaeochromocytoma and thyroid carcinoma. Williams (3) demonstrated in 1966 that MTC derives from the calcitonin-producing parafollicular C cells. The disease occurs both in a sporadic and in a familial form, the latter inherited as a dominant autosomal disorder (4–5).

MTC is a rare disease and there have been only few investigations of the incidence rate in a defined population (6–7). The estimated proportion of MTC among all malignant tumours of the thyroid has varied between 3 and 10% (6–10). The familial form has been claimed to account for 10–25% of all MTC cases (7, 9–10. Most published data, however, derive from hospital-based series and are therefore difficult to generalize.

The aim of the present study was to determine the incidence rate of sporadic and familial MTC in the total Swedish population by age, gender and geographical area during the period 1959–1981.

Material and Methods

The Swedish Cancer Registry. Since 1958 all physicians in hospitals and other establishments for medical treatment in Sweden must report to the National Cancer Registry all cases of diagnosed cancer. The majority of cases are notified in two reports, one from the clinician and one from the pathologist (11–12). The pathologist's report also includes a morphological description of the tumour and in most instances a specified histopathological diagnosis. The incidence rates published annually by the Cancer Registry (13) also include cases of cancer found incidentally at autopsy. All patients with thyroid cancer are registered in the Cancer Registry under the same code

Accepted for publication 15 October 1988.

number, according to the International Classification of Diseases (14).

Identification of patients with MTC. All reports from the pathologists to the Cancer Registry concerning notified cases of thyroid cancer (n=6513) during the period of study (1959–1981) were scrutinized. We excluded the first year of cancer registration (1958), as it was assumed that the reporting would be incomplete. According to the reports, 822 cases were impossible to classify and required further investigation by reading the original pathologist's report. Also investigated further were 364 tumours described as solid, squamous cell, spindle cell, or small cell anaplastic carcinomas, where a finding of MTC could be expected (1, 15). A histopathological reexamination of the tumour specimen was necessary in 85 of those 1186 not classifiable cases.

From the review we eventually identified a total of 286 patients who were suspected as having MTC, and tumour specimens from all of them were reexamined histologically and histochemically. Thirty-one of these patients were excluded after the histophathological reexamination, which revealed that they had follicular (8 cases), papillary (3 cases), anaplastic (6 cases) or non-classifiable (7 cases) tumours; seven of the 31 patients had MTC, but their disease was primarily diagnosed before 1959. In addition to the 255 remaining patients—retrieved from the Cancer Registry—21 non-notified MTC cases had been identified at other hospitals at an earlier reinvestigation of thyroid tumours and were also included in our material after a new reexamination. Thus, a total of 276 patients were finally included in the study.

Underdiagnostics of MTC. After the final reclassification, MTC constituted 2.7% (72/2593) of all malignant thyroid tumours notified to the Registry in 1959–1969, and 5.2% (204/3920) in 1970–1981 (Fig. 1). The difference can be explained by underreporting of MTC during the first period. The awareness of MTC increased successively among pathologists during the 1960s and it was generally recognized as a separate disease entity from about 1970 (Grimelius, personal communication). Most misclassified MTC would probably have been diagnosed as poorly differentiated follicular or anaplastic carcinoma, and less likely as papillary carcinoma (1).

In order to estimate the extent of underreporting of MTC before 1970, we sampled 20% (n=170) of all follicular (n=810) and 10% (n=46) of all anaplastic (n=467) carcinomas notified to the Cancer Registry during 1959 through 1969. We managed to collect and reexamine 179 (83%) of the 216 tumours in the sample, 143 (84%) of the follicular and 36 (78%) of the anaplastic ones. Nine MTC cases were identified, 7 of which were initially reported as follicular and 2 as anaplastic carcinomas. These cases were not included in the analysis, but they gave reason to the conclusion that reliable incidence rates could not be derived from the period 1959 through 1969 because of underreporting of MTC.

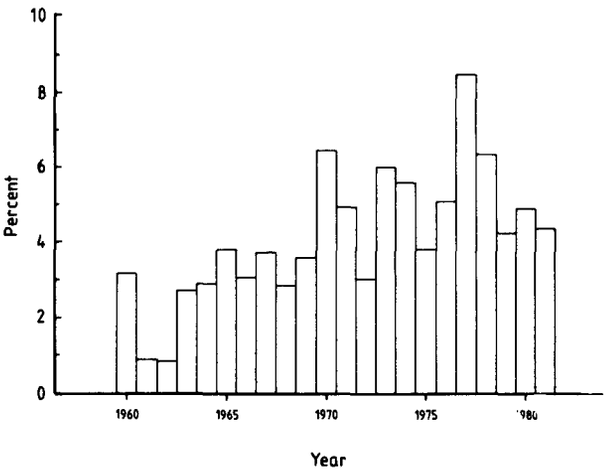

Fig. 1. Proportions of the final reclassified cases of medullary thyroid carcinoma out of all thyroid carcinomas diagnosed in Sweden 1959–1981.

Table 1

Criteria for classification of the 276 patients with medullary thyroid carcinoma

Category	Histological and clinical criteria	Number of patients (%)
Sporadic[1]	Unilateral MTC on histological reexamination and negative histological, clinical and/or biochemical evidence for MTC and/or phaeochromocytoma among blood relatives	54 (20)
	Unilateral MTC on histological reexamination and negative anamnestic information about MTC and/or phaeochromocytoma among blood relatives	124 (45)
	Unilateral MTC on histological reexamination and family history unknown	30 (10)
Total		208 (75)
Familial	Uni- or bilateral MTC and histological, clinical and/or biochemical evidence of MTC and/or phaeochromocytoma among blood relatives	55 (20)
	Uni- or bilateral MTC and general C-cell hyperplasia and family history unknown	10 (4)
	MEN IIb characteristics[2] irrespective of family screening results	3 (1)
Total		68 (25)

[1] In about 30% of the patients considered to have sporadic disease, the histopathological examination was not complete, since only one thyroid lobe was removed at surgery.
[2] Bilateral MTC, phaeochromocytoma, mucosal neuromas, marfanoid habitus, ganglioneuromatosis.

Table 2

Distribution of 276 patients with sporadic or familial medullary thyroid carcinoma by sex and mean age (years) at diagnosis

Category	Male			Female			M/F ratio
	No.	Mean age	(SD)	No.	Mean age	(SD)	
Sporadic (all)	88	56.0	(13.5)	120	58.2	(16.2)	0.7
Diagnosed from symptoms	79	54.3	(12.9)	107	55.8	(15.1)	0.7
Detected at autopsy	9	71.2	(8.6)	13	77.9	(9.9)	0.7
Familial (all)	37	42.6	(15.4)	31	42.5	(19.8)	1.2
Diagnosed from symptoms	16	44.3	(11.8)	11	53.3	(19.7)	1.5
Detected by screening	18	37.0	(14.7)	18	34.7	(16.2)	1.0
Detected at autopsy	3	67.0	(13.5)	0	–	–	–

Table 3

Mean age-standardized annual incidence of sporadic and familial medullary thyroid carcinoma per 10^5 in Sweden, comparing two time periods, 1959–1969 and 1970–1981

Diagnostic group	1959–1969			1970–1981		
	Male	Female	Both sexes	Male	Female	Both sexes
Sporadic[1]	0.08	0.07	0.07	0.12	0.18	0.15
Familial[1]	0.02	0.01	0.01	0.06	0.05	0.06
All						
Including autopsy cases	0.09	0.08	0.09	0.18	0.23	0.21
Excluding autopsy cases	0.09	0.07	0.08	0.16	0.21	0.19

[1] Cases diagnosed at autopsy included.

Diagnostic criteria and histopathological review. In 268 cases the definitive diagnosis of MTC was based on a histological reexamination. Tumours were available as paraffin blocks from the primary tumour or from a metastasis in 258 instances, whereas in 10 cases this definitive classification had to be based on original haematoxylin-eosin stained slides. Of the remaining 8 of the 276 patients, cytological specimens from fine-needle aspiration biopsies were available in 4 patients and in another 4 there was no tumour left in the paraffin block. Among these latter 4 patients one had an unequivocal MEN II syndrome and 3 were described as having MTC in the original pathologist's report. In 2 of these 4 patients, in whom tumour specimens could not be reviewed, the preoperative serum levels of calcitonin were elevated.

Paraffin blocks were cut and stained with haematoxylin-eosin. After identification of representative tumour material, the specimen block was serially cut and stained with 1) a modified argyrophil stain (16), 2) alkaline Congo red for amyloid (17), and 3) an immunohistochemical technique as described by Sternberger (18) for demonstration of calcitonin. For a diagnosis of MTC, the tumour had to fulfil classical criteria of this carcinoma (1, 19) and at least one of the staining methods had to be positive.

Sporadic and familial disease. Clinical data were retrieved from hospital records and further information about screening of patients and relatives was obtained from earlier reports (20–21). In addition a questionnaire was sent to 17 surviving patients or their doctors in order to complete the anamnestic information about the occurrence of endocrine diseases among their families. A tota! of 208 patients (75%) were finally considered to have sporadic and 68 (25%) familial MTC (Table 1).

In the group considered to have sporadic disease, there were 54 patients who had unilateral MTC according to the hospital records and whose available relatives had shown no sign of MTC or phaeochromocytoma on screening. In the remaining 154 patients the probable classification was

based on anamnestic data concerning the absence of MTC in the family and on the histological review of the tumours (Table 1). Familial MTC was diagnosed when MTC occurred together with phaeochromocytoma in the patient and/or his/her blood relatives. In 10 cases no such anamnestic or clinical data were available, but the histological picture of uni- or bilateral MTC together with bilateral C-cell hyperplasia was typical of familial disease (22).

Statistical methods. Simple frequency calculations were made by the SAS statistical program (23). A χ^2-test was used for comparisons between the sporadic and familial groups. Unless otherwise stated, the incidence rates also include cases first diagnosed at autopsy. The incidence rates were adjusted to the Swedish population in 1970 (13), using the direct method of standardization (24). Mean age-adjusted and age-specific incidence rates were calculated as means of the annual rates. The age-specific incidence rates were calculated as the annual number of cases per 10^5 for each 20-year-age group.

Geographical differences were studied by means of the indirect method of age standardization, as this has less variance than that of direct standardization (24). The standardized morbidity ratio (SMR), standardized for age and gender, was calculated as the ratio of observed-to-expected number of cases ×100. The expected number in each of 6 health care regions was estimated by multiplying the age- and sex-specific rates of MTC in Sweden during the period 1970–1981 by the number of individuals in each region in 1975 (24). Fisher's exact test was used to test the differences between SMR in the 6 health case regions.

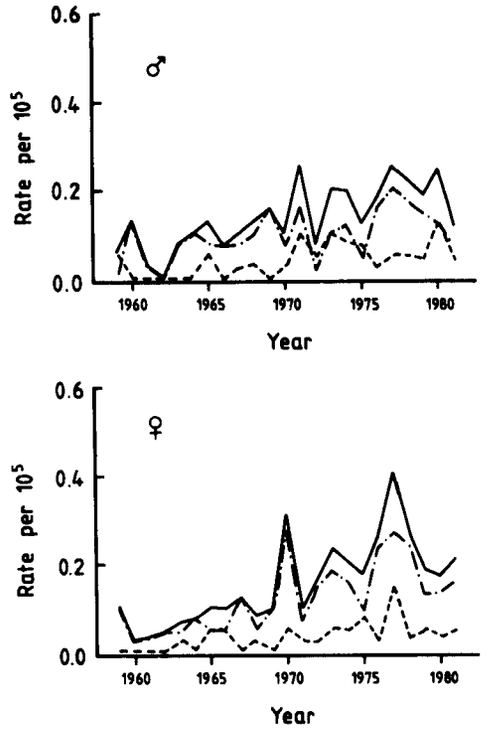

Fig. 2. Age-adjusted annual incidence rate of sporadic and familial medullary thyroid carcinoma in Sweden 1959–1981 (adjusted to the Swedish population in 1970). All patients ————. Sporadic ——·——. Familial MTC ----.

Results

Overall results. The 276 patients diagnosed as having MTC comprised an average of 4.2% of all cases of thyroid cancer reported to the Cancer Registry in 1959 through 1981; 72 of these were reported in 1959–1969 (6 diagnosed at autopsy) and 204 in 1970–1981 (21 at autopsy). Among the living patients, 36 (13%) were detected at a screening procedure and the remaining 213 (77%) on the basis of clinical symptoms. In 223 cases the MTC diagnosis was confirmed in connection with the primary operation (n=196) or at autopsy (n=27), whereas in 53 patients it was revealed during the follow-up period after operation.

Distribution of sporadic and familial cases of MTC by age and gender. The male-to-female ratio was 0.7 in the sporadic and 1.2 in the familial group ($p>0.05$) (Table 2). The mean age at diagnosis was significantly lower in the familial group (42±17 years) than in the sporadic one (57±15 years) ($p<0.001$). There was also a significant age difference between the familial cases detected by screening (35±15 years) and those diagnosed from clinical symptoms (50±16 years) ($p<0.05$). The mean age in each diagnostic group, for males and females separately, is shown in Table 2.

Age-standardized incidence. The annual age-adjusted incidence rate of MTC doubled from the first part of the study period 1959 through 1969 to the second part 1970 through 1981, for both males and females (Table 3). Exclusion of autopsy cases changed the incidence rates only marginally. The increase in mean incidence rate per 10^5 of the sporadic and familial MTC during the study period is also illustrated in Fig. 2.

Age-specific incidence. The age-specific incidence rates during the period 1970–1981 are shown in Fig. 3 and further specified by gender in Table 4. The peak incidence in males occurred at a younger age in the familial group than in the sporadic one. No such peak was seen among females. In the sporadic group the incidence rate among females increased with age and was after the fourth decade of life somewhat higher than in males. In the familial group, there was a slight male predominance in the age group 40–59 years (Table 3).

Geographical differences. The observed and expected numbers of patients with MTC were calculated separately for each of the six health care regions in Sweden (Table 5). A significantly higher SMR of sporadic MTC was found only in region 4 ($p=0.03$). The SMR of familial MTC in regions 4 and 5 were higher than the national average and in regions 1 and 2 lower (Table 5).

Separate calculations by gender also revealed a higher risk of having sporadic MTC among females in region 4

Table 4

Mean age-specific and age-standardized annual incidence of medullary thyroid carcinoma per 10^5 in Sweden 1970–1981

Age (years)	Sporadic			Familial		
	Male	Female	Both sexes	Male	Female sexes	Both
0–19	–	0.01	0.01	0.02	0.02	0.02
20–39	0.06	0.06	0.07	0.07	0.06	0.07
40–59	0.14	0.30	0.23	0.13	0.06	0.10
60–79	0.33	0.38	0.36	0.01	0.06	0.04
80–	0.19	0.53	0.41	–	–	–
All ages[1]	0.12	0.18	0.15	0.06	0.05	0.06

[1] Directly standardized to the Swedish population in 1970.

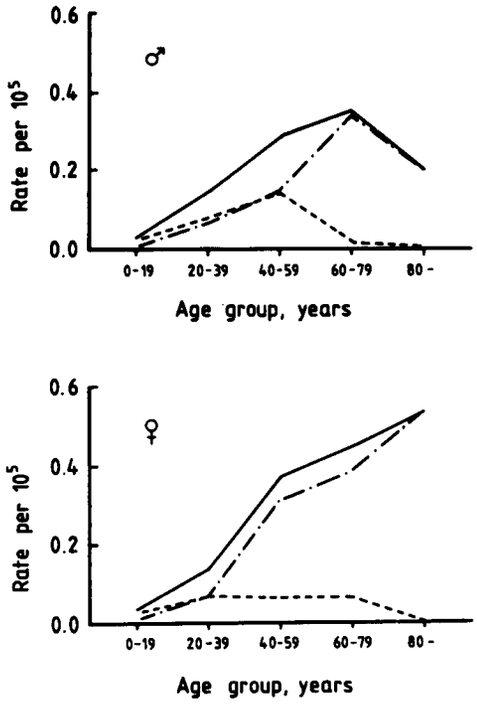

Fig. 3. Annual age-specific incidence rate of medullary thyroid carcinoma per 10^5 in males and females in Sweden 1970–1981. All patients ————. Sporadic ——·——. Familial MTC ----.

and a lower risk in region 3. In region 3 as well as in region 6 males had a lower risk of having familial MTC.

In separate calculations, in which autopsy cases were excluded, the same general pattern as in Table 5 was seen for sporadic MTC, with a slightly higher SMR in region 4 (SMR=128; 90% CI 90–177). Separate calculations for familial MTC without autopsy cases were not meaningful as there were only two autopsy cases in this group. Exclusion of screening-detected patients from calculations of SMR in the group with familial MTC did not materially alter the results, but the magnitude of the geographical variations decreased to some extent (Table 5).

Discussion

A population-based study of medullary thyroid carcinoma in Sweden based on annual obligatory reports to the National Cancer Registry revealed that MTC constituted 5.2% of all reported thyroid carcinoma, with an overall age-standardized incidence rate per 10^5 inhabitants of 0.21. There was a significant age difference between patients with sporadic and familial disease, with the lowest mean age found in the familial group detected by screening. SMR in 6 different health care regions showed a difference in the distribution of sporadic and familial cases, the latter group being concentrated to the south-western part of the country and the former showing a more limited geographical variation.

This study was facilitated by the availability of a reliable National Cancer Registry (11–13) based on reports from both physicians and pathologists. Our selection of the patients was based on the reporting pathologist's description of the tumour, since all thyroid tumours are registered under the same code number (25). Since the diagnosis MTC was relatively unknown before 1970 and a sample review from the period 1959 through 1969 indicated substantial misclassification of this form of carcinoma, our incidence analyses were focused on the period 1970–1981, when MTC had become a well established disease entity.

The observer variation among Nordic pathologists in the diagnosis of MTC has been found to be high (26). In our study the tumours suspected of being MTC were allocated to separate geographical regions, for reexamination by an experienced pathologist (totally four) with special interest in endocrine tumours. All four pathologists used the same morphological criteria and the same special stainings. This procedure should have entailed a high diagnostic validity.

Reporting to the Swedish Cancer Registry during recent years is established to be close to 100% of all diagnosed cases (11–13). The autopsy rate for all deaths—which is only 40% in Sweden, including forensic autopsies (27)—will, however, influence the incidence rates (28–30). Regional differences in autopsy rates in the present study might have contributed to the higher incidence of sporadic MTC in the Malmö-Lund region than in other parts of Sweden (Table 5), since 22 of 27 autopsy cases in our material were of the sporadic type and were almost exclusively reported from this region by one and the same pathologist.

The reliability of the classification into sporadic and familial disease is influenced by differences in screening activity between time periods and geographical regions. The distribution of our sporadic and familial cases according to the classification criteria is presented in Table 1. It is probable, however, that some patients with familial disease are misclassified, since proper screening as recommended today (21, 31) was not carried out uniformly. Furthermore, 30% of the patients classified as having sporadic MTC underwent only unilateral extirpation of the thyroid; a possible lesion or C-cell hyperplasia in the contralateral lobe might thus have been overlooked and familial disease erroneously classified as sporadic if biochemical screening among blood relatives was negative or not performed.

We have found no other reports on age-specific and age-standardized incidence rates of sporadic MTC. The sex and age distributions in the sporadic group in our study were similar, however, to those in other studies, as was the incidence in older age groups (7, 9–10, 20).

Calculations of incidence rates of familial MTC give rise to more specific validity problems. When no positive evidence emerges from screening of relatives, anamnestic information or histological investigation, the tumour is assumed to be of sporadic origin. Thus, screening activity and meticulous histological investigation with immunocytochemical staining for calcitonin in both thyroid lobes are mandatory; otherwise underestimation of familial MTC will occur (32). Ponder et al. (32) recently estimated that proper screening among relatives of patients with apparently sporadic MTC would reveal at least 10–15% as having familial disease. We have found no other reports on separate incidence rates for sporadic and familial MTC, but the proportion of familial cases among patients with MTC in the present material is similar to that in other studies (9–10). The difference in age between patients with sporadic and familial MTC and the equal sex distribution are also as described by other authors (7, 9–10).

Differences in the geographical distribution of familial MTC have been found in Norway (7), with high rates in the coastal areas, where inbreeding might contribute to an aggregation of cases. In Sweden inbreeding might also explain the higher SMR in the southern and south-western health care regions (Table 5). If the geographical differences between incidence of sporadic and familial MTC were due solely to discrepancies in screening activity between the southern and northern parts of Sweden, some index cases of familial MTC should have been diagnosed due to symptoms from the tumour during the 19-year study period, but this was not so.

Table 5

Indirectly standardized morbidity ratio (SMR) of medullary thyroid carcinoma in six health care regions in Sweden during the period 1970–1981

Region	SMR (90% confidence interval)		
	Sporadic	Familial (all)	Familial (screening detected excluded)
1. Stockholm–Gotland	115 (83–155)	9 (1–44)	25 (1–120)
2. Uppsala–Örebro	97 (70–131)	16 (3–50)	21 (1–99)
3. Linköping	64 (36–107)	50 (14–130)	84 (15–263)
4. Lund–Malmö	140 (104–184)	306 (221–416)	244 (127–426)
5. Gothenburg	103 (74–142)	195 (129–283)	208 (104–376)
6. Umeå	62 (34–105)	0 (0–49)	0 (0–129)

Screening for MTC among families with the inherited type of MTC started in 1969, when the characteristic cytology of the malignant C cells was detected (33). From 1972 it was further improved when the radioimmunoassay method for serum calcitonin measure became available (34). An extensive screening programme has been established in regions 4 and 5, and in the central part of Sweden (regions 1–3) a more moderate form of screening has been carried out (20–21). During the following years, the annual reports of MTC to the Cancer Registry increased when younger patients with small and even clinically undetectable carcinomas were diagnosed and on the basis of elevated serum calcitonin levels were operated upon.

The total age-standardized incidence rate of MTC—sporadic and familial combined—was substantially higher in Sweden in 1970–1981 (0.21 per 10^5) than in Norway in 1960–1974 (0.1 per 10^5) (7). According to Franssila et al. (6), in 1960 the incidence rate of MTC was lower in Norway than in Sweden, but in a recently presented joint Nordic study the increase in all thyroid carcinomas was found to be higher in Norway than in Sweden in 1950–1980 (35), and so we assume that the difference between Sweden and Norway might be at least partly explained by underdiagnosis of MTC on notification to the Norwegian Cancer Registry during 1960–1974.

ACKNOWLEDGEMENTS

This work was supported by grants from the Swedish Cancer Society, the Lions Cancer Foundation, Uppsala, Sweden, and the Swedish Medical Research Council (M. Telenius-Berg). We are greatly indebted to the staff at the Swedish Cancer Registry for kind cooperation and particularly to Pär Sparén for statistical help.

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Appendix

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