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PAPILLARY THYROID CARCINOMA IN ICELAND

A study of the occurrence in families and the coexistence of other primary tumours

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Abstract

This paper presents evidence from Iceland which indicates that papillary thyroid carcinoma occurs in certain families more often than expected. Thyroid carcinoma was also seen to coexist with some other cancer types more often than expected. We studied all families (n=373) with papillary thyroid carcinoma diagnosed between 1955 and 1984 in Iceland. Familial papillary carcinoma occurrred in 3.8% of these families. This frequency was higher than expected but not significantly increased. Second primaries in women, and especially the incidence of kidney and breast cancer, were significantly increased. Cancer of the kidney and CNS tumours were significantly increased in propositi when both sexes were taken together. No increase in the incidence of other malignancies was observed in first degree relatives of patients with papillary thyroid carcinoma.

Key words: Thyroid, papillary carcinoma, familial, multiple primaries.

The incidence of thyroid carcinoma in Iceland is high (1). Papillary carcinoma comprises 80% of all thyroid malignancies in this country (2). It is well known that medullary thyroid carcinoma aggregates in families, and a genetic component in the etiology has been established (3). For other types of thyroid carcinoma less is known concerning hereditary factors. Papillary carcinoma is usually sporadic but it has been reported that it can be a familial disease (4, 5). The relative frequency of familial versus sporadic papillary carcinoma is uncertain. In the present study we examined the frequency of familial papillary thyroid carcinoma during a 30-year period in Iceland.

Carcinomas of the thyroid are known to occur in patients with malignancies in other specified organs, such as breast (6–9), female genital organs (8) and kidneys (7, 10). In order to look further into this matter we also studied the frequency of other types of malignancy in patients with papillary carcinoma of the thyroid and malignant neoplasms in first degree relatives of these patients.

Material and Methods

All cases (n=383) of papillary thyroid carcinoma diagnosed in Iceland between 1955 and 1984 (both years included) form the basis of this study. The histopathology was reexamined by one of the authors (JGJ) (2). If there was more than one case of papillary thyroid carcinoma in a family the one first diagnosed was designated a propositus. Familial papillary thyroid cancer is used for those cases who are known to have a first degree relative with thyroid carcinoma. The number of families traced was 373 since 10 patients with papillary thyroid carcinoma were first degree relatives of previously diagnosed propositi. All the first degree relatives of the propositi, parents, siblings and offspring, were identified. All these families were followed until December 1985. This is one year longer than the period on which the choice of propositi was based. During that year (1985) one first degree relative with papillary carcinoma was diagnosed.

Incidence data on cancer before 1955 were not available. The studied risk period therefore started in January 1955 or at birth (for persons born after January 1955) and ended in December 1985 or at death if it occurred before December 1985. The 373 families consisted of 3266 individuals of whom 2700 contributed to the man-year calcu-

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lations on which expected numbers are based. The remaining 566 had died before 1955 and therefore did not contribute to the man-year calculations. The information on the first degree relatives was obtained from the Genetical Committee of the University of Iceland (11). This committee has a computerized family tracing resource based on the 1910 Census, birth records for 1840–1910 and linked with the National Register and death records for later periods. The years at risk were stratified according to the following variables: sex, 5-year age groups and 5-year periods of calendar time. Age- and sex-specific incidence rates for the different cancer types for each of the calendar time periods were then used for obtaining expected number of cases by the summation of products of years at risk and incidence rates. Standardized incidence ratio (SIR) was calculated as the ratio between observed and expected number of cases. Confidence interval (CI) for SIR was obtained by first calculating confidence limits for number of observed cases according to Haenszel et al. (12) and then dividing these by number of expected cases. χ^2-test and Fischer's exact test were used to test difference between groups.

The following items were documented: carcinoma of thyroid and cancers at other sites among first degree relatives of patients with papillary thyroid cancer and other primary neoplasms in patients with papillary thyroid carcinoma. Incidentally diagnosed carcinomas of the thyroid were included in the study.

Results

Fourteen of the 373 (3.8%) propositi had a first degree relative with thyroid carcinoma (one of those 14 propositi had two first degree relatives with thyroid malignancy). These 29 cases are called familial in the following. Eleven of these 15 first degree relatives had papillary thyroid carcinoma, two had follicular and two anaplastic carcinoma. Therefore a total of 25 familial cases of papillary thyroid carcinoma were observed (14 proposity, 11 first degree relatives), 11 males and 14 females. The mean age at diagnosis for females was significantly higher for the familial cases than for the non-familial ones (66.0 years (SE 4.0) vs. 54.7 years (SE 1.1)). For males the mean ages were similar for the familial and non-familial cases (61.7 years (SE 2.2) vs. 58.5 years (SE 1.9)). The sex ratio in the familial papillary cases (14 women and 11 men) was significantly different ($p<0.05$) from that of the non-familial papillary carcinoma cases (270 women and 88 men).

Table 1 shows the number of cases which had first degree relatives with thyroid carcinoma and how they were related.

In Table 2 the observed and expected number of cases are shown. There was a significantly increased risk in male relatives (SIR 3.7 with 95% CI 1.8–6.8). In the combined group of siblings and children a significant excess was noted.

Table 1

Frequency of thyroid cancer in first degree relatives, and types of relatives affected

	Male propositus	Female propositus	Both sexes
Pedigrees with multiple cases	4	10	14
Total pedigrees	93	280	373
Affected first degree relative			
Father	0	1	1
Mother	0	0	0
Brother	3	3	6
Sister	1	3	4
Son	0	3	3
Daughter	1	0	1
Total	5	10	15

Table 2

Observed and expected number of cases of thyroid cancer cases among first degree relatives of propositi by sex and generations

	Observed (O)	Expected (E)	SIR (O/E)	(95% confidence interval)
Male relative	10	2.7	3.7	(1.8–6.8)
Female relative	5	6.8	0.7	(0.2–1.7)
Total relative	15	9.5	1.6	(0.9–2.6)
Parents	1	2.3	0.4	(0.0–2.4)
Brothers and sisters	10	5.6	1.8	(0.9–3.3)
Children	4	1.4	2.9	(0.8–7.3)
Siblings and children	14	7.0	2.0	(1.1–3.4)

Table 3

Number of propositi having another primary malignant neoplasm

	Observed (O)	Expected (E)	SIR (O/E)	(95% confidence interval)
Males	13	13.9	0.9	(0.5–1.6)
Females	55	32.6	1.7	(1.3–2.2)
Total	68	46.5	1.5	(1.1–1.9)

Malignant neoplasms were documented for all the 142 first degree relatives of the 14 propositi with familial papillary thyroid carcinoma. There was no excess in number of malignancies in these families (observed 15 and expected 14.8). A cancer in the gastrointestinal tract was observed in 7 of these 15 cases.

Table 3 shows the observed and expected number of cases of multiple primaries in patients with papillary thy-

Table 4

Double primaries. Observed and expected number of cases of selected cancer sites in females with papillary carcinoma of the thyroid

	(ICD-7)	Observed (O)	Expected (E)	SIR (O/E)	(95% confidence interval)
Stomach	(151)	1	3.5	0.3	(0.0–1.6)
Colon	(153)	4	2.4	1.7	(0.5–4.3)
Pancreas	(157)	2	1.1	1.8	(0.2–6.6)
Breast	(170)	15	7.5	2.0	(1.1–3.3)
Endometrium	(172)	5	1.7	2.9	(0.9–6.8)
Ovary	(175)	3	2.0	1.5	(0.3–4.4)
Kidney	(180)	7	1.1	6.4	(2.6–13.1)
CNS	(193)	2	0.9	2.2	(0.2–8.0)
Leukemia	(204)	1	0.6	1.7	(0.0–9.3)

roid carcinoma. There was a significant excess of another primary malignancy in patients with papillary carcinoma. This significant excess was found among females only. Double primaries were observed in 3 of the familial papillary propositi as compared to 1.8 expected.

Table 4 illustrates observed and expected number of cases for selected sites in female patients with papillary thyroid carcinoma as well as excess cases for these tumour types. The excess was largely due to breast, kidney and endometrial cancer. The site showing the greatest deficit was the stomach. The risk was significantly increased for breast and kidney cancer. We found 15 patients with both thyroid and breast cancer. Ten out of 15 had breast cancer diagnosed first, in two cases the diagnoses were made in the same year and in three cases the thyroid carcinoma was the first to be diagnosed. Relative risk for double primaries involving breast in our series was 2.0.

For kidney cancer there was an increased risk in both sexes combined (SIR 5.0 with 95% CI 2.3–9.8). The number of CNS (central nervous system) tumours was greater than expected (SIR 4.0 with 95% CI 1.1–10.4). The histopathology of these double primaries was studied and no unusual morphological types were found, especially no apudomas.

Relatives of patients with papillary thyroid carcinoma were studied in order to trace other malignancies. No excess of malignant tumours was found in these relatives. A total of 286 cases of malignancies were observed whereas 306.3 would have been expected (SIR 0.93 with 95% CI 0.8–1.05).

Discussion

This study found that 3.8% of papillary thyroid carcinoma patients had a first degree relative with primary carcinoma of the thyroid gland. In an earlier study by Williams et al. (13) covering thyroid cancer in Iceland 1944–1963 no evidence for inheritance was found. In the present study the observation period was longer and the number of tumours about 4 times larger, which may explain the difference. In our study relatively more males were found among the familial cases than among the sporadic ones, in contrast to the report of Stoffer et al. (5). The mean age at diagnosis in the familial cases was higher than in the sporadic cases. This might be explained by the fact that first degree relatives of older propositi are themselves older and therefore at a higher risk or getting thyroid carcinoma. Lote et al. (4) found the reverse in their study and could not find any association with previous irradiation, Gardner's syndrome or multiple endocrine adenomatoses. Among our families we have not been able to find any such connection either.

The incidence of breast carcinoma among women with papillary thyroid carcinoma was significantly increased in this study. We looked at the total number of double primaries involving breast and thyroid. Ron et al. (7) found a significantly elevated risk of breast cancer following thyroid carcinoma and thyroid carcinoma following breast cancer. Several authors, such as McTiernan et al. (6), Tucker et al. (9) and Schottenfeld & Berg (8), have found this same connection.

Significantly increased risk of kidney carcinoma in females with papillary thyroid carcinoma was found in our study. Similar results have been reported earlier (7, 9).

Besides breast cancer Schottenfeld & Berg (8) showed significantly increased incidence of thyroid carcinoma in patients with endometrial and ovarial carcinomas when studying multiple primaries in female genital organs. For thyroid as the first diagnosed carcinoma there was no significant increase in the tumour types mentioned above (8). In the present study we observed 5 cases with endometrial carcinoma and papillary carcinoma of the thyroid when 1.7 were expected. The risk of ovarial carcinoma was elevated but not significantly so (Table 4).

An increase in the ratio observed/expected CNS tumours in individuals with papillary thyroid carcinoma was noted in the present study ($p<0.05$). Österlind et al. (10) found a significant excess of brain tumours in patients with papillary thyroid cancer.

Stoffer et. al. (5) also noted a high frequency of colon carcinoma in relatives of familial papillary carcinoma patients. In our series only two cases of colon carcinoma were observed in the studied 14 families, but gastrointestinal malignancies in general were more frequent than expected. Smith & Kern (14) in discussing familial polyposis have suggested that papillary thyroid carcinoma and all varieties of brain malignancies should be included in the genetic extracolonic manifestations of familial polyposis. However, no cases of familial polyposis are known in Iceland.

No increase in leukemias was noted in the thyroid carcinoma patients in our material in contrast to some other studies (15).

This study lends further support to the notion of an increased risk of thyroid carcinoma among first degree relatives of papillary thyroid carcinoma patients, although this did not reach a 95% significance. It suggests that further work is needed for conclusive evidence of familiality of this disease. The significant excess of breast and kidney carcinomas among patients with papillary thyroid carcinoma suggests common etiological factors for carcinomas at these sites, environmental or genetic.

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