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Frequency and Morphology of Malignant Tumours of the Thyroid Before and After the Introduction of Iodine-Prophylaxis

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Summary. Reclassification of malignant goitres surgically removed between 1952–1975 reveals remarkable epidemiological alterations. There is a proportional decrease in undifferentiated carcinoma, which in males also represents an absolute decrease. The decrease is due to a change in maximum incidence from the 5th to the 7th decade. Differentiated carcinomas, especially the papillary tumours, increase.

Comparison with findings in Switzerland shows many conformities. Iodine-prophylaxis apparently influences the morphology of thyroid carcinoma, as indicated by the time lag between the introduction of iodine-prophylaxis and the appearance of alterations in incidence. Iodine-prophylaxis, acting in this way, will improve survival rates in thyroid cancer.

Key words: Thyroid tumours – Iodine prophylaxis.

Introduction

The WHO-classification of thyroid tumours (Hedinger and Sobin, 1974) makes it possible to compare the histo-morphology of thyroid carcinomas from different areas (Cabanne et al., 1974; Cady et al., 1976; Figg et al., 1978; Georgii, 1977; Grimelius et al., 1978; Heitz et al., 1976; Krisch et al., 1977; Lindahl, 1975; Löhrs et al., 1977; Neracher and Hedinger, 1975; Rasmusson, 1978; Röher et al., 1977; Schottenfeld and Gershman, 1977; Shields and Farringer, 1977). The findings from our endemic goitre area are of special interest, because we have carried out a general iodine-prophylaxis (10 mg/1 kg salt) for 18 years. A comparison of our results with those from the Swiss endemic goitre area (Bubenhofer and Hedinger, 1977; Heitz et al., 1976; Kind 1966; Thalmann, 1954; Walthard, 1963) will demonstrate whether the changes in histological tumour types are caused by iodine-prophylaxis or whether they are stimulated by other factors (Cady et al., 1976; Röher et al., 1977).

In a retrospective investigation of the histological specimens, we compare changes in the morphological pattern of malignant thyroid tumours to alterations

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in surgically removed benign goitres (Hofstädter et al., 1979) and to the Swiss results (Bubenhofer and Hedinger, 1977; Heitz et al., 1976; Kind, 1966; Thalmann, 1954).

Material and Methods

The histological specimens of all surgically removed malignant or suspicious goitres from the years 1952–1975 have been reclassified according to the histological criteria of the WHO (Hedinger and Sobin, 1974). Because of divergent opinions concerning the biological behaviour of papillary tumours (Wegelin, 1926) all tumours which had been designated as "papillary adenoma" in the initial histological report have been included. Histological examination was carried out without any knowledge of the clinical data or the year in which the operation was performed. Moreover, the differentiated carcinomas according to the WHO-classification have been separated into the following sub-groups: Nonencapsulated sclerosing papillary carcinoma and encapsulated papillary carcinoma (EPC), and encapsulated follicular carcinoma (EFC) according to Lang et al. (1979). The latter two tumour subgroups are characterized by their encapsulation and moderate to minimal invasiveness.

Results

Malignancy was confirmed in 447 out of 460 cases listed in the records of the Pathological Institute (malignant goitre, adenoma with papillary structures). For 6 cases neither sections nor blocks were available. In 7 cases malignancy could not be confirmed for histological reasons. 5 cases were identified as metastases from their natural history, 3 of these cases were metastases from renal hypernephroid carcinoma.

Table 1 shows the pattern of malignant goitres in comparison with the total number of histological specimens. The proportion of non-malignant goitre decreased after the introduction of iodine-prophylaxis, with an increase in the ratio of women to men. Malignant tumours became more common amongst surgically removed goitres, although their share of the total number of histological specimens did not change. The sex incidence of malignant thyroid tumours

Table 1. Number of benign and malignant surgically removed goitres before (1952–1959) and after (1960–1969, 1970–1975) the introduction of iodine-prophylaxis

Period of diagnosis	No. of surgical specimens	No. of thyroid specimens	Ratio females/ males (all goitres)	No. of specimens with thyroid malignancy[a]	Ratio females/ males (malignant goitres)	Proportion of thyroid malignant tumours in all surgicals
1952–1959	84893	3324 (3.9%)	2.6	114 (3.4%)	0.9	0.1%
1960–1969	160825	5638 (3.5%)	4.5	201 (3.6%)	1.4	0.1%
1970–1975	113307	2169 (1.9%)	5.1	138 (6.4%)	1.9	0.1%
All years	359025	11131 (3.1%)	3.8	453 (4.1%)	1.4	0.1

[a] Proportion of malignant tumours in all surgically removed goitres given in parentheses

Table 2. Results of the histological reclassification of the surgically removed malignant goitres. WHO-classification (Hedinger and Sobin, 1974)

	$n=447$	%
Follicular carcinoma	169	37.8
Papillary carcinoma	94	21.0
Differentiated carcinoma, not classified	10	2.2
Squamous cell carcinoma	6	1.4
Undifferentiated carcinoma:		
spindle cell type	20	4.5
giant cell type	52	11.6
small cell type	17	3.8
not classified	39	8.7
Medullary carcinoma	3	0.7
Fibrosarcoma and other sarcomas	12	2.7
Carcinosarcoma	1	0.2
Malignant hemangioendothelioma	13	2.9
Malignant lymphoma	6	1.4
Teratoma	0	0.0
Metastasis	5	
Adenoma	7	
Material not available	6	

differs markedly from that of benign goitres but it shows a similar tendency (increase in female incidence).

Table 2 shows the results of reclassification according to the WHO principles (Hedinger and Sobin, 1974). Although 10 tumours were identified as "differentiated carcinomas", a differential diagnosis into "follicular" or "papillary carcinoma" was not possible with certainty. 39 undifferentiated carcinomas could not be specified into their respective subtypes (giant-cell type, small-cell type, spindle-cell type). The statistical analysis of the non-adjusted material shows that the percentage of differentiated carcinomas (papillary, follicular) amongst all malignant goitres increased significantly from 57.5% (1952–1969) to 66.7% (1970–1975) $\hat{z}=2.0>z$; $\alpha=0.05$). Amongst the differentiated carcinomas the ratio follicular carcinoma to papillary carcinoma has significantly decreased: 1952–1959: 50–10; 1960–1969: 77–38 ($\hat{\chi}^2=5.3>\chi^2\alpha=0.05$; 1970–1975: 40–46 ($\hat{\chi}^2=20.3>\chi^2$; $\alpha=0.001$).

Figure 1 shows that the increase in the incidence of malignant goitre is mainly caused by increase in the differentiated tumour types (*P, F*). Furthermore, undifferentiated carcinomas decreased in males in the last group examined (1970–1975). The increase in differentiated tumours (*P, F*) can be explained by the increase in papillary subtypes. Follicular tumours increased only minimally in females, while in males they actually decreased – analogous to the undifferentiated carcinomas.

Figure 2 clarifies these findings. The decrease in the undifferentiated carcinomas is caused by a displacement of the incidence peak to old age. By comparison, the differentiated carcinomas show a displacement of their incidence peak

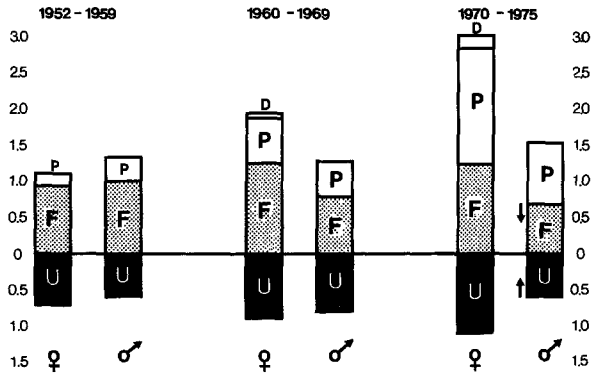

Fig. 1. Incidence of follicular *(F)*, papillary *(P)* and undifferentiated carcinomas *(U)*. *D*: Differentiated carcinomas, differential diagnosis into follicular or papillary carcinoma not possible with certainty. Sex- and age-adjusted (Österreichische Volkszählung 1971) annual rate per 100,000

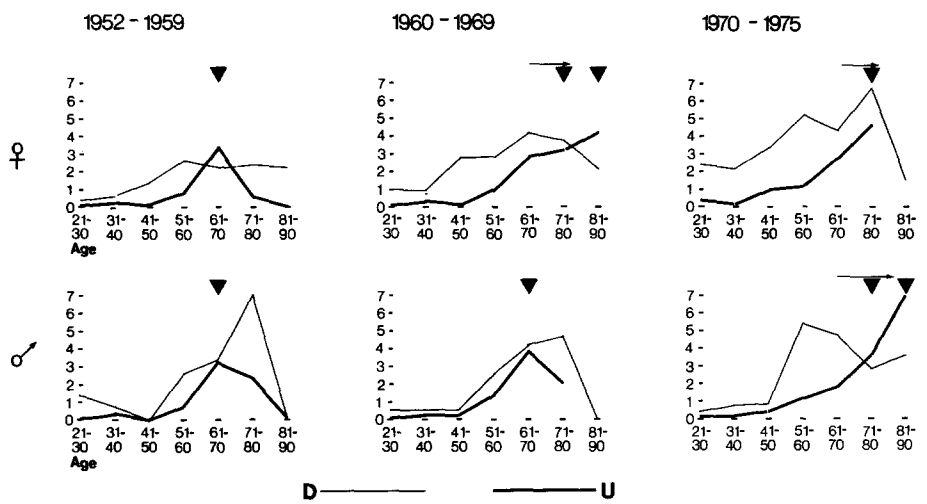

Fig. 2. Incidence of differentiated carcinomas *(D)* and undifferentiated carcinomas *(U)*. Annual rates per 100,000 (males/females) for the respective age group (decades)

from the 7th to the 5th decade in males, while in females the increase appears in all age groups proportionally. The displacement is caused by the appearence of papillary carcinomas in males as shown by Fig. 3. The result – for males at least – is an age structure of thyroid tumours that is characteristic of non-endemic goitre areas, with the incidence peak of papillary carcinomas lying around the 5th decade and total incidence higher than that of follicular carcinoma. The increase in incidence of papillary carcinoma occurs in females in the youngest age groups (20–40).

The analysis of the suptypes of papillary carcinoma (nonencapsulated sclerosing papillary carcinoma, EPC) and follicular carcinoma (EFC) is given in Table 3. The number of sclerosing papillary carcinomas is very low in our material.

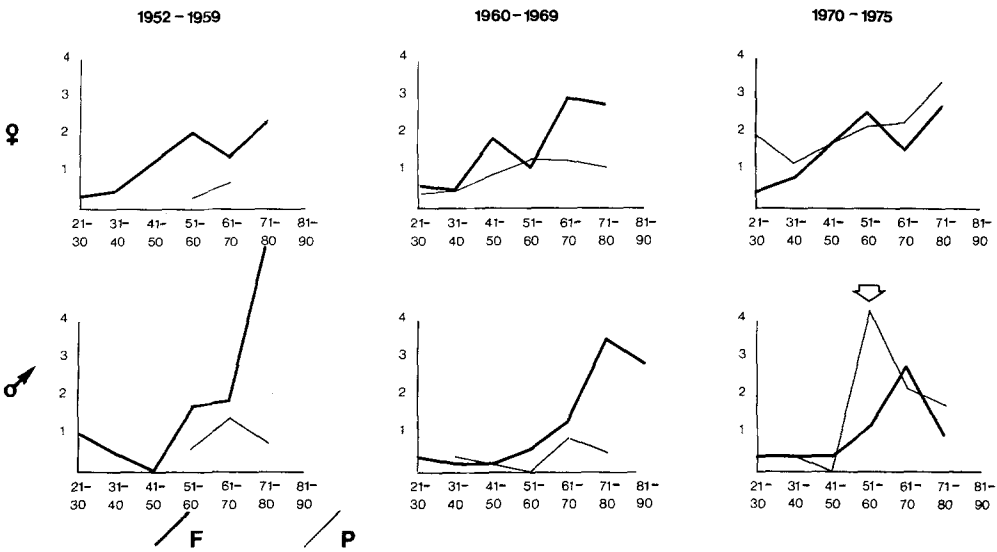

Fig. 3. Incidence of follicular *(F)* and papillary *(P)* carcinoma. Annual rates per 100,000 (males/females) for the respective age group (decades)

Table 3. Number of organoid early type carcinomas (nonencapsulated sclerosing papillary carcinoma, encapsulated papillary carcinoma and encapsulated follicular carcinoma

	Number of cases	1952–1959	1960–1969	1970–1975
Nonencapsulated sclerosing papillary carcinoma	6/94[a] (6.4%)	1	4	1
Encapsulated papillary carcinoma (EPC)	22/94[a] (23.4%)	3/10[a] (30.0%)	9/38 (23.7%)	10/46 (21.7%)
Encapsulated follicular carcinoma (EFC)	83/169[b] (49.1%)	20/52[b] (38.5%)	35/77 (45.5%)	28/40[c] (70.0%)

[a] Number of all papillary carcinomas

[b] Number of all follicular carcinomas. Percentages of respective subtypes amongst all papillary/follicular carcinomas are given in parentheses

[c] The increase in the percentage of EFC amongst all follicular carcinomas between the year groups 1960–1969 and 1970–1975 is statistically significant ($\hat{\chi}^2 = 6.382 > \chi^2\alpha = 0.05$; chi-square test)

EPC shows increasing incidence parallel to increasing total number of papillary carcinomas. The percentage of EPC amongst all papillary carcinomas did not change significantly, on the contrary, EFC shows an increase in rate from 38% to 70% amongst all follicular carcinomas.

Discussion

Comparison between histological types of thyroid cancer reveals remarkable differences between endemic and non-endemic goitre areas (Balázs and Krasznai,

1974; Cuello et al., 1969). The reasons for these differences are difficult to explain. Apart from the complex problem of histological classification, which was not uniform in earlier years (Wegelin, 1926; Woolner et al., 1968), problems of selection are important (incidence of goitres, frequency of surgical operations, indication for operation, preoperative diagnostic methods). One crucial selective factor is the operation rate. In non-endemic areas the willingness of patients and physicians to perform operations is much higher than in endemic goitre areas. Thus the ratio of surgically removed goitres to non-operated (or medically not observable) goitres is higher than in endemic goitre areas. The intensity of histological investigation also influences the results: The higher the number of sections investigated per case, the more papillary carcinomas can be found (Georgii, 1977; Sampson et al., 1971). For these reasons comparisons between results from different institutes are difficult. Autopsy results give little information, especially for thyroid tumours, because of the low autopsy-rate cited for these tumours, and results in the literature and our own findings clearly demonstrate the low value of statistics based on post-mortem examinations. Some individual results exhibiting extremly high rates of latent carcinomas (Fukunaga and Lockett, 1971; Fukunaga and Yatani, 1975) cast doubt on the relevance of the histological criteria used.

In animal experiments thyroid tumours can be reproduced precisely and studied exactly (Thomas, 1977), but the relevance of these tumours to human lesions is doubtful since they show a pattern of morphology and behavior that is strictly different from human tumours.

The first observations concerning alterations of the pattern of malignant thyroid tumours after the introduction of iodine-prophylaxis came from Switzerland (Walthard, 1963; Thalmann, 1954). These results were confirmed in principle by comparative analysis of autopsy material and surgical specimens (Kind, 1966) as well as by investigations using the new WHO classification (Bubenhofer and Hedinger, 1977; Heitz et al., 1976). The latent period between iodine-prophylaxis and the increase in papillary carcinoma was 25 years (Walthard, 1963). The iodine dosage in Switzerland was 5 mg/1 kg table salt (10 mg/1 kg salt since 1962). Our results confirm the Swiss findings and permit the clear conclusion that iodine prophylaxis has a specific influence on the morphology of thyroid tumours. The time-lag between the Swiss results – taking into consideration the initially lower dosage of iodine in the Swiss endemic area – and our own findings and the parallelism of the results confirm this hypothesis. Comparison with alterations of the patterns of non-malignant goitre show that in Switzerland, too, prophylaxis is more effective in males (Hofstädter et al., 1979). The translocation of the incidence peak of undifferentiated carcinomas from the 5th to the 7th decade also observed in the Swiss endemic goitre area (Heitz et al., 1976) resembles the movement of the incidence peak of non-malignant goitre towards middle age (Hofstädter et al., 1979; Bauer et al., 1971). The appearence of undifferentiated carcinomas at a later age, the parallel decrease in follicular and undifferentiated carcinomas and the general interrelationship of both these tumours in endemic goitre areas supports the hypothesis that undifferentiated carcinomas may develop from long-standing differentiated tumours (Aldinger et al., 1978; Gaal et al., 1975; Hutter et al., 1965; Ibanez

et al., 1966; Jao and Gould, 1975). It is not possible to draw practical clinical consequences from that theory, because of the long latent period and because of the impossibility of verifying the connection in each case.

The alterations observed in the organoid early type carcinomas (EPC, EFC) are of considerable practical interest. The increase in the incidence of EFC (Lang et al., 1979) is in agreement with observations in non-endemic (Cady et al., 1976) and endemic goitre areas (Röher et al., 1977) and seems to be an effect of improved preoperative diagnostic methods. The clinical preoperative situation in EPC is quite different from EFC because of the early metastasis to cervical lymph nodes (Meissner and Warren, 1969). We believe this special feature of papillary carcinoma to be the reason that EPC – in contrast to EFC – did not show a percentage increase amongst all papillary carcinomas.

Our main findings of a percentage increase in differentiated carcinomas, especially papillary ones, a percentage decrease in undifferentiated carcinomas and an absolute decrease in males in the last 6 years have important implications for the prognosis of thyroid cancer. The alterations observed are now improving the survival rates of these patients – which were formerly very poor in endemic goitre areas (Huber and Riccabona, 1969).

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