OCCULT THYROID CARCINOMA IN OLMSTED COUNTY, MINNESOTA: PREVALENCE AT AUTOPSY COMPARED WITH THAT IN HIROSHIMA AND NAGASAKI, JAPAN

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Nine occult carcinomas of the thyroid were found in 157 autopsies of deceased residents of Olmsted County, Minnesota, a prevalence of 5.7%. This rate is significantly lower than that reported from a previous autopsy series from Hiroshima–Nagasaki, Japan, in which similar pathologic methods and diagnostic criteria were used. Sex ratio, age distribution, and radiation exposure are considered not to explain this difference. A true difference between the Japanese and American populations with respect to the prevalence of occult thyroid carcinoma is the most likely explanation of these findings.
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ALTHOUGH CLINICALLY EVIDENT THYROID carcinoma is rare, small "occult" thyroid carcinomas are present in a substantial portion of the general population. Estimates based on careful examination of the thyroid at autopsy show an apparent difference in the prevalence of these small tumors between American series[1,2,8–10,14] (0.45–4%) and Japanese series[3,11,18] (13–24%). Although these differences are impressive, comparisons between series reported by different authors are difficult and may be misleading, because the small size of many of these tumors and the lack of uniformity of their diagnosis make the observed prevalence rates highly dependent on the exact methods used in their detection.

In 1969, one of us (R.J.S.) was the principal author of a study[11] of the prevalence of occult thyroid carcinoma in the Atomic Bomb Casualty Commission (ABCC) autopsy series, which is drawn from a large fixed population in Hiroshima and Nagasaki, Japan. This study yielded the highest prevalence of occult thyroid carcinoma of any autopsy series, and concluded that there probably was a substantial difference between the prevalence rate of this tumor in Japan and in the United States, even if all Japanese patients exposed to ionizing radiation at the time of the atomic bomb explosion are excluded. In the present study we used the same pathologic methods and diagnostic criteria as in the Japanese study and examined thyroid glands from the Olmsted County autopsy series. This series is drawn from a population for which the clinical incidences of thyroid carcinoma[16] and of the other thyroid diseases[4–6] have already been reported. The total number of autopsies in the present series (157) is relatively small but, because of the uniformity in the investigative methods and the large differences in the previous Japanese and American series, it was considered to be sufficient to detect any difference between the two populations as large as that suspected from the earlier studies.

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MATERIALS AND METHODS

During the period October 10, 1969, through May 22, 1970, there were 362 deaths among the residents of Olmsted County (1970 census, 83,955). Postmortem examination, either at the Mayo Clinic or at Olmsted Community Hospital, was performed in 202 (56%). The reason for this relatively high autopsy rate

is that an attempt is made to obtain an autopsy on all county residents regardless of place of death. Most deaths among the residents of Rochester either occur in a hospital or a nursing home or occur as "sudden deaths," which are considered coroner's cases. Among residents of the county outside of Rochester, there is a lower autopsy rate, particularly in regard to deaths among the elderly at home and in nursing homes.

In 157 of these 202 autopsies, the entire formalin-fixed thyroid gland and routine sections taken at autopsy were available for study. In the remaining 45 cases, the formalin-fixed thyroid gland was not available. These 45 cases were compared to the 157 study cases with respect to sex ratio, age at death, and autopsy diagnosis of thyroid disease; there were no significant differences between these two groups. Thus, the loss of thyroid tissue that occurred during the autopsy is interpreted as an unbiased loss and should not affect the prevalence figures obtained.

The method of examination was chosen to conform to that of the previous study,[11] the thyroid material examined being similar to the "complete thyroid" category in that study. The same pathologist (R.J.S.) performed the gross and microscopic examination of the thyroid tissue in both studies. The glands were cut with a scalpel into blocks at 2- to 3-mm intervals in the plane of section used by the pathologist who performed the autopsy. The thyroid sections were examined for nodules, with the particular purpose of identifying small thyroid carcinomas. A nodule was defined as an area of the thyroid different in color or consistency from the surrounding tissue. Histologic sections were prepared of all nodules. Those that proved microscopically to be carcinomas were generally white, less than 0.5 cm in maximal dimension, firm, and without gross encapsulation. In addition to sections of nodules, at least one histologic section was prepared from each lobe of the gland even if no gross lesion had been seen. Blocks of thyroid tissue not sectioned were stored in formalin. Additional histologic sections were

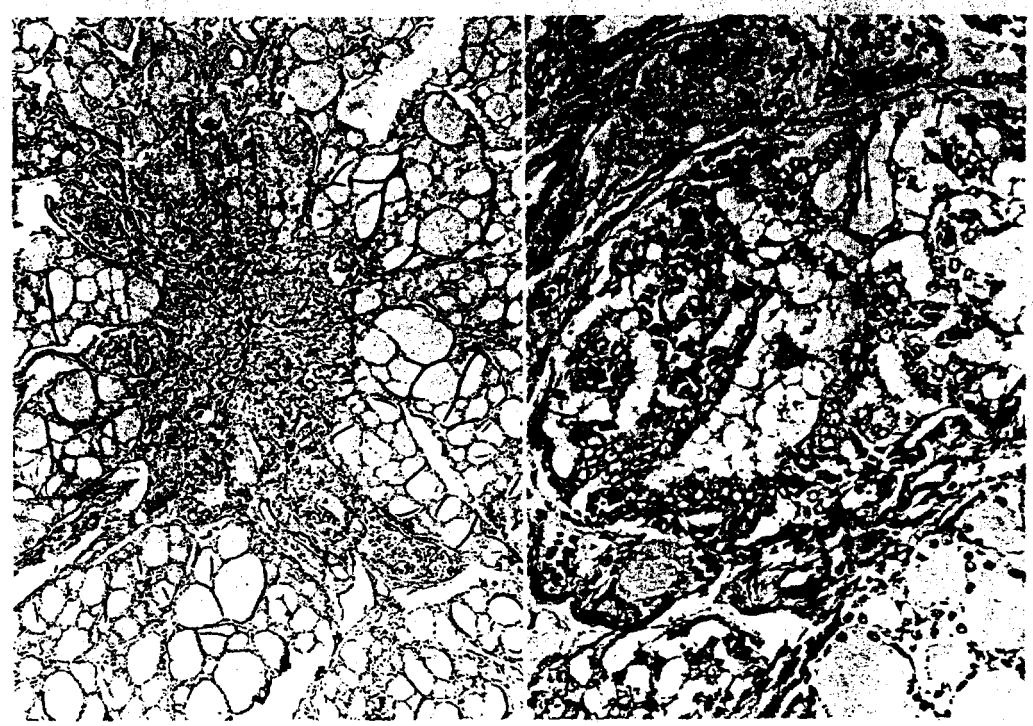

FIG. 1. Occult papillary carcinoma (*0.3 × 0.3 cm*). Surrounding thyroid tissue is infiltrated by neoplastic follicles and poorly formed papillae. The cells lining these have the irregular vesicular nuclei characteristic of papillary carcinoma. There is stromal sclerosis (H & E; *left*, ×40; *right*, ×225).

prepared later from this tissue when necessary. In most instances, however, the reserved, grossly normal tissue was not examined microscopically.

All microscopic slides of the thyroid glands, whether made at autopsy or as part of the present study, were arranged in order of autopsy number and re-examined separately by the same pathologist. Histologic abnormalities were coded and recorded in the same manner as in the Japanese study. Additional sections were made and stained with elastic tissue stains when a slide was suspected of containing carcinoma. After this systematic examination, all positive and suspected cases of carcinoma were re-examined by two pathologists (R.J.S. and L.B.W.), and final decisions as to cancer type, measurements, and other histologic features were made.

The criteria for the diagnosis and classification of thyroid cancer were the same as in the Japanese study. These were based on Hazard's[7] criteria for the diagnosis of thyroid carcinoma, and are consistent with the criteria used in previously published Mayo Clinic studies[17] of occult thyroid carcinoma in surgically resected glands.

FIG. 2. This small tumor (0.05 × 0.03 cm) has cells similar to those in Fig. 1, but there is no invasion or sclerosis. This is a typical "circumscribed microcarcinoma"[12] (H & E, ×200).

RESULTS

There were 9 cases of thyroid carcinoma found in the 157 study cases (5.7%). The sex-specific rates were 7/99 (7.1%) for males and 2/58 (3.5%) for females. These sex-specific rates are not significantly different.

There were too few tumors to permit computation of a meaningful age-specific rate, but there was no suggestion of an increase in prevalence of these tumors with age. The mean age of all males was 65.8 years; for all males with occult thyroid carcinoma the mean age was 64.8 years. The mean age for all females was 68.6 years; for all females with occult thyroid carcinoma it was 64.5 years.

Eight of the 9 tumors in this series were of the papillary type, having the irregular vesicular nuclei that Hazard[7] regarded as characteristic of this type of tumor. The carcinomas were similar in size, distribution, and microscopic appearance to the tumors found in the ABCC series. All were less than 1.5 cm in maximal dimension, and thus were properly classified as "occult" thyroid carcinomas (Fig. 1). The 2 smallest tumors were identical to the 86 "circumscribed microcarcinomas" described previously for the ABCC series (Fig. 2).[12] Three of the 8 Olmsted County cases of papillary carcinoma were multifocal. This is very close to the prevalence of multifocality in the ABCC papillary carcinomas (170/525, 32.4%). The single medullary carcinoma was a small invasive tumor, similar to the single such tumor in the ABCC series.

DISCUSSION

Method of Examination

Comparisons of the prevalence of thyroid carcinoma by different authors (Table 1) are difficult because differences in methods of examination and in criteria of diagnosis can cause a marked difference in the recorded prevalence. The high prevalence in the present series relative to previous American series is probably a reflection of such variation. Comparison between the present study and the previous study[11] of the prevalence of thyroid carcinoma in Hiroshima and Nagasaki is more reliable, because the examination of all the thyroid glands in each study was by the same pathologist and the present study was

TABLE 1. Prevalence of Thyroid Carcinoma at Autopsy in American and Japanese Series in Which Thyroid Gland Has Been Thoroughly Examined

Reference	City	Thyroid carcinoma		
		Cases (no./total)	Prevalence (%)	95% confidence interval (%)
	American studies			
Hazard and Kaufman[8]	Cleveland	4/429	0.9	0.3–2.4
Hull[9]	Denver	3/221	1.4	0.3–4.0
Queen[14], cited by Hull[9]	Portland, OR	20/1,217	1.6	1.0–2.5
Silverberg and Vidone[14]	New Haven, CT	8/300	2.7	1.2–5.3
Mortensen et al.[10]	Rochester, MN	28/1,000	2.8	1.9–4.1
Brierre and Dickson[1]	Bethesda, MD	4/100	4.0	1.1–10.2
Farooki[3]	Philadelphia, PA	1/220	0.45	0.0–2.6
Present study	Olmsted County, MN	9/157	5.7	2.6–10.8
	Japanese studies			
Yagawa et al.[18]	Iwate and Shinshu	44/320	13.7	10.0–18.5
Sampson et al.*[11]	Hiroshima and Nagasaki	196/1,096	17.9	15.5–20.6
Sampson et al.†[11]	Hiroshima and Nagasaki	111/391	28.4	23.4–34.2
Fukunaga and Lockett[3]	Honolulu‡	24/100	24.0	15.4–35.7

* Includes only cases in the "complete thyroid" category and not exposed to direct radiation at the time of the bomb fall (comparable to the present study).
† Microscopic slides were made from each section (comparable to Fukunaga and Lockett's[3] study).
‡ Japanese residents.

similar to the previous study in both the methods of finding the carcinomas and in their classification.

Sex, Age, and Radiation Exposeure

The marked female preponderance of patients with clinically apparent thyroid carcinoma is well known. However, previously published autopsy series show only a slight excess of cases of occult thyroid carcinoma in females. The ABCC series[11] had a small but significant female preponderance, but it was demonstrated[18] that this may have been the result of the greater size of these tumors in females with consequent greater ease of recognition. The higher rate for males in the present series is not statistically significant. These data suggest that occult thyroid carcinoma is probably about as frequent in males as in females, but progression to the larger, clinically apparent tumors is more frequent in females.

Differences in the age distribution of an autopsy series could affect the prevalence of

TABLE 2. Composition of Autopsy Series and Prevalence of Thyroid Carcinoma by Age and Sex

Series	Sex	Observation	Age groups (years)				
			0–20	21–40	41–60	61–80	>80
Hiroshima–Nagasaki	Males (1,614)	Total autopsies (% of series)	0.9	6.4	16.9	63.3	12.5
		Thyroid carcinomas (age-specific prevalence)	7.1	7.8	16.8	16.4	15.3
Olmsted County	Males (99)	Total autopsies (% of series)	1.0	4.0	26.3	44.4	22.2
		Thyroid carcinomas (age-specific prevalence)	0	0	15.3	4.5	0
Hiroshima–Nagasaki	Females (1,453)	Total autopsies (% of series)	0.4	5.6	19.1	53.4	21.5
		Thyroid carcinomas (age-specific prevalence)	0	14.8	18.8	21.5	16.3
Olmsted County	Females (58)	Total sutopsies (% of series)	6.8	1.7	13.8	48.3	29.3
		Thyroid carcinomas (age-specific prevalence)	0	0	12.5	3.5	0

occult thyroid carcinoma, if this prevalence varied with age. In the Japanese and American series, however, neither the differences in age distributions nor the differences in age-specific prevalence rates vary enough to affect the comparison greatly (Table 2). The greater prevalence of occult thyroid carcinoma in the Hiroshima-Nagasaki series is not due to exposure to radiation from the atomic bomb since, in this comparison, only those Japanese patients were included who either were not in Hiroshima or Nagasaki at the time of the bombing or were so far away from the hypocenter as to receive no direct radiation.

Geographic Differences

Since differences in the age distribution, sex distribution, and radiation exposure cannot account for the differences between the ABCC series and the present series and since the method of examination and diagnostic criteria were uniform, we conclude that there is indeed a much higher prevalence of occult thyroid carcinoma among the Japanese than among the residents of Olmsted County. Environmental differences are great between the two groups; many of these are known to affect the thyroid. The iodine intake among the Japanese is higher than in Minnesota and virtually all from natural sources. Exposure to carcinogens through the air and water pollution may be greater in Japanese cities than in Olmsted County. But the study of occult thyroid carcinomas among the Japanese of Hawaii showed a prevalence as high as in the Hiroshima-Nagasaki series with no difference between first- and second-generation Japanese, so that genetic as well as social and cultural factors should be considered as etiologic possibilities.

Despite the high prevalence of occult thyroid carcinoma, the Japanese have a very low incidence rate and death rate of thyroid carcinoma. The factors that cause a small tumor to form may be dissociable from those that make it grow to be a clinically evident tumor or to be aggressive enough to cause death.

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