Thyroid Carcinoma in Sendai, Japan

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FUKUNAGA, F.H., YATANI, R. and SASANO, N. Thyroid Carcinoma in Sendai, Japan. Tohoku J. exp. Med., 1974, 113 (2), 181-185 — Microscopic examination of serially step-sectioned thyroid glands from 102 unselected autopsies of Japanese adults living in northeastern Honshu, Japan, revealed 28.4% occult papillary carcinomas. This is essentially similar to the findings reported in the Japanese living in Hawaii and the Atomic Bomb Casualty Commission group in Southern Japan. The prevalence of occult thyroid carcinomas in the Japanese appears to be approximately the same in Northern and Southern Japan and in Hawaii. —— serial step-section; occult carcinoma; papillary carcinoma

The reported prevalence of occult carcinomas of the thyroid gland varies considerably. The thyroid glands in unselected autopsies revealed 24% occult carcinomas in the Japanese living in Hawaii (Fukunaga and Lockett 1971) and 17.9% of native Japanese in the Atomic Bomb Casualty Commission (ABCC) study in Hiroshima and Nagasaki, Japan (Sampson et al. 1969). American reports, however, revealed only a 0.45 to 4.0% prevalence (Hazard and Kaufman 1952; Mortensen et al. 1954; Briere and Dickson 1964; Farooki 1969a, b). This variation may be due in part to the lack of standardized methods of examination and different diagnostic criteria. Only grossly recognized lesions were examined in the American series. Hazard and Kaufman sectioned the glands at 1 to 3 mm intervals and removed grossly identified lesions for histologic examination (Hazard and Kaufman 1952). Mortensen et al. (1954) cut the glands at 2 mm intervals and removed representative nodules for histologic sectioning. Briere and Dickson (1964) identified lesions grossly by transillumination using an x-ray viewbox. Farooki (1969a) sectioned the glands at 3 mm intervals and examined microscopically only grossly abnormal areas. Sampson et al. (1969) sliced the glands at 2 to 3 mm intervals and examined microscopically all nodules which were defined as areas that differed in color and consistency from the surrounding gland. However, one group of glands at the ABCC was serially sliced at 3 to 4 mm intervals and

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a microscopic slide was made from each. In the first study of thyroid glands from Hawaii-Japanese in this institution, the entire gland was serially step-sectioned and a microscopic slide was made from each section. The criteria for diagnosis of carcinoma were those described by Hazard (1964). The slides of tumors were reviewed and the diagnoses were concurred by Dr. Hazard. The ABCC group in Japan used the same diagnostic criteria. A study of thyroid glands from the Japanese living in Northeastern Honshu using the same criteria and methods was initiated to determine the relative prevalence of carcinomas and to compare the results with the studies in Southern Japan and Hawaii.

**MATERIALS AND METHODS**

A series of 105 unselected thyroid glands were removed at autopsies performed at the Tohoku University Hospital in Sendai, Japan. Three cases were eliminated because only the right lobe was available in two and the third was from a year old infant. The glands were fixed in a formaldehyde solution and shipped to Kuakini Hospital in Honolulu, Hawaii. Each gland was serially sliced at 2 to 3 mm intervals and a histologic slide was made from each section. Each slide was examined separately by two pathologists (FHF and RY) and all lesions were re-examined by both.

The carcinoma was classified as occult if it was less than 1.5 cm in diameter and unsuspected clinically. The histologic diagnosis of papillary carcinoma described by Hazard (1964) is based upon cytologic features. The tumor cells have a pale cytoplasm and large vesicular to ground-glass appearing nuclei with prominent nuclear membranes that appear etched (Fig. 1). Most of the lesions show delicate papillae with a fibrovascular stalk lined by the neoplastic cells but some lesions have a predominantly follicular pattern with the same type of cell. There usually is some degree of fibrosis varying from small foci to the typical nonencapsulated sclerosing tumor pattern.

**RESULTS**

All of the carcinomas found in this study were occult and papillary. There were 29 cases of carcinomas in 102 thyroid glands. The prevalence of occult carcinomas did not appear to be influenced by sex or age. There were 16 carcinomas in 59 men (27.1%) and 13 in 43 women (30.2%). There were 10 tumors in the 32 individuals less than 50 years of age (31.2%) and 19 in the 70 persons over 50 years (27.1%). Five cases had two or more primaries. There were 14 cases with one or more lesions in the right lobe, 2 in the isthmus, 9 in the left lobe, 3 in both lobes and 1 case in the isthmus and right lobe. Fifteen of the carcinomas were noted grossly as a gray-white lesion, but there were 13 other cases that had similar gross lesions that were negative microscopically. Fourteen of the carcinomas were missed grossly but most of these were less than 0.1 cm in diameter. The tumors varied from less than 0.1 cm to 1.4 cm in diameter (Table 1).

The glands varied in weight from 6 to 52 g with a mean of 21.1 g (S.D. 8.6 g) and median of 20 g. The glands with a carcinoma did not differ significantly. They weighed 6.5 to 52 g with a mean of 23.9 g (S.D. 11.0 g). If 35 g is considered to be the upper limits of normal, 7 glands could be classified as goitrous and 5 of these had an occult papillary carcinoma. If 30 g is the preferred upper normal, then there were 11 goitrous glands and 6 had an occult carcinoma. There were 22
glands with nodules of varying sizes and numbers and 5 of these had an occult carcinoma including 2 glands with a single carcinomatous nodule.

Psammoma bodies were found in only 1 gland which also had an occult carcinoma. There was significant lymphocytic infiltration in 3 cases but none showed an occult carcinoma. There were 2 cases of cryptococcosis. The gland of a 24-year-old man with disseminated lupus erythematosus had discrete granulomas with organisms and that from a 43-year-old woman with idiopathic thrombocytopenic purpura showed numerous groups of organisms without any cellular reaction. Both patients were on long term prednisolone therapy and had systemic cryptococcosis. Six thyroids showed metastatic carcinomas, one each from the lung, stomach, pancreas, rectum, maxillary sinus and one unknown primary. Solid cell nests described by Yamaoka (1973) were found in 25 glands, heterotopic cartilage in 2 and both solid cell nests and cartilage in 2 glands. There were bone marrow emboli in 2 glands.

Fifty eight of the cases died of some type of neoplasm and 15 of these had an occult thyroid carcinoma (25.9%). There were 14 occult thyroid carcinoma in the remaining 44 cases who died of non-neoplastic diseases (31.9%).

**Table 1. Size of occult carcinomas**

<table>
<thead>
<tr>
<th>Size</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1 mm</td>
<td>4</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>1 to 2.99 mm</td>
<td>7</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>3 to 9.99 mm</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>10 to 15 mm</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>13</td>
<td>29</td>
</tr>
</tbody>
</table>
**TABLE 2. Prevalence of thyroid carcinoma at autopsy**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>City</th>
<th>Number of glands</th>
<th>Number of carcinomas</th>
<th>Preval. (%) with 95% confidence limits*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard &amp; Kaufman (8)</td>
<td>1952</td>
<td>Cleveland</td>
<td>429</td>
<td>3</td>
<td>0.14- 0.70- 2.94</td>
</tr>
<tr>
<td>Mortensen et al. (9)</td>
<td>1954</td>
<td>Rochester, Minn.</td>
<td>1000</td>
<td>28</td>
<td>1.84- 2.80- 4.02</td>
</tr>
<tr>
<td>Brierre &amp; Dickson (1)</td>
<td>1964</td>
<td>Bethesda, Md.</td>
<td>100</td>
<td>4</td>
<td>1.09- 4.00-10.24</td>
</tr>
<tr>
<td>Farooki (3)</td>
<td>1969</td>
<td>Philadelphia</td>
<td>220</td>
<td>1</td>
<td>0.01- 0.45- 2.53</td>
</tr>
<tr>
<td>Sampson et al.†</td>
<td>1973</td>
<td>Olmsted, Minn.</td>
<td>157</td>
<td>9</td>
<td>2.62- 5.73-10.88</td>
</tr>
<tr>
<td>Sampson et al. (12)</td>
<td>1969</td>
<td>Hiroshima, Japan</td>
<td>950</td>
<td>170</td>
<td>15.28-17.89-20.77</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serially blocked and sectioned</td>
<td>391‡</td>
<td>111</td>
<td>23.30-28.39-34.13</td>
</tr>
<tr>
<td>Fukunaga &amp; Lockett (4)</td>
<td>1971</td>
<td>Honolulu</td>
<td>100‡</td>
<td>24</td>
<td>15.16-24.00-35.46</td>
</tr>
<tr>
<td>Fukunaga et al.†</td>
<td>1971</td>
<td>Canada</td>
<td>100‡</td>
<td>6</td>
<td>2.20- 6.00-13.06</td>
</tr>
<tr>
<td>Present series</td>
<td>1973</td>
<td>Sendai, Japan</td>
<td>102‡</td>
<td>29</td>
<td>18.82-28.43-40.59</td>
</tr>
</tbody>
</table>

* 95% confidence limits (Poisson).
† Unpublished data.
‡ Microscopic slides were made from each slice from a serially-sectioned thyroid gland while only grossly visible lesions were examined microscopically in the other studies.

**DISCUSSION**

The 28.4% prevalence of occult thyroid carcinomas in Sendai is essentially similar to that found in Southern Japan in the ABCC study and in the Hawaii-Japanese where the thyroid glands were examined in an identical manner (Table 2). There is a markedly increased prevalence of occult thyroid carcinomas in the Japanese when compared to studies in Canada and the United States. However, the age-adjusted death rates due to thyroid malignancies do not differ significantly in these countries (Segi and Kurihara 1972).

Carcinomas are believed to be initiated by some carcinogen and their growth chemical or ionizing radiation but heredity is a constant modifier of host response (Furth 1963). The relatively greater number of occult and small number of clinical thyroid carcinomas in the Japanese suggest increased sources of carcinogens but less active promoting factors.

The high prevalence of occult carcinomas and the absence of fatalities due to thyroid carcinomas suggest their slow growth and relative innocuous behavior. However, the reported incidence of regional metastases from occult sclerosing carcinomas has been as high as 43% (Woolner et al. 1961), as high as 90% in clinically diagnosed papillary carcinomas (Noguchi et al. 1970), and rare cases of hematogenous spread have been reported (Patchesky et al. 1970). Well differentiated papillary carcinomas and their metastases generally are slow growing and survival for over 35 years in comfort with metastases has been reported (Shelly et al. 1973). Most papillary carcinomas probably remain occult until death and only a few become clinically detectable and only rarely cause death.

The absence of any influence of age upon the frequency of these tumors suggests either that they are all formed in youth and show little progression, or that tumors are continuously being formed and undergoing involution.
References