High frequency of cancer in cold thyroid nodules occurring at young age

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Abstract. In order to evaluate the risk of malignancy of cold thyroid nodules occurring in young as compared with adult patients, we studied a consecutive series of 2327 patients with a solitary cold thyroid nodule over a 6-year period. None of these patients had been previously irradiated in the neck or head. Fine needle aspiration of the nodule and cytologic examination were carried out in all patients and, on the basis of this evaluation and clinical examination 391 patients were selected for surgery; 109 patients were 4–20 years old and 2218 patients were older than 20 years. Malignancy was found in 11 (10.1%) and in 112 (5.0%) of cold thyroid nodules occurring in young and adult patients, respectively. The annual incidence of cold thyroid nodules in the population of the area studied was 5.2 vs 55.9 (per 10⁵ inhabitants) in the young and in the adult group, respectively, and the annual incidence of thyroid cancer was 0.53 vs 2.82 (per 10⁵ inhabitants) in the young and in the adult patients, respectively. The present study indicates, therefore, that in the absence of head or neck irradiation, cold thyroid nodules are much less frequent in young age, but that the malignancy rate of cold nodules occurring in young patients is 2-fold higher than in adults patients.

A high malignancy rate of thyroid cold nodules, ranging from 14 to 40%, has been reported in children and adolescents (1,2). This high frequency has been related to a previous head or mediastinum exposure to therapeutic irradiation (3, 4). Whether thyroid cold nodules are more frequently malignant in young patients, even in the absence of irradiation is not known.

In the attempt to assess the role of age as a risk factor for thyroid cancer, we carried out a cross-sectional study to evaluate the incidence rates of both thyroid cold nodules and thyroid cancer in the young as compared with adults. The risk for a solitary thyroid cold nodule to be cancerous was also estimated in the two groups.

All cold nodules were examined by cytology after fine-needle aspiration biopsy (FNAB). Our experience, as well as that of others is that cytology is a valid method for the pre-operative selection of patients with a cold nodule (5,6) and can, therefore, be applied to an epidemiologic survey of malignancy in cold thyroid nodules.

Our study meets the following requirements: a) no patient studied had a previous history of exposure to neck/head irradiation or was coming from iodine-deficient areas, factors known to have a role in the development of thyroid cancer (4,7,8); b) identical criteria have been used in the two age group to select patients for surgery and to classify tumour histotype.

Our results, showing a higher frequency of cancer in thyroid cold nodules occurring at young age support the possibility that age is a factor to be considered in the evaluation of the malignancy risk of thyroid nodules.
Patients and Methods

Patient population and study design

This study includes 2327 consecutive patients with a diagnosis of a solitary cold thyroid nodule, referred to our Thyroid Clinic in the 6-year period of 1980–1985.

All patients fulfilled the following criteria:

1) They were born and living in the town of Catania or in the surrounding suburbs and small towns, an area with a sufficient iodine intake (goitre prevalence in school children: 2.2%; daily urinary iodine excretion: 113.8 ± 8.4 μg/day; radiiodine uptake 31.6 ± 1.5%) (9). As previously reported, the majority of all thyroid patients living in this area are referred to our clinic and are seen by the same medical staff (10).

2) They had one palpable thyroid nodule at clinical examination that was non-hyperactive (cold) at thyroid scanning with either 131I or 99mTc.

3) They had no previous history of neck or head irradiation (7 adult patients and 1 child with a positive history were excluded from this study).

The diagnosis of solitary cold nodule was made on a clinical and scintigraphic basis by the team examining the patient (the endocrinologist, the nuclear medicine doctor, and the thyroid cytologist).

This series of patients is partially different from the one described in a previous report (5) mainly because it comes from a larger area and concerns a period of time that is only in part similar, and because of the aforementioned exclusion criteria. Patients were divided into two groups according to their age at the time of diagnosis: a) 109 patients 4–20 years old; b) 2218 patients older than 20 years.

Cytologic examination of thyroid cold nodules

Fine needle aspirates of all thyroid nodules were obtained by means of a 23-gauge hypodermic needle as previously described (11). Smears (at least 3 for each nodule) were fixed in alcohol and stained by a Papanicolau method. They were then independently examined by two cytologists. When disagreement occurred between the two cytologists (less than 4% of the cases) the findings were discussed with a third cytologist. The ‘worst’ diagnosis was accepted when an agreement was not reached (less than 1% of the cases). Smears were classified (11,12) as follows:

Class 0: inadequate sample (due to insufficient material collected).

Class 1: benign lesion: normal follicular thyroid cells with or without some benign abnormality or sign of inflammation.

Class 2: follicular lesion: cells uniform in size and shape with mild to moderate atypia.

Class 3: suspicion of malignancy: cell characteristics compatible with thyroid cancer even if the finding was not generalized and certain.

Class 4: malignant (papillary, medullary and anaplastic): epithelial cells with unequivocally atypical characteristics (nuclear inclusions, psammoma bodies, papillary fragments).

Surgery and histologic examination

Immediate surgery was strongly recommended to all patients classified in the classes 3 and 4. Patients with class 2 lesions were also advised to undergo surgical excision of the nodule for histologic examination. In addition, surgery was recommended to all patients who showed one or more clinical findings suggesting the possibility of malignancy, either at the first observation or during the follow-up period (suspicious laterocervical lymph nodes, dysphonia owing to vocal cord paresis, recurrent hemorrhagic cyst, nodule growth despite suppressive L-thyroxine treatment). Histopathologic diagnoses reported in the present study were graded according to the thyroid malignancy WHO classification (13). Mixed (papillary-follicular) thyroid carcinomas were classified as papillary carcinomas.

Table 1.

Cytologic and histologic diagnoses of 109 solitary cold thyroid nodules occurring in young patients.

<table>
<thead>
<tr>
<th>Cytologic diagnosis</th>
<th>Patients examined by FNAB (No.)</th>
<th>Surgery at histology (%)</th>
<th>Cancer (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant</td>
<td>9</td>
<td>9 (100)</td>
<td>9</td>
</tr>
<tr>
<td>Suspicious of malignancy</td>
<td>2</td>
<td>2 (100)</td>
<td>1</td>
</tr>
<tr>
<td>Follicular lesion</td>
<td>17</td>
<td>6 (35.3)</td>
<td>1</td>
</tr>
<tr>
<td>Benign</td>
<td>78</td>
<td>5 (6.4)</td>
<td>0</td>
</tr>
<tr>
<td>Inadequate</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>109</td>
<td>22 (20.2)</td>
<td>11</td>
</tr>
</tbody>
</table>

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Thus, was who patients (112/2218 in noses diagnosis group). The patients underwent surgery. A clinical malignancy (mean = 29.2% ±sd 5.0%) was observed in the young vs 8.8 in the adult patients.

All patients with a thyroid nodule classified by cytology as malignant or highly suspicious of malignancy underwent surgery. Similarly, all the patients with a nodule suspected of malignancy on a clinical basis, during the period of observation, but with a benign or inadequate cytology also underwent surgery (2 in the young and 48 in the adult group). Surgery was also performed in 35.3 and 29.2% of young and adult patients with a cytologic diagnosis of follicular lesion. The cytologic diagnoses in both young (Table 1) and adult (Table 2) patients were compared with the histologic diagnoses obtained in patients from the two groups who underwent surgery. At histology, a carcinoma was found in 11 young and in 112 adult patients. Thus, the observed frequency of thyroid cancer in the young patients with a cold nodule (11/109 - 10.1%) was significantly higher (p < 0.02) than in the group of adult patients with a cold nodule (112/2218 = 5.0%). This finding indicates a 2-fold higher risk of malignancy in cold thyroid nodules of young patients, which reflects an increase in the frequency of all types of differentiated carcinomas (Table 3).

Considering the age distribution of the population in the area of Catania (345,389 inhabitants were ≤20 years old and 660,188 were older than 20 years) (14) we estimated the incidence of clinically evident cold nodules and clinically evident thyroid carcinomas in the two age groups. The observed annual incidence of cold thyroid nodules was 5.2 vs 55.9 cases/10^5 inhabitants in the young and in the adult population, respectively. Cold thyroid nodules, therefore, are about 10-fold more frequent in adults. The annual incidence of thyroid cancer was calculated to be 0.53 vs 2.82/10^5 inhabitants in the young and in the adult population, respectively; the incidence of thyroid cancer, there-

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**Table 2.**
Cytologic and histologic diagnoses of 2218 cold thyroid nodules occurring in adult patients.

<table>
<thead>
<tr>
<th>Cytologic diagnosis</th>
<th>Patients examined by FNAB (No.)</th>
<th>Surgery (No.) (%)</th>
<th>Cancer at histology (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant</td>
<td>93</td>
<td>93 (100)</td>
<td>89</td>
</tr>
<tr>
<td>Suspicious of malignancy</td>
<td>29</td>
<td>29 (100)</td>
<td>6</td>
</tr>
<tr>
<td>Follicular lesion</td>
<td>400</td>
<td>117 (29.2)</td>
<td>12</td>
</tr>
<tr>
<td>Benign</td>
<td>1550</td>
<td>119 (7.7)</td>
<td>4</td>
</tr>
<tr>
<td>Inadequate</td>
<td>146</td>
<td>11 (7.5)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2218</td>
<td>369 (16.6)</td>
<td>112</td>
</tr>
</tbody>
</table>

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**Statistical analysis of the data**
The Pearson chi-square test was used for contingency-table analysis.

**Results**

One hundred and nine patients were studied in the young group (mean age ± sd = 16.25 ± 3.3 years, median age = 17) and 2218 in the adult group (mean age ± sd = 43.5 ± 13.5 years, median age = 45). A clear prevalence of the female sex, similar in both groups examined, was observed (female to male ratio 8.0 in the young vs 8.8 in the adult patients).

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**Table 3.**
Histologic classification of thyroid carcinomas in the young and adult groups.

<table>
<thead>
<tr>
<th></th>
<th>Young group (%)</th>
<th>Adult group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients examined</td>
<td>109</td>
<td>2218</td>
</tr>
<tr>
<td>Total cancers</td>
<td>11 (10.1)</td>
<td>112 (5.0)</td>
</tr>
<tr>
<td>Papillary</td>
<td>8 (7.3)</td>
<td>86 (3.9)</td>
</tr>
<tr>
<td>Follicular</td>
<td>2 (1.8)</td>
<td>23 (1.0)</td>
</tr>
<tr>
<td>Medullary</td>
<td>1 (0.9)</td>
<td>3 (0.1)</td>
</tr>
</tbody>
</table>

a: p < 0.02 young vs adult group.
b: p < 0.07 young vs adult group. c: NS.
d: p < 0.05 young vs adult group.
fore, is 5 times more frequent in the adult population. In contrast to the similar female to male ratio (8.9 vs 8.8), a significant difference in the sex distribution was found in patients of the two age groups with a cold nodule. The female to male ratio for patients with a thyroid cancer was 4.5 in the young and 7.0 in the adult group. Therefore, in patients younger than 20 years and with a cold nodule of the thyroid, the risk of malignancy is about 2-fold higher in males than in females. This risk declined sharply in the 3rd decade of age, and when the group of patients 21–40 years old was examined, the annual incidence rate for both nodules (53.8 cases/10^5 inhabitants) and thyroid cancer (2.7 cases/10^5 inhabitants) was similar to what was observed in the whole adult population.

The average nodule size of the cancers observed was not significantly different in the two groups examined. Mean diameter, in fact, was 2.1 ± 0.8 vs 2.9 ± 2.4 cm in young and adult patients, respectively. Cancers smaller than 1.5 cm were 0/11 vs 13/112 in the young and in the adult group, respectively. In addition, no significant difference in tumour aggressiveness was observed between the two groups. Distant metastases were seen in 1/11 (9.1%) patients and metastatic lymph nodes in 3/11 (27.3%), in the young group vs 8/112 (7.1%) and 44/112 (39.3%) patients in the adult group. A goitre was associated in 2/11 of the young patients and in 36/112 adult patients with cancer. No significant associated disease and no family history positive for thyroid cancer were recorded in the young patients with a thyroid malignancy.

Discussion

A correct approach to cancer in terms of prevention, early diagnosis and treatment requires an assessment of the impact of different risk factors in cancer incidence and evolution (15, 16). Genetic (17, 18), racial (19) and environmental factors such as iodine deficiency (5,8) and neck/head irradiation (3,4,20,21) are generally believed to be risk factors for thyroid cancer.

Tumour characteristics such as histologic type, size of tumour, presence of local invasion, lymph node involvement and metastases to distant sites are some of the factors that may influence the prognosis of patients with thyroid cancer (15, 22).

The role of age as a risk factor for thyroid cancer is not well established. The increased frequency reported in young patients (from 14 to 40% of children with cold nodules) (1), has been attributed to the previous therapeutic irradiation of the neck and/or head received during infancy for benign diseases. A clear association between head or neck irradiation in childhood and the susceptibility to develop both benign and malignant lesions of the thyroid (23,4) and the salivary gland as well as neural tumours (24, 25) is well established. When the use of therapeutic neck irradiation was discontinued, a decreasing incidence of thyroid cancer in children was reported (26). Previous irradiation, therefore, clearly increases the malignancy rate in thyroid nodules of young patients, but no accurate estimation of cancer in non-irradiated young patients has been made.

In this study we have compared the prevalence and the characteristics of thyroid cancer in two groups of patients living in the same iodine-sufficient area with no history of head or neck irradiation, but differing in age. Different evidences suggest that the procedures used were adequate in the evaluation of the risk of cancer in the cold thyroid nodules occurring in the two age groups of patients examined. First of all, our clinic sees the majority of thyroid patients in the area studied (10); our series, therefore, represents an adequate sample of the age group under study. Second, the therapeutic use of radiation for benign diseases has rarely been used in this area and has not been used at all in the last 20 years. Also, all patients studied were negative for head/neck radiation history. Third, the possible bias of the pre-operative selection of thyroid nodules was minimized by routine use of cytologic examination by fine needle biopsy. Because of its diagnostic accuracy, this technique represents a valid method for the epidemiological detection of malignant lesions (5, 6). In our study, all patients with a nodule malignant at cytology or suggestive of malignancy either at cytology or at clinical examination, underwent surgery. Subjective selection criteria were, therefore, avoided. Fourth, the cytologic and pathologic diagnoses were always made by the same cytologists and by the same team of pathologists; homogeneity in the classification was, therefore, obtained. Using these procedures and in accordance with other studies (27), we observed that thyroid nodules occur less frequently in young patients.
than in adults. Moreover, the estimated annual incidence of 0.055% for thyroid nodules in the adult population represents a value very similar to that reported in other epidemiological studies (1), thereby supporting the validity of our cross-sectional survey.

In contrast to the lower frequency of thyroid nodules in young age, we observed that the risk of malignancy for a cold thyroid nodule occurring in a young patient is about 2-fold higher than in an adult patient. This observation suggests the possibility that age itself, independently of radiation, is a risk factor for thyroid cancer and that therefore, this factor should be considered when evaluating and managing the thyroid nodule occurring in young patients. Cold thyroid nodules are more frequent in females and we have observed a similar female/male ratio in both young and adult patients: the risk of malignancy of cold nodules occurring in the young group, however, is about 2-folds higher in males than in females. Thus, our study suggests that young males with a cold thyroid nodule represent a high-risk group for thyroid cancer.

The reasons for the higher frequency of thyroid cancer in cold thyroid nodules occurring in young patients compared with adults is not clarified by our study. It may merely reflect an increased susceptibility of the young thyroid tissue to various environmental factors (e.g. viral, hormonal, increased background radioactivity (28)) other than the well recognized therapeutic irradiation. In support to this explanation is the increased sensitivity of the thyroid of young subjects to a variety of known goitrogenic and oncogenic agents (22). Thyroid carcinomas observed in the group of young patients did not show, however, a higher degree of aggressiveness in comparison to carcinomas occurring in the adults. This observation differs from that reported by Schlumberger et al. (29) indicating a high aggressiveness in thyroid cancer occurring at young age. Different selection criteria and different age cut-off (16 years was the cut-off considered in the report of Schlumberger) may explain these non-univocal findings.

Given the high risk for cancer in thyroid nodules also occurring in young patients without previous neck/head irradiation, all patients under the age of 20 with a cold thyroid nodule should be carefully evaluated by accurate history, clinical examination, and FNA biopsy. When the nodule is benign at cytology and there is no clinical sign to suspect malignancy, a trial with a suppressive dose of L-thyroxine could be attempted. However, we would recommend surgery if a significant reduction of the nodule size is not achieved with adequate treatment.

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References


