

# Gastric Carcinoma and Thyroid Status

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Gastric carcinoma is reported to be more frequent in geographical areas where diets are either iodine-deficient or iodine-excessive. Reports have also shown an association between thyroid diseases and some of the risk factors for gastric carcinoma. We investigated the frequency of thyroid disorders in 61 patients with gastric carcinoma compared with 55 healthy control subjects. Thyroid health was evaluated by physical examination and by measuring the serum levels of thyroid hormones and thyroid autoantibodies.

More patients with gastric cancer had goitre compared with healthy controls (49.1% versus 20%, respectively). Significantly more patients with gastric cancer had non-toxic goitre compared with control subjects. There was also a significant difference in the incidence of autoimmune thyroid disease – 27.8% of patients with gastric cancer versus 10.9% of control subjects were affected. These results indicate that there is a significant association between gastric cancer and thyroid disorders.

KEY WORDS: GASTRIC CARCINOMA; AUTOIMMUNE THYROID DISEASE; THYROID

## Introduction

Gastric cancer remains a major cancer in terms of both incidence and mortality; worldwide, it is the second most common neoplasm.<sup>1</sup> There are well-known risk factors for gastric carcinoma, including the presence of precursor conditions such as chronic atrophic gastritis and intestinal metaplasia, pernicious anaemia and gastric adenomatous polyps. Genetic and environmental factors include a family history of gastric cancer, low consumption of fruit and vegetables, consumption of salted, smoked or poorly preserved foods and smoking cigarettes.<sup>1</sup> There is increasing evidence that *Helicobacter pylori* infection of the stomach is associated with both the initiation and promotion of gastric cancer.<sup>2,3</sup>

Gastric carcinoma may be more prevalent in iodine-deficient areas.<sup>4</sup> The incidence of

gastric cancer is also high in countries such as Japan, China and Korea, where people consume food containing excess iodine.<sup>1</sup> Previous reports have demonstrated an association between thyroid diseases and some of the risk factors for gastric carcinoma: some authors report that *H. pylori* infection, a well-known risk factor for gastric cancer, is putatively associated with extragastrointestinal disorders and may also play a role in the development of autoimmune thyroid diseases (AITD).<sup>5,6</sup> In addition, an association between chronic gastritis and thyroid disorders has been demonstrated in some studies.<sup>7-9</sup>

These findings suggest that there is a possible link between thyroid abnormalities and gastric cancer, and that iodine may play a role in carcinogenesis in the stomach. In the literature, there are insufficient data on

the association between gastric cancer and thyroid abnormalities.<sup>4,10-12</sup> Therefore, we investigated the frequency of thyroid disorders in patients with gastric cancer.

## Patients and methods

### PATIENT POPULATION

This study was undertaken at our Medical Oncology and Endocrinology Departments. Patients with histologically proven gastric cancer were included in this study. All patients were included in the study irrespective of the stage and histological type of gastric tumour. Age- and sex-matched healthy subjects served as controls. Healthy volunteers were recruited among visitors and clinical staff, and their relatives. All of the subjects provided informed written consent prior to their participation in the study. Ethical approval was not required as there were no invasive interventions beyond obtaining blood samples from participants.

### EVALUATION OF THYROID HEALTH

For all subjects, thyroid function was evaluated by measuring serum free  $T_3$ , free  $T_4$ , thyroid stimulating hormone (TSH), thyroid peroxidase antibody (Anti-TPO), and thyroglobulin antibody (Anti-Tg) levels, and performing thyroid ultrasonography and scintigraphy. Serum free  $T_3$  and free  $T_4$  levels were determined using a solid-phase  $I^{125}$  radioimmunoassay, designed for the quantitative measurement of free  $T_3$  and free  $T_4$  levels in serum using the Coat-A-Count™ kit containing radioactive  $I^{125}$ - $T_3$  or  $T_4$  analogue (DPC, Los Angeles, CA, USA). Serum TSH levels were also measured using an immunoradiometric assay designed for quantitative measurement of TSH in serum, which utilized a Coat-A-Count™ kit containing radioactive  $I^{125}$ -polyclonal anti-TSH (Diagnostics Products Corporation, Los Angeles, CA, USA). The normal ranges were:

free  $T_3$ , 2.2 – 6.8 pmol/ml (1.4 – 4.4 pg/ml); free  $T_4$ , 0.8 – 2.0 ng/dl; and TSH, 0.3 – 5.0  $\mu$ IU/ml.

Blood samples from all patients underwent serological determination of thyroid autoantibodies using a direct anti-TPO radioimmunoassay kit for quantitative determination of anti-TPO autoantibodies (Immunotech, Prague, Czech Republic). Autoantibodies specific for thyroglobulin were also measured using a quantitative indirect enzyme immunoassay, based on the sandwich method (antithyroglobulin immunoradiometric assay kit; Immunotech). The normal range for anti-thyroglobulin antibodies was 0 – 60 IU/ml and the range was 0 – 20 IU/ml for anti-TPO antibodies.

Thyroid gland size and the presence of nodular lesions were evaluated by palpation and ultrasonographic examination. Ultrasonographic examination of the thyroid gland was performed by the same radiologist for all subjects, using an ultrasound scan fitted with a hand-held 6.6 – 11 MHz linear transducer (Ultrasound scan, Toshiba 270 SSA, Japan).

### STATISTICAL ANALYSIS

Any differences between the two study groups were analysed using the  $\chi^2$  test. A *P*-value of < 0.05 was considered statistically significant.

## Results

Sixty-one patients with gastric cancer were included in this study; 55 healthy subjects formed the control group. Thyroid gland abnormalities identified on examination in patients with gastric carcinoma and controls are listed in Table 1. The frequency of nodular goitre was significantly higher in the patients with gastric carcinoma compared with the control subjects (*P* = 0.012).

The incidence of functional thyroid

**TABLE 1:**  
The incidence of thyroid gland abnormalities in patients with gastric carcinoma ( $n = 61$ ) and healthy control subjects ( $n = 55$ ) as detected by palpation and ultrasonographic examination

	Patients with gastric cancer $n$ (%)	Control subjects $n$ (%)	$P$ -value
Normal thyroid gland	31 (50.8)	44 (80.0)	0.001
Diffuse goitre	6 (9.8)	1 (1.8)	NS
Nodular goitre	24 (39.3)	10 (18.2)	0.012

NS, non-significant.

disease in patients with gastric carcinoma and control subjects is reported in Table 2. Significantly more of the patients with gastric cancer had non-toxic goitre compared with the control subjects (25 [40.9%] versus 11 [20%], respectively;  $P = 0.015$ ).

Autoimmune thyroid disease was defined by increased serum levels of at least one thyroid autoantibody, and the incidence of autoimmune and non-autoimmune thyroid disorders in patients with gastric carcinoma and control subjects is given in Table 3. The difference in the frequency of AITD between patients with gastric carcinoma and control subjects was statistically significant ( $P = 0.022$ ).

## Discussion

Increased incidence of thyroid cancer and higher rates of mortality due to this tumour

have been reported in geographical areas where the diet is either iodine-deficient or where it contains excess iodine.<sup>13</sup> Deficient and excess iodine levels are also associated with AITD,<sup>13-16</sup> and epidemiological studies demonstrate that the incidence of gastric cancer is high in the same geographical areas where iodine deficiencies and excesses have been reported.<sup>14</sup> There is also a strong association between chronic gastritis and thyroid diseases.<sup>9</sup> In a study performed by Centanni *et al.*,<sup>7</sup> one-third of the patients with AITD also had atrophic gastritis, whereas Syrigos *et al.*<sup>10</sup> reported that significantly more patients with gastric cancer had AITD compared with control subjects. Venturi *et al.*<sup>17</sup> suggested that this association between the thyroid gland and the stomach might be attributable to common organ-specific antigens that occur

**TABLE 2:**  
The incidence of functional thyroid disease in patients with gastric cancer ( $n = 61$ ) and healthy control subjects ( $n = 55$ )

	Patients with gastric cancer $n$ (%)	Control subjects $n$ (%)	$P$ -value
Hyperthyroidism	2 (3.2)	0	NS
Hypothyroidism	3 (4.9)	0	NS
Non-toxic goitre	25 (40.9)	11 (20.0)	0.015

NS, non-significant.

**TABLE 3:**  
 The incidence of autoimmune and non-autoimmune thyroid disorders in patients with gastric cancer ( $n = 61$ ) and healthy control subjects ( $n = 55$ )

	Patients with gastric cancer <i>n</i> (%)	Control subjects <i>n</i> (%)	<i>P</i> -value
Normal	22 (36.1)	40 (72.7)	0.0001
Non-AITD	22 (36.1)	9 (16.4)	0.017
AITD	17 (27.8)	6 (10.9)	0.022

AITD, autoimmune thyroid disorder.

as a result of these organs sharing a common embryonic origin. Chronic atrophic gastritis is regarded as a predisposing factor for gastric carcinoma associated with *H. pylori*.<sup>3</sup> There is increasing evidence for the systemic effects of gastric *H. pylori* infection, which may result in extragastrintestinal disorders. A study has shown that the prevalence of *H. pylori* infection was increased in patients with AITD, and that it resulted in abnormalities of the gastric secretory function.<sup>6</sup> Recently, monoclonal antibodies to an *H. pylori* strain with cytotoxicity-associated antigen A (CagA)-positivity were also shown to react with follicular cells of the thyroid gland.<sup>5</sup> Another study reported that iodine inhibited the vacuolation toxin activity of *H. pylori*.<sup>18</sup> These results suggest that *H. pylori* antigens might be involved in the development of AITD, or that the autoimmune function in patients with AITD might increase the likelihood of *H. pylori* infection.

The role of iodine in the pathophysiology and carcinogenesis of the stomach is unknown. Geographical variations in the incidence of gastric cancer have been attributed to differences in dietary iodine intake, and an effect of iodine on the stomach has been postulated. Venturi *et al.*<sup>4,17,19</sup> have carried out extensive studies on this subject, and have hypothesized that dietary

iodine is associated with the development of some gastric cancers. Their studies have attempted to define the role of iodine in the pathophysiology and carcinogenesis of the stomach using data from various sources. The human stomach and thyroid share many morphological and functional similarities; they both have the ability to concentrate iodides using a membrane-active transport mechanism and an efficient peroxidase activity. Inorganic iodine has a regulatory role in the production of epidermal growth factor in thyroid cells, and it controls DNA synthesis and cell proliferation.<sup>20</sup> Venturi *et al.*<sup>4,17</sup> have shown a trophic regulatory action of iodine on gastric mucosa similar to its action on the thyroid. They have also shown, by studying gastric biopsies, a correlation between iodine deficiency, goitre and atrophic gastritis. Iodine has an antioxidant function. Iodide acts as an optimal electron donor in the presence of hydrogen peroxide and peroxidase. Gastric peroxidase is an endogenous glycoprotein which transfers electrons from iodides to the oxygen of hydrogen peroxide, and scavenges intracellular hydrogen peroxide and hydroxyl radicals; in doing so it protects cells from the damage caused by lipid peroxidation.<sup>21,22</sup> The concentration of iodide is inhibited by nitrates, nitrites,

thiocyanate, some glycosides and salt.<sup>23</sup> It is well known that a high intake of nitrates and related compounds is associated with an increased risk of gastric cancer.<sup>1</sup> The iodide concentration is also inhibited by an excessive quantity of iodine.<sup>23</sup> Marani *et al.*<sup>24</sup> reported that iodine deficiency impairs immunity and so might reduce the endogenous immunological defence against tumour cells.

Other reports show the possible role of iodine in the carcinogenesis of the stomach. Stevens *et al.*<sup>25</sup> found that radioactive iodine (<sup>131</sup>I) caused stomach cancer in the first generation of exposed pregnant rats. Using an experimental extrathyroidal carcinogenesis model, Guernsey and Leuthauser<sup>26</sup> reported that thyroid hormone is a very powerful co-factor and its mechanism of action might be via tumour suppressor genes.

Additional data on the role of iodine in the development of gastric cancer have come from one recent study. Wang *et al.*<sup>27</sup> found that an alteration in the thyroid hormone

receptor  $\alpha$ -gene was associated with the development of distant metastases and a high expression of Nm23 protein in gastric cancer.

In this study, we found a higher frequency of goitre in patients with gastric cancer compared with healthy control subjects. In particular, the frequency of nodular goitre was significantly higher in patients with gastric cancer than in the control subjects. Our study showed that there was also a significant difference between the groups in the incidence of AITD. These results indicate a significant association between gastric cancer and thyroid disorders. The role of iodine in the pathophysiology and carcinogenesis of the stomach still remains to be clarified, however.

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## Conflicts of interest

No conflicts of interest were declared in relation to this article.

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