HYPOTHESIS

A new hypothesis: iodine and gastric cancer

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(Received 1 September 1992; accepted 1 October 1992)

The authors have hypothesized that iodine-deficiency (I-def) or in some cases iodine-excess (I-excess) is associated with the development of gastric cancer. They report a short review of their own work and general literature on this subject in three fields: (1) epidemiology, where geographical and temporal correlations between territories with I-def (or I-excess) endemic goitre and high GC-death rate are reported; (2) immunology, where the possible correlations between I-def, immune-deficiency and GC are reported; and (3) thyroid gland and stomach correlations, both being embryologically derived from primitive gut and able to concentrate iodine. This ability is impaired by nitrates, thiocyanate, salt and by I-excess, which in fact can cause goitre. In our study I-def goitrous people have shown more atrophic gastritis than normal subjects. These data enable us to hypothesize that I-def or I-excess might constitute a new risk factor for gastric cancer, both by regulating gastric trophism and by antagonizing the action of those I-inhibitors (such as nitrates, thiocyanate and salt) previously studied as risk factors for gastric cancer.

Key words: Atrophic gastritis, gastric cancer, goitre, immunity, iodine, iodine prophylaxis.

Introduction

According to current WHO statistics more than one billion people in the world live in iodine-deficient countries, including Europe, Germany, Spain, Portugal and Italy (Stanbury and Hetzel, 1980; European Thyroid Association, 1985; Lotfi and Mason, 1988). The urinary iodine excretion (UIE) in the populations examined was less than 100 μg per day, while the RDA of iodine is 150 μg and FAO recommends 400 μg in order to compensate environmental dietary goitrogens (Costa, 1978). The UIE in Scandinavian countries, thanks to iodized salt, nowadays reaches 250 μg compared to more than 500 μg per day in the USA (Ingbar and Woeber, 1980; European Thyroid Association, 1985). The UIE in the Italian population of the Central Apennines is lower among older people, farmers and the poorer social classes, who are those more subject to goitre, as well as to GC (Venturi, 1985; Venturi et al., 1990).

In vegetables the role of iodine is not known. Two billion years ago, algae, which contain the highest level of iodine, were the first living cells to produce oxygen. So we believe that the algae cell required a protective redox mechanism in which iodine might have had a specific role; in fact, iodides reduce the oxygen in thyroid hormonogenesis and are able to defend the brain and liver cells from the lipid peroxidation in rats with an iodine-supplemented diet (Katamine et al., 1985).

In humans the extra-hormonal inorganic iodine is about 30–40 mg (Margaria and De Caro, 1967) and its role is unknown, while the well-known hormonal and thyroidal iodine is less than 10 mg (Ingbar and Woeber, 1980). Dietary iodine is rapidly absorbed
from the small intestine. Iodine is not only concentrated in the thyroid but also in the salivary glands, mammary gland, etc., and above all in the gastric mucosa and secretions where there is a concentration of 20-30% of the $^{131}$I injected intravenously (Brown-Grant, 1961; Wolf, 1964; Ingbard and Woeger, 1980). The gastric cells with iodine-concentrating capacity are the mucoid cells of the mucosa surface and of the neck of the gastric glands (Logothetopoulus and Myant, 1956). Mucous cells of metastases from gastric cancer also show iodine-concentrating ability (Lewitus, 1973). However, iodine concentration was not observed in the duodenum, jejunum, ileum or colon, whose cancer incidence have different trends, distributions and probably different risk factors from gastric cancer (Lewitus, 1973). The iodine concentration is, however, inhibited by nitrites, thiocyanates (Logothetopoulus and Myant, 1956), salt and also parasitically, by an excessive quantity of iodine (Haynes and Murad, 1980). The peptic and oxyntic cells do not have an iodine-concentrating ability. In fact the concentration and secretion of iodine in gastric juice are independent from chloride-peptic secretion (Brown-Grant, 1961). In addition an excess of iodine impairs the iodide pump and the cellular tropism of iodine-concentrating tissues, resulting in functional damage including the well-known Wolff-Chaikoff effect, which occurs in the thyroid even with a dosage just in excess of 2 mg (Ingbard and Woeger, 1980), as well as degenerative and necrotic lesions in the iodine-concentrating tissues (thyroid, salivary glands and gastric mucosa) in the case of greater and prolonged quantities (Edmunds, 1955).

The fact that the iodine-excess is able to damage the stomach, should be examined carefully if we consider that the coastal populations of Japan (Suzuki et al., 1965) and China (Tai Ma et al., 1982), which have the highest rate of gastric cancer mortality in the world, frequently eat marine algae (seaweeds), which are very rich in iodine (up to 200 mg per day). The iodine-concentrating capacity in the thyroid, in the stomach and in the salivary glands is determined by the same chromosomal gene (Brown-Grant, 1961), owing to the same embryogenesis from the primitive gut, which is able to concentrate iodine and produce thyroid hormones (Ingbard and Woeger, 1980). This fact explains the morphological and functional similarities between stomach and thyroid such as cell polarity and apical microvilli, secretion of glycoproteins and amino acid hormones and digesting and reabsorbing ability. However, the gastric iodide pump differs from the thyroidal one, having a lower affinity for iodide and not being responsive to thyroid stimulating hormone (TSH) and to low serum (and diet) iodide levels (Halmi and Stuelke, 1959).

In previous studies, Stocks (1924), Spencer (1954), Ellerker (1955), Eskin (1970, 1976), Eskin et al (1975) and Stadel (1976) found a correlation between goitre, iodine and cancers; and Venturi recently found such a correlation with gastric cancer (Venturi, 1985; Venturi et al., 1987, 1990). Inorganic iodide also regulates the production of epidermal growth factor (EGF) in the thyroid cells and controls DNA synthesis and cell proliferation (Tramontano et al., 1987); this action might also occur in gastric mucosa and salivary glands.

In this work we attempt to point out the role of iodine in the physiopathology and carcinogenesis of the stomach using data from three different fields: epidemiology, immunology and thyroid gland and stomach correlations.

**Epidemiology**

We have found a geographic and temporal correlation between territories with a higher rate of mortality from gastric cancer and those with iodine-deficient goitre. We summarize the results in Figure 1 and Table 1 (Stocks, 1924; Spencer, 1954; Venturi, 1985; Venturi et al., 1990).

In Italy, quantitative regional data of iodine-deficient goitre indirectly based on the incidence of thyroidecomies (Figure 2) and thyroid cancer (Lampertico, 1982) are correlated with gastric cancer mortality. In fact surgical thyroid pathologies including goitre and tumours are correlated, though not exclusively, with iodine-deficiency or (more rarely) iodine-excess (Walner et al., 1966).

In countries where iodized salt has been used in sufficient concentration for many years (not less than 15 mg of potassium iodide per kg of salt), goitre and gastric cancer have been disappearing almost in parallel (Figure 3). Australia, Canada, New Zealand and the USA have used the most iodized salt since 1920-30 with 100 mg of KI per kg of salt, and have shown similar gastric cancer mortality trends. Also, in Switzerland a relevant drop of gastric cancer mortality was observed after 1970 by the fact that the Swiss government had to double the iodine content of the salt in 1962; the same happened in Finland after 1950. It is interesting to follow the gastric cancer mortality trend in the province of Aosta (110,000 inhabitants), whose population was the only one in Italy to carry out a partial iodine prophylaxis (Ip) from 1930 to 1975,
when it was interrupted. In contrast, the neighbouring province of Cuneo had never carried out significant Ip, despite the fact that it is an endemic goitre area (Venturi, 1985). Some years after interrupting the Ip, gastric cancer (which in Aosta had previously been much lower than in the neighbouring provinces) started to increase (Figure 4). The same happened in Guatemala where, after a substantial gradual decrease of Ip between 1965 and 1976, gastric cancer mortality increased by 36% from 5.8 in 1976 to 7.9 in 1984 (males + females per 100,000), while mortality for all cancers increased from 27.8 to 29.9. The progressive decrease of gastric cancer mortality in Cuneo, in Italy and all over the world, where iodized salt is not used, might have been favoured by greater iodine intake due, in the last decades, to the increased use of dietary iodized additives such as preserving, stabilizing and colouring agents. Other involuntary sources of iodine are drugs, dietary mineral integrators, X-ray contrast media and indirectly via agricultural seaweed fertilizers. Goitre and gastric cancer in Italy have a similar decreasing gradient from north to south and are more frequent in cold climates and far from the sea, where there is less iodine in the environment. The sea is rich in iodine since this is where most of the iodine removed and washed away from the soil accumulated by the last glacial age.

According to Doll and Peto (1981), dietary additives (many of which contain iodine) have not only caused less than 1% of the overall cancer death rate in the USA, but they have probably decreased it (with an acceptable interval estimate from -5 to +2%) thanks to the potential protecting action of antioxidants, especially with regards to gastric cancer.

**Immunity**

The UN Nutrition Policy Discussion Paper has reported that iodine has a significant action on the immune system (Lotti and Mason, 1988). We also have recently reported a significant immune deficiency (Marani et al., 1985) in our population affected by high gastric cancer, goitre and thyroid cancer. In addition, Weetman et al (1983) had already demonstrated that iodine could increase immunoglobulin-G synthesis in human lymphocytes in vitro.

Immune defences might have an important role in various types of tumours, and perhaps also in gastric cancer. Tucker et al (1988) have described the
Table 1. Correlation between goitre prevalence (1980–85), iodine intake (1980–85) and gastric cancer mortality rate (1984) in Europe. In endemic goitre nations the gastric cancer mortality is generally higher than in non-endemic countries. Note that Greece and Rumania show endemic goitre only in a small part of their territory.

<table>
<thead>
<tr>
<th>Country</th>
<th>Iodine intake*</th>
<th>Goitre prevalence*</th>
<th>Gastric cancer mortality†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No endemic goitre</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>S</td>
<td>0</td>
<td>20.1</td>
</tr>
<tr>
<td>Norway</td>
<td>S</td>
<td>0</td>
<td>20.3</td>
</tr>
<tr>
<td>Sweden</td>
<td>S</td>
<td>0</td>
<td>17.2</td>
</tr>
<tr>
<td>Denmark</td>
<td>B/S</td>
<td>0</td>
<td>14.7</td>
</tr>
<tr>
<td>Iceland</td>
<td>S</td>
<td>0/±?</td>
<td>20.0</td>
</tr>
<tr>
<td>Ireland</td>
<td>S</td>
<td>0/±?</td>
<td>14.7</td>
</tr>
<tr>
<td>UK</td>
<td>S</td>
<td>0/±?</td>
<td>20.8</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulgaria</td>
<td>S</td>
<td>+</td>
<td>27.2</td>
</tr>
<tr>
<td>Czechoslovakia</td>
<td>S</td>
<td>+</td>
<td>24.9</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>S</td>
<td>+</td>
<td>17.1</td>
</tr>
<tr>
<td>Switzerland</td>
<td>S</td>
<td>+</td>
<td>16.7</td>
</tr>
<tr>
<td>Belgium</td>
<td>B</td>
<td>0/±?</td>
<td>18.3</td>
</tr>
<tr>
<td>Endemic goitre</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>B</td>
<td>++</td>
<td>29.6</td>
</tr>
<tr>
<td>Hungary</td>
<td>B</td>
<td>++</td>
<td>31.2</td>
</tr>
<tr>
<td>Poland</td>
<td>B</td>
<td>++</td>
<td>23.2</td>
</tr>
<tr>
<td>Yugoslavia</td>
<td>B</td>
<td>++</td>
<td>25.5</td>
</tr>
<tr>
<td>German Dem. Republic</td>
<td>I</td>
<td>++</td>
<td>25.5</td>
</tr>
<tr>
<td>German Fed. Republic</td>
<td>I</td>
<td>++</td>
<td>25.4</td>
</tr>
<tr>
<td>Greece</td>
<td>I</td>
<td>++</td>
<td>14.1</td>
</tr>
<tr>
<td>Italy</td>
<td>I</td>
<td>+++</td>
<td>27.0*</td>
</tr>
<tr>
<td>Portugal</td>
<td>I</td>
<td>+++</td>
<td>29.1</td>
</tr>
<tr>
<td>Rumania</td>
<td>B</td>
<td>++</td>
<td>18.0</td>
</tr>
<tr>
<td>Spain</td>
<td>I</td>
<td>+++</td>
<td>20.3*</td>
</tr>
<tr>
<td>Turkey</td>
<td>I</td>
<td>+++</td>
<td>?</td>
</tr>
</tbody>
</table>

Goitre: 0, practically none; +, <10%; ++, 10–30% (or more); ++++, risk of endemic cretinism.
Iodine intake (including iodine prophylaxis): S, sufficient; B, borderline sufficient; I, insufficient.
*Data from the European Thyroid Association (1985).
†Data from the World Health Statistics Annuals: *in 1981; †in 1980.

patients; and a higher rate of gastric cancer is reported in the survivors from nuclear explosions, who were exposed to high quantities of radio-iodine.

Thyroid gland and stomach correlations

Previous studies have demonstrated the frequent association between atrophic gastritis and goitre-dysthyroidisms, well known as thyro-gastric syndrome, and between gastric antimucosa and antithyroid antibodies (Ingbar and Woeber, 1980), which might be attributed to common organospecific antigens due to the same embryogenetic derivation. In fact injected antithyroid serum can cause experimental gastritis in the stomach (Roitt et al, 1988).

In addition iodine concentration in the stomach and in the thyroid is impaired both by iodine-excess and by substances such as nitrate, nitrites, thiocyanates and salt (Wolff, 1964), which can cause goitre and probably gastric cancer. Cooking causes losses of 20–30% of iodine through evaporation (I DD-Newsletter, 1989), so fresh food and fresh veget-
In Italy there is a significant correlation ($p < 0.01$) between the incidence of thyroidectomies (correlated to iodine-deficiency) and gastric cancer mortality rate (per 100,000).

Figure 3. Different national trends of gastric cancer mortality in relation to the beginning (arrows) of iodine prophylaxis (Ip) and to the percent age of the population in which Ip is used. Japan and most of Chile and Italy never used iodized salt. In the USA iodized salt has been used since 1920–30 and is the most iodine-concentrated (100 mg of potassium iodide per kg). Canada, Australia and New Zealand show similar trends to the USA, since they have used similar iodized salt during the same period of time.

Figure 4. Gastric cancer mortality trend in Italy compared with the trends of the near endemic provinces of Cuneo and Aosta. Only Aosta had carried out iodine prophylaxis since 1930–35, but it was interrupted in 1975. After some years its trend started to reverse and increase. The same happened in Guatemala after 1976.

Ables, containing more iodine, are protective against gastric cancer and also against goitre and thyroid cancer (Franceschi et al., 1989). In previous work we have shown a trophic regulating action of iodine on gastric mucosa similar to the action on the thyroid and have shown a correlation between iodine-deficiency, goitre and atrophic gastritis (Venturi et al., 1990), by means of gastric biopsies, in three randomized and homogeneous groups of persons having different degrees of iodine-deficiency and goitre: Group A (40 subjects), in which 100% of the subjects had goitre (as a sample of persons with prolonged and severe iodine-deficiency); Group B (128 subjects), with goitre in 30–40% of persons (as a sample of persons with less severe iodine-deficiency); and Group C (136 subjects), with goitre in less than 10%, living in non-iodine-deficient territory.

The prevalence of atrophic gastritis in the three groups was correlated to the degree of iodine-deficiency and goitre ($p < 0.001$; Figure 5; Degli Albidzi et al., 1988). In addition, we studied the intracellular concentrations of the stomach and we have found that a normal gastric mucosa contains more iodine than that affected by atrophic gastritis (preliminary results; Degli Albidzi et al., 1988).

In conclusion we hypothesize that iodinedeficiency or iodine-excess are new risk factors for gastric cancer and propose the study of this trace element as a regulator of gastric trophism. This trophic regulating action on the gastric mucosa could
provide a new interpretation (by impairing iodine intracellular concentration) of the pathogenetic mechanism of previously studied risk factors for gastric cancer such as nitrates, thiocyanates and salt.

References


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