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Goiter Frequency Is More Strongly Associated with Gastric Adenocarcinoma than Urine Iodine Level

Mohammad Tabaeizadeh*, Vahid Haghpanah*, Abbasali Keshtkar[1], Shahryar Semnani[2], Gholamreza Roshandel[2], Khadijeh Adabi, Ramin Heshmat[3], Davood Rohani[2], Alireza Kia[4], Ehsan Hatami[5], Ataollah Jahangirrad[5], Ramin Nabizadeh[6], and Bagher Larijani

Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Endocrinology and Metabolism Research Institute, [1]Osteoporosis Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, [2]Golestan Research Center of Gastroenterology and Hepatology, Golestan University of Medical Sciences, Gorgan, [3]Chronic Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, [4]Department of Radiology, [5]Department of Oncology, Golestan University of Medical Sciences, Gorgan, [6]Department of Environmental Health Engineering, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

Purpose: We designed our study to evaluate the hypothesis that gastric cancer is correlated with iodine deficiency or thyroid dysfunction.
Materials and Methods: We investigated the total body iodine reserve, thyroid function status and autoimmune disorder in 40 recently diagnosed gastric adenocarcinoma cases versus 80 healthy controls. The participants came from a region with high gastric cancer rate but sufficient iodine supply due to salt iodination. The investigation included urine iodine level, thyroid gland clinical and ultrasonographic examination, and thyroid function tests.
Results: Goiter was detected more frequently in the case group (P=0.001); such a finding, however, was not true for lower than normal urine iodine levels. The free T3 mean level was significantly lower in the case group compared to the control group (P=0.005).
Conclusions: The higher prevalence of goiter rather than low levels of urinary iodine in gastric adenocarcinoma cases suggests that goiter, perhaps due to protracted but currently adjusted iodine deficiency, is more likely to be associated with gastric adenocarcinoma compared to the existing iodine deficiency itself.

Key Words: Stomach neoplasms; Goiter; Iodine; Thyroid function tests; Autoimmune diseases

Introduction

Well-known risk factors for gastric adenocarcinoma include genetic and environmental factors like positive family history of gastric cancer, low consumption of fruit and vegetables, high intake of salted, smoked or poorly preserved foods, smoking cigarettes and being infected with *Helicobacter pylori*.[1,2] Recent comparative epidemic studies in different regions suggest iodine deficiency as a removable cause of gastric adenocarcinoma, breast and thyroid cancer as it emphasized by "Venturi hypothesis".[3-8] Other studies suggested a possible link between overall thyroid abnormalities, other than inappropriate iodine intake, and gastric adenocarcinoma.[9-11]

The thyroid gland is, embryogenically and phylongenetically, derived from the primitive gut and thyroid follicular cells have gastroenteric origin.[12] The stomach and the thyroid share many morphological and functional similarities including iodine-concentrating capacity probably because of common embryologic origin.[12-16] It is possible that iodine in vertebrates, competes with free radicals as an antioxidant to bind the membrane lipids, proteins, and DNA to stabilize them.[8]

In 1994, in accordance with Universal Salt Iodization campaign,

Correspondence to: Bagher Larijani
Endocrinology and Metabolism Research Center (EMRC), Fifth floor, Dr. Shariati Hospital, North Kargar Ave., Tehran 14114, Iran
Tel: +98-21-88220037-8, Fax: +98-21-88220052
E-mail: emrc@tums.ac.ir
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*These authors contributed equally to this work.

a government act prohibited manufacturing and trading of non-iodized salt in all Iranian provinces (including Gorgan province, where the study took place). National consensus indicated that the diet of more than 90% of Iranian population had been supplemented with iodized salt by year 2000. It also reported that goiter was hyperendemic in 20 provinces of the country (including Gorgan which was a division of Mazandaran province at that era) in 1989 but the prevalence declined by 23~40% in the same provinces by 2001.[17]

Two distinct hypotheses have been investigated by several previous studies. The first one suggests a nutritional or an environmental parameter, iodine deficiency, as a predisposing factor for gastric adenocarcinoma. On the other hand, second hypothesis based on a positive correlation between different types of thyroid diseases and gastric adenocarcinoma, concludes that common embryological origin of two organs may play the essential role.

We designed a case-control study, to investigate the frequency of both thyroid disorders and iodine deficiency in a group of patients with gastric adenocarcinoma compared to their matched controls.

Materials and Methods

1. Population and sampling

We performed a case-control study including 40 cases and 80 controls which were enrolled from a region with high incidence of gastric adenocarcinoma and a history of iodine deficient diet compensated after introducing supplementary iodine during recent years. All the cases were selected from recently diagnosed gastric adenocarcinoma patients based on their pathological biopsy samples obtained by endoscopy. All clinical and laboratory tests in our study were done prior to surgical resection or other major therapeutic approaches for the cases. The staging and grading of adenocarcinoma was not considered in the study. These patients did not have a history of receiving usual anti *H. pylori* treatments (triple or quadriple drugs) or a long history of taking antacids.

The controls were enrolled from the neighbors of the patients who voluntarily participated in the study; we enrolled the controls approximately at the same time course when our patients were diagnosed with their cancer and joined the study (year 2006 and 2007); they were native people from Gorgan province which were selected from the neighbours of the patients (1 or 2 houses around) in the same range of age and sex (every 2 persons of the control group with the least possible age gaps from each person in the case group) to achieve the most probable socioeconomic and lifestyle similarity. None of them suffered from other types of cancer or received treatment for major gastrointestinal problems including *H. pylori* infection. None of the participants was a known case of hypo or hyperthyroidism prior to this study.

The study was conducted regarding the principles of the Declaration of Helsinki and was approved by the Ethical Committee of the Golestan Research Center of Gastroenterology and Hepatology (IRB No. g/p/35/2700 on 15.08.2006). All the participants were informed and signed a written consent before entering the study.

2. Method

The participants completed a written questionnaire and were examined clinically by a trained physician. Thereafter, they underwent blood and urine sampling and ultrasound examination.

Serum levels of free T3, free T4, total T3, total T4, thyroid-stimulating hormone (TSH) and antibody against thyroid peroxidase (Anti-TPO) were measured using Kaveshiar kit by radioimmunoassay. Ultrasound imaging of thyroid gland as well as the measurement of urine iodine levels was also conducted.

The iodine level was measured in 24-hour urine collection samples of the participants using chemophotometric models.

All the ultrasonographic exams for the participants including its size and the presence of any nodules were performed by a single radiologist. Thyroid volume in the range of 11 ± 3 ml was considered normal.[18] The ultrasound, rather than physical examination, was considered as the definite method to detect goiter. Diffuse and multinodular goiters were different types of goiter reported in our study. The enlarged size of the gland (more than 14 ml) was the main criteria for establishing the diagnosis of goiter; furthermore the presence of multinodular appearance was an inclusion criteria. Simple nodular gland, smaller than 14 ml was not considered as goiterous to avoid overestimation.

3. Statistical analysis

The data was analyzed using SPSS version 16 (SPSS Inc., Chicago, IL, USA). We applied the descriptive χ^2 test (chi-square) to compare the incidence rate of goiter and the proportion of persons having lower than normal urine iodine level in the case and control groups (odds ratio with 95% confidence interval). After confirming the normal distribution of quantitative variables, the mean levels were compared using independent t-test. Nonparametric Mann-Whitney U test was also used to compare variables not having normal distribution. P-values less than 0.05 were considered statis-

tically significant.

Results

In this study we compared 40 gastric adenocarcinoma cases and 80 age and sex matched controls. Forty-two point five percent of the cases and 43.8% of the controls were female. Twenty-four members of the case group (60%) and 35 of the control group (43.8%) aged over 60 and the remainder were between 40 to 60 years old; there was no significant difference between two groups regarding their age distribution (P=0.09).

Neither the cases nor the controls were known for thyroid problems or iodine deficiency in the past. The family history for thyroid diseases was also negative for all the participants. None of the participants had a history of taking anti *H. pylori* treatment.

The prevalence of diffuse or multinodular goiter was significantly higher (P=0.001) in the case group (Table 1). In detail, 10 individuals in the case group (25%) versus 5 in the control (6.3%) had diffuse goiter. Multinodular goiter, on the other hand, was reported in only 3 cases (7.5%) whereas no one in the control group was reported to have multinodular goiter. The mean thyroid gland volume was 11±8.2 in the case and 6.8±2.8 in the control group; there was a significant difference between the gland volume of these two groups (P=0.003).

Totally, 33 participants were detected to have at least one nodule or cyst in their thyroid lobes; there was no significant difference between the frequency of affected individuals in two groups (P=0.39).

There was no statistically significant difference between mean urine iodine levels two groups (P=0.074). Furthermore, 3 persons in the case group had urine iodine level lower than normal, while only one person in the control group was in this range. The difference between two groups was not significant (P=0.107) (Table 1).

Significant difference, was not shown between TSH, T4, T3 and free T4 mean levels of two groups (P-values 0.115, 0.993, 0.944, 0.073 respectively). Mean free T3 levels were higher in the control group (P=0.003). The median serum levels of Anti-TPO was not significantly different between two groups (P=0.052). The median of this variable was used instead of its mean because of the absence of normal distribution (Table 1).

Discussion

Iodide (I-) is an essential constituent of the thyroid hormones triiodothyronine (T3) and tetraiodothyronine (T4). A cornerstone of I- metabolism is active uptake of iodine in the thyroid, a process mediated by sodium/iodide symporter.[14,15] I- is presumed to be absorbed in the small intestine and mainly excreted via the kidneys.[15]

Venturi et al.,[4] reported in 1993 that iodine deficiency might represent a risk factor for gastric cancer and atrophic gastritis. Large studies in China and Poland demonstrated a correlation between iodine deficiency and incicence and mortality rate of gastric cancer reversible by iodine supplementation.[3,6] Behrouzian and Aghdami.[11] showed that gastric cancer patients had lower, urine iodine/creatinine ratio than controls. Kandemir et al.[9] reported that 49% of gastric cancer cases versus 20% of controls had a positive history of goiter. Thyroid autoimmune diseases were also more frequently reported among the cases in this study. In contrast, Rossi et al.[19] failed to report any relation between having a positive history of various benign thyroid diseases and increased gastric cancer risk in

Table 1. The differences between parameters obtained from patient (case) and healthy (control) groups

Major exposure	Parameter	Case group (SD)	Control group (SD)	P-value	Odds ratio	Normal range
Iodine deficiency related factors	Diffuse or multinodular goiter (frequency)	13 (32.50%)	5 (6.30%)	0.001	7.2 (2.4~22.2)	
	Low urine iodine level (frequency)	3 (7.50%)	1 (1.25%)	0.107	-	
	Urine iodine level (mean level)	20.13 (8.47)	23.06 (7.94)	0.072	-	Less than 9.9 μg/dl
Thyroid function tests	TSH (mean level)	2.18 (0.99)	1.87 (1.04)	0.115	-	0.4~6.1 mU/L
	Total T3 (mean level)	1.60 (0.90)	1.59 (0.45)	0.944	-	0.52~1.85 nmol/dl
	Free T3 (mean level)	1.95 (0.37)	2.20 (0.55)	0.003	-	1.6~3.7 pg/ml
	Total T4 (mean level)	1.11 (24.58)	1.11 (25.91)	0.993	-	4.4~11.6 μg/dl
	Free T4 (mean level)	1.21 (0.45)	1.32 (0.35)	0.073	-	0.86~1.78 ng/dl
Thyroid antibody	Anti-TPO (median level)	16.57 (48.06)	5.63 (13.66)	0.052	-	Less than 40 IU/ml

SD = standard deviation; TSH = thyroid-stimulating hormone; Anti-TPO = antibody against thyroid peroxidase.

a hospital-based case-control study in Italy. Other epidemiological studies have demonstrated a higher incidence of gastric cancer in the same geographical areas where iodine deficiency or excess have been reported.[1]

Consistent with many other studies, we found a higher prevalence of goiter, either diffuse or nodular, in gastric adenocarcinama patients. However, similar to the study conducted by Kandemir et al.,[9] we did not find a significant correlation between gastric adenocinoma and hyper- or hypothyroidism based on TSH serum levels. In fact, euthyroid goiter was more frequent among gastric adenocarcinoma patients. Until 1990s the prevalence of goiter was the only indicator of iodine deficiency in population-based studies; however it might overestimate the problem because a long time is required for goiter to disappear following the supplementation of iodized salt. Therefore the test was replaced with urinary iodine, a more sensitive indicator of recent changes in iodine intake.[20] However, more recent studies conducted to evaluate the correlation between gastric cancer and thyroid abnormalities reevaluated goiter as a better indicator of protracted iodine deficiency. Goiter also detected more accurately a previous iodine deficiency which is removed now following consumption of iodized salt.[20,21]

In contrast with Behrouzian and Aghdami, we did not find a statistically significant lower mean level of urine iodine in gastric adenocarcinoma cases compared to controls. One possible explanation for this contradiction is the smaller size of our sample, which is also a limitation of our study. The calculated P-value, quite near the cut point (0.074), is also consistent with this explanation. We should also remind the incompetency of urine iodine level to detect recently adjusted iodine deficiencies. It is also possible that other goitrogens including polycyclic aromatic hydrocarbons and bacterial contamination of water supplies which are not necessarily associated with iodine deficiency have caused the gastric adenocarcinoma.[3,22]

Analyzing thyroid function indices, we found lower mean level of free-T3 in case group compared to control group. Other tests like mean levels of total T4 and T3, and TSH were not significantly different between two groups. Kandemir et al.[9] did not find any significant correlation between gastric cancer and hypo or hyperthyroidism. Beletskaia[23] reported an augmented total T3 clearance in a review of the investigations designed to study T3 pharmacokinetics under malignant tumors of the stomach and large intestine. Using an experimental extrathyroidal carcinogenesis model, Guernsey and Leuthauser[24] reported that thyroid hormone is a very powerful co-factor and its mechanism of action might be via tumor suppressor genes. Our study did not show any significant association between thyroid gland dysfunction and gastric adenocarcinoma. Significantly lower free-T3 mean level in the case group compared to the control group is attributable to the sick euthyroid syndrome which is commonly reported secondary to serious illnesses such as infections and malignancies specifically in their acute phase[25]; so this finding is not a reliable evidence for an exclusive association between thyroid gland dysfunction and gastric adenocarcinoma. Unfortunately we did not evaluate rT3, which is commonly tested in suspected cases of sick euthyroid syndrome.[25]

We also found that the median level of Anti-TPO was not significantly higher in our case group versus the control group although the P-value was only a bit larger than the cut point (P=0.052). Furthermore, none of our participants had a history of autoimmune thyroid disease. Syrigos et al.[10] reported that significantly more patients with gastric cancer suffered from autoimmune thyroid diseases compared to control subjects; Kandemir et al.[9] also found more gastric cancer in patients with a history of self-reported thyroid autoimmune disease than their matched controls. Syrigos et al.[10] measured anti thyroglobulin and antimicrosomal antibodies while the target antibody in our study was antiperoxidase antibody. It should be emphasized that gastric cells do not secrete thyroglobulin while peroxidase activity is common in both thyroid and gastric cells.[16] The distribution of the amounts reported for anti-TPO was not normal, therefore the median value was calculated instead of its mean and this can confound the precision of the study.

In conclusion, we demonstrated that iodine deficiency is more frequent in gastric adenocarcinoma cases compared to controls and this is not necessarily associated with thyroid dysfunction. Our study was a case-control survey which cannot basically find the etiology of the disorder, only suggesting an association between gastric adenocarcinoma and iodine deficiency. Consequently, further cohort studies are required to indicate if iodine deficiency is a real etiologic factor for gastric adenocarcinoma or this association has more reasonable explanations.

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