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Association between Serum Gamma-Glutamyl Transferase and Thyroid Cancer in an Ultrasonographically Screened Population

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Background and Objectives: We reported recently a positive correlation between obesity and thyroid cancer in women. Serum gamma-glutamyl transferase (GGT) is regarded as a marker of exposure to environmental pollutants, cancer-causing xenobiotic. This study was conducted to evaluate the mechanism behind the association of obesity with thyroid cancer. We hypothesized serum GGT may be a surrogate for persistent organic pollutants to explain the connection between obesity and thyroid cancer. **Materials and Methods:** We obtained data from 15,131 subjects who underwent a routine health checkup including thyroid ultrasonography from 2007 to 2008 at the Health Screening and Promotion Center of Asan Medical Center. Suspicious nodules were examined by ultrasonography-guided aspiration. Those with a history of hepatobiliary disease and abnormal result of liver function test were excluded. Serum GGT cut-off points were the 25th, 50th, and 75th sex-specific percentiles. **Results:** A total of 15,131 subjects (7662 men and 7469 women) were screened by thyroid ultrasonography. Thyroid cancers were diagnosed in 260 patients. After adjustment of age, smoking status, alcohol intake, body mass index, compared with the lowest serum GGT quartile, odds ratios (95% confidence intervals) of risk of thyroid cancer were 0.54 (0.28-0.99) for 2nd quartile, 0.92 (0.56-1.50) for 3rd quartile, and 0.61 (0.34-1.09) for 4th quartile in men. In women, the adjusted odds ratios were 1.06 (0.66-1.72), 1.18 (0.77-1.85), and 0.63 (0.38-1.06) for the 2nd, 3rd, and 4th quartile, respectively. **Conclusion:** Elevated GGT is not associated with a higher prevalence of thyroid cancer in either gender when evaluated in a routine health checkup setting.

Key Words: Gamma-glutamyl transferase, Persistent organic pollutant, Thyroid cancer, Obesity

Introduction

The incidence of thyroid cancer is increasing in many countries.[1-3] The main risk factors for thyroid cancer are exposure to radiation, a history of benign thyroid disease, and a family history of thyroid cancer.[4-6] A meta-analysis showed that obesity was associated with the development of many cancers, including those of the esophagus, colon, kidney, breast, skin, rectum and gallbladder.[7] Recently, we reported a positive correlation between obesity and thyroid cancer prevalence in women, when evaluated in a routine health checkup setting.[8] The underlying mechanism between obesity and cancer is unclear.

We considered persistent organic pollutants (POPs)

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as a possible basis of the association between obesity and thyroid cancer. POPs (such as PCB153, oxychlordane, etc.) are persistent lipophilic xenobiotic that accumulate in adipose tissue after exposure to environmental pollution. The International Agency for Research on Cancer (IARC; www.iarc.fr/index.php) defines POPs as carcinogens. Lee et al.[9] reported that serum gamma-glutamyl transferase (GGT) was linearly associated with concentration of POPs, and that GGT might be a biomarker reflecting exposure to environmental pollutants. Although serum GGT has traditionally been used as a marker of hepatobiliary disease or alcohol consumption,[10,11] a recent prospective study demonstrated that it was independently associated with several types of cancers.[12] To the best of our knowledge, no study evaluating the relationship between GGT and thyroid cancer has been reported.

This study was conducted to evaluate the mechanism behind the association of obesity with thyroid cancer. We hypothesized that serum GGT may be a surrogate marker of exposure to POPs and examined this connection in a systematically screened population by ultrasonography.

Materials and Methods

Study Population

This cross-sectional study initially enrolled 24,935 subjects who underwent a routine health checkup from January 2007 to December 2008 at a Health Screening and Promotion Center. Thyroid ultrasonography was included in each checkup. If a subject received two or more health checkups during the study periods, only the first one was included in the analysis. We selected 20,366 subjects who had normal liver enzyme levels (AST and ALT <40 IU/L). We excluded those with a prior history of thyroid disease (thyroid dysfunction, n=799; thyroid nodule, n=648; thyroid cancer, n=10; surgery on thyroid, n=154; medication for thyroid disease, n=466), a family history (first-degree relatives only) of thyroid cancer (n=1142), or a prior history of hepatobiliary disease (HBV carrier, n=973; chronic hepatitis C, n=123; liver cyst, n=330; hepatocellular carcinoma, n=14; cholangiocarcinoma, n=3; surgery on gall bladder, n=387). The final analysis included 15,131 subjects (7662 men and 7469 women) for whom we had data on GGT level, alcohol consumption, blood pressure, fasting glucose, cholesterol, triglyceride and insulin levels, and smoking status. We reviewed the medical records and analyzed risk factors for thyroid cancer separately in men and women. The local ethics committee approved the study protocol.

Biochemical and Anthropometric Measurements

Venous blood was collected from 12-hour fasting subjects in the morning and analyzed for glucose, cholesterol, triglyceride, insulin, and GGT at a central laboratory. Glucose, cholesterol, triglyceride, and GGT levels were quantified with a TBA-200FR auto-analyzer (Toshiba Medical System Co., Ltd, Tokyo, Japan), and insulin was measured by radioimmunoassay (Insulin IRMA kit; Izotop, Budapest, Hungary). We divided serum GGT levels into four groups by quartiles (the cut-off points of serum GGT were the 25th, 50th, and 75th sex-specific percentiles). At the initial visit, height and weight were measured. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). BMI was categorized as follows: <18.5, 18.5-22.9, 23.0-24.9, 25.0-29.9, ≥30 for underweight, normal weight, overweight, obesity, and severe obesity, respectively, following the WHO (World Health Organization) guidelines for Asians.[13] We used questionnaires to collect information on alcohol consumption and smoking status. We estimated alcohol consumption by frequency of drinking per week, not quantity and type of drinking. Smokers included both ex-smokers and current smokers.

Identification of Thyroid Cancer

Patients with abnormal thyroid ultrasonography findings were referred to endocrinologists, regardless of nodule size or characteristics. Fine needle aspiration (FNA) cytology was performed for thyroid nodule(s) of larger than 1 cm, or of smaller than 1 cm when there were suspicious sonographic features such as micro-calcification, hypo-echogenicity, "taller than wide" shape, irregular margins, or neck lymph node en-

largement.[14] Of the study subjects, 260 were finally diagnosed with thyroid cancer by surgery.

Statistical Analysis

Categorical variables are presented as numbers and percentages. Continuous variables are expressed as means (standard deviations) or medians (inter-quartile range). Comparisons of continuous variables were performed by Student's t-test. Trends across BMI categories were performed by the chi-square test. Quartiles of variables were calculated based on values of the sex-specific populations. R (version 2.12) and R libraries survival (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org) were used for statistical analysis. The associations between variables and thyroid cancer are presented as an odds ratio (OR) with a 95% confidence interval (CI) calculated by binominal logistic regression. $p<0.05$ was considered statistically significant.

Results

Baseline Characteristics of Healthy Subjects and Those with Cancer

A total of 15,131 subjects (7662 men and 7469 women) without any history of thyroid disease or hepatobiliary disease were included in this study. Thyroid cancer was diagnosed in 260 patients. A comparison of clinical characteristics between healthy subjects and those with cancer revealed significant differences in all variables between men and women (Table 1). Therefore, the data were analyzed separately based on gender. Male subjects with thyroid cancer were significantly younger than subjects without cancer. Females with cancer had higher systolic blood pressure and lower high density lipoprotein levels than those without cancer. BMI of those with cancer was higher than non-cancer subjects in both male and female, but the differences were not significant. The percentage of obese subjects (BMI≥25) was greater among the males with cancer than among the males without

Table 1. Comparison of the clinical characteristics of subjects without thyroid cancer and those with thyroid cancer

	Male		p value	Female		p value
	Non-cancer (n=7561)	Cancer (n=101)		Non-cancer (n=7310)	Cancer (n=159)	
Age (years)	52.6±9.0	50.9±7.8	0.038	50.8±9.4	51.1±8.6	0.672
Smoking	6130 (81%)	80 (79%)	0.276	634 (9%)	6 (4%)	0.330
GGT (U/L)*	25 (17-40)	26 (20-36)	0.618	12 (10-17)	12 (10-15)	0.931
BMI (kg/m^2)			0.070			0.090
<18.5 (Underweight)	84 (1%)	1 (1%)		302 (4%)	3 (2%)	
18.5-22.9 (Normal weight)	1934 (26%)	20 (20%)		3824 (52%)	64 (40%)	
23.0-24.9 (Overweight)	2315 (31%)	28 (28%)		1681 (23%)	48 (30%)	
25.0-29.9 (Obesity)	3046 (40%)	46 (45%)		1376 (19%)	35 (22%)	
≥30.0 (Severe obesity)	182 (2%)	6 (6%)		127 (2%)	9 (6%)	
Systolic BP (mmHg)	117.5±9.4	118.4±7.7	0.261	111.4±11.4	114.7±10.6	0.001
Glucose (mg/dL)	101 (94-110)	100 (95-108)	0.949	95.0 (89-102)	96.0 (90-105)	0.078
Insulin (mU/L)	6.3 (4.4-8.8)	6.5 (4.6-8.6)	0.967	5.7 (4.1-8.1)	6.5 (4.7-9.2)	0.083
Cholesterol (mg/dL)	191.2±33.1	189.8±29.9	0.631	193.0±35.3	192.4±37.3	0.842
HDL (mg/dL)	50 (43-59)	50 (42-61)	0.789	60 (51-71)	57 (50-65)	0.001
Alcohol consumption			0.067			0.272
1 time per week	3058 (40%)	39 (39%)		6378 (87%)	137 (86%)	
2-3 times per week	2660 (35%)	39 (39%)		734 (10%)	17 (10%)	
4-6 times per week	1221 (16%)	21 (20%)		137 (2%)	4 (3%)	
7 times per week	622 (8.2%)	2 (2%)		61 (1%)	1 (1%)	

BMI: body mass index, BP: blood pressure, GGT: gamma-glutamyl transferase, HDL: high density lipoprotein

cancer (51% vs. 42%) and also among the female (28% vs. 21%).

Association between GGT and Thyroid Cancer Risk

The prevalence of thyroid cancer, unadjusted for other factors, in the 1st, 2nd, 3rd, and 4th GGT quartiles was 1.7%, 0.8%, 1.6%, and 1.1%, respectively, in men, and 2.1%, 2.2%, 2.6%, and 1.6%, respectively, in women (Fig. 1). No continuous increase or decrease in thyroid cancer frequency was thus evident according to increasing serum GGT level. We examined the possible relationships between GGT and thyroid cancer according to 4 models involving adjustment for increasing numbers of factors. Before adjusting for other factors, high serum GGT level did not correlate with frequency of thyroid cancer in either men or women (Table 2: Model 1). After adjusting for clinical variables, no association between serum GGT levels and frequency of thyroid cancer was observed in any models (Table 2). In model 3 (adjustment of age, smoking status, alcohol intake, BMI), compared with the lowest quartile, ORs (95% CI) were 0.54 (0.28–0.99) for the 2nd quartile, 0.92 (0.56–1.50) for the 3rd quartile, and 0.61 (0.34–1.09) for the 4th quartile in men. In women, elevated serum GGT was also unrelated to the frequency of thyroid cancer. Adjusted ORs were 1.06 (0.66–1.72), 1.18 (0.77–1.85), 0.63 (0.38–1.06) for the 2nd quartile, 3rd quartile, and 4th quartile, respectively. In model 4 (adjustment of all variables), the risk of thyroid cancer was significantly lower in the 2nd quartile for men (OR 0.52, CI 0.27–0.96) and in the 4th quartile for women (OR 0.59, CI 0.35–0.99), but these results do not follow any dose re-

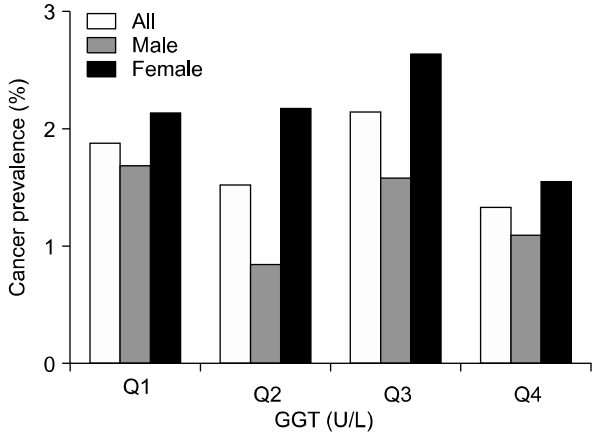

Fig. 1. The prevalence of thyroid cancer according to GGT quartiles. These prevalence estimates are not adjusted for other factors. Quartiles for GGT: 4.0–16.9, 17.0–24.9, 25.0–39.9, and 40.0–614.0 U/L in men; 4.0–9.9, 10.0–11.9, 12.0–16.9, and 17.0–309.0 U/L in women. GGT: gamma-glutamyl transferase.

Table 2. Unadjusted and adjusted odds ratios for presence of thyroid cancer according to GGT quartiles

	Baseline serum GGT (U/L)							
	Q1	Q2		Q3		Q4		
		Odds ratio	p value	Odds ratio	p value	Odds ratio	p value	
Male								
Cases/controls	34/1993	14/1653		32/1994		21/1918		
Model 1	1	0.50 (0.26–0.91)	0.029	0.94 (0.58–1.53)	0.807	0.65 (0.37–1.10)	0.115	
Model 2	1	0.52 (0.27–0.94)	0.037	0.93 (0.57–1.51)	0.763	0.60 (0.35–1.04)	0.071	
Model 3	1	0.54 (0.28–0.99)	0.054	0.92 (0.56–1.50)	0.735	0.61 (0.34–1.09)	0.099	
Model 4	1	0.52 (0.27–0.96)	0.043	0.95 (0.58–1.56)	0.847	0.65 (0.36–1.17)	0.156	
Female								
Cases/controls	31/1426	38/1723		59/2188		31/1952		
Model 1	1	1.01 (0.63–1.64)	0.954	1.23 (0.81–1.93)	0.343	0.73 (0.44–1.21)	0.225	
Model 2	1	1.02 (0.63–1.65)	0.942	1.23 (0.80–1.93)	0.349	0.73 (0.44–1.20)	0.209	
Model 3	1	1.06 (0.66–1.72)	0.780	1.18 (0.77–1.85)	0.46	0.63 (0.38–1.06)	0.080	
Model 4	1	1.07 (0.67–1.74)	0.769	1.14 (0.74–1.79)	0.568	0.59 (0.35–0.99)	0.046	

Model 1: unadjusted
Model 2: adjusted for matching factors age
Model 3: adjusted for matching factors age, BMI, smoking, and alcohol consumption
Model 4: adjusted for matching factors age, BMI, smoking, alcohol consumption, systolic blood pressure, serum glucose, serum cholesterol, serum HDL, and serum insulin

sponse relationship.

Discussion

We have found that obesity is associated with a higher prevalence of thyroid cancer, especially in women (OR 1.63, 95% CI 1.24–2.10, p<0.001) when evaluated in a routine health checkup setting.[8] The relationship between obesity and carcinogenesis is not yet well understood. This study was conducted to evaluate the mechanism behind the association of obesity with thyroid cancer. Hyperinsulinemia and/or increased levels of insulin like growth factors have been recognized as potential contributors, especially in colon, breast, endometrial, and pancreatic cancer.[15–17] However, we found no association between serum insulin level and thyroid cancer risk in a previous study.[8] This means that other mechanism(s) are responsible for the link between obesity and thyroid cancer.

Measurement of serum GGT level is commonly used as an indicator of hepatobiliary disease and a biological marker of excessive alcohol intake. However, several epidemiologic studies have reported that elevated GGT is an independent predictor of death from causes other than liver disease, such as cardiovascular disease, chronic kidney disease, and type 2 diabetes.[18–22] Interestingly, a recent prospective study showed that elevated GGT significantly increased overall cancer risk and was associated with several site-specific cancers, such as those of the digestive organs, respiratory system, intra-thoracic organs, and urinary organs.[12]

It is unclear what mechanisms are involved in the relationship between serum GGT and cancer. Lee et al.[9] demonstrated that GGT may be a biomarker of exposure to cancer causing xenobiotic, including POPs. There is evidence from several experimental models that cellular GGT in involved in antioxidant/antitoxic defense mechanism via glutathione metabolism.[23,24] After exposure to POPs, detoxification reactions occur to lower toxicity and increase the water solubility of POPs. Thus, serum GGT may increase in such situation when there is a need for conjugation to glutathione.[25,26]

The aforementioned finding led us to hypothesize that the role of POPs, as carcinogenic xenobiotic accounts for the association between obesity and thyroid cancer. Obese people have a lot of adipose tissue. As adipose tissue is a reservoir of POPs, the organs of individuals with higher amounts of adipose tissue are more likely to be exposed to accumulated POPs. We considered that serum GGT levels might reflect the extent of exposure to POPs in terms of carcinogenesis. Unfortunately, we did not find any relationship between serum GGT and thyroid cancer in either gender. Future studies on the possible mechanisms for this association are essential.

The present study had some limitations. First, the study population was limited to individuals attending for a voluntary health checkup, and was not representative of the general population. Second, we did not measure metabolic variables repeatedly. A single value might be insufficient for cancer risk analysis. Third, there was no information on potential confounding factors, such as physical activity, diet, genetic and psychosocial variables. Fourth, we used GGT level as a surrogate for accumulation of POPs, instead of measuring serum POPs. Hence it would be wrong to infer that there is no association between POPs and thyroid cancer from our results with serum GGT.

Despite of these limitations, this study had several strengths. First, all 15,131 subjects underwent thyroid ultrasonography, regardless of subjective symptoms. For this reason, almost all thyroid cancer cases were detected at very early stages, and this might represent the true prevalence of the disease. Second, this is the first study investigating the association of GGT and thyroid cancer within a single cohort. Third, thyroid ultrasonography and biochemical data were available from a single time point. Fourth, we applied same diagnostic and follow-up strategies for thyroid nodules to avoid selection bias.

In conclusion, elevated GGT levels being regarded as a measure of exposure to POPs were not associated with a higher frequency of thyroid cancer in either gender when evaluated in a routine health checkup setting.

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