Original Article

Association among Body Mass Index, Genetic Variants of *FTO*, and Thyroid Cancer Risk: A Hospital-Based Case-Control Study of the Cancer Screenee Cohort in Korea

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Purpose Obesity has been determined to be associated with fat mass and obesity-associated (*FTO*) gene and thyroid cancer risk. However, the effect of combined interactions between obesity and the *FTO* gene on thyroid cancer needs further investigation. This study aimed to examine whether interactions between body mass index (BMI) and the *FTO* gene are associated with an increased risk of thyroid cancer.

Materials and Methods A total of 705 thyroid cancer cases and 705 sex- and age-matched normal controls were selected from the Cancer Screenee Cohort in National Cancer Center, Korea. A conditional logistic regression model was used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) for the measure of associations and the combined effect of BMI and *FTO* gene on thyroid cancer.

Results BMI was associated with an increased risk of thyroid cancer in subclasses of overweight (23-24.9 kg/m^2; adjusted OR, 1.50; 95% CI, 1.12 to 2.00) and obese ($\geq$ 25 kg/m^2) (adjusted OR, 1.62; 95% CI, 1.23 to 2.14). There were positive associations between the *FTO* genetic variants rs8047395 and rs8044769 and an increased risk of thyroid cancer. Additionally, the combination of BMI subclasses and *FTO* gene variants was significantly associated with thyroid cancer risk in the codominant (rs17817288), dominant (rs9937053, rs12149832, rs1861867, and rs7195539), and recessive (rs17817288 and rs8044769) models.

Conclusion Findings from this study identified the effects of BMI on thyroid cancer risk among individuals carrying rs17817288, rs9937053, rs12149832, rs1861867, rs7195539, and rs8044769, whereas the effects of BMI may be modified according to individual characteristics of other *FTO* variants.

Key words Thyroid neoplasms, *FTO*, Body mass index, Obesity, BMI-gene interaction

Introduction

The worldwide incidence of thyroid cancer has continuously increased in recent decades [1]. Thyroid cancer is the most common cancer in Korea [2], and its incidence rate is among the highest worldwide and has been increasing rapidly over the past decade [3]. This phenomenon of a thyroid cancer epidemic in Korea is mainly attributed to increased detection by thyroid ultrasonography screening and the easy accessibility of screening programmes [4].

In addition to the increased detection of thyroid cancer cases, multiple environmental factors may explain the increase in thyroid cancer incidence, such as lack of physical activity, oversupply of dietary iodine, and obesity [5-7]. The epidemiology of thyroid cancer is also affected by environmental variations, such as geographical area, ethnicity, and exposure to radiation [8].

In recent years, genetic factors that may play important roles in the molecular mechanisms underlying thyroid carcinogenesis have been investigated. Genome-wide association studies (GWASs) have reported loci in *FOXE1*, *NKX2-1*, *DIRC3*, and *NRG1* [9,10] that may be related to susceptibility to thyroid cancer. The results of target sequencing studies indicate that certain genes, such as *FAS*, *TP53*, and *XRCC1*, may be associated with thyroid cancer risk [11]. Collectively, these findings suggest that the genetic variants of multiple genes should be investigated to identify candidates for susceptibility to thyroid cancer.

Several studies have suggested a strong link between obesity and the risk of thyroid cancer [12,13]. The fat mass and obesity-associated (*FTO*) gene, which is located on chromosome 16, is closely associated with obesity. Several GWASs have provided evidence that *FTO* is associated with body size, composition, adiposity, and metabolic disorders. Because
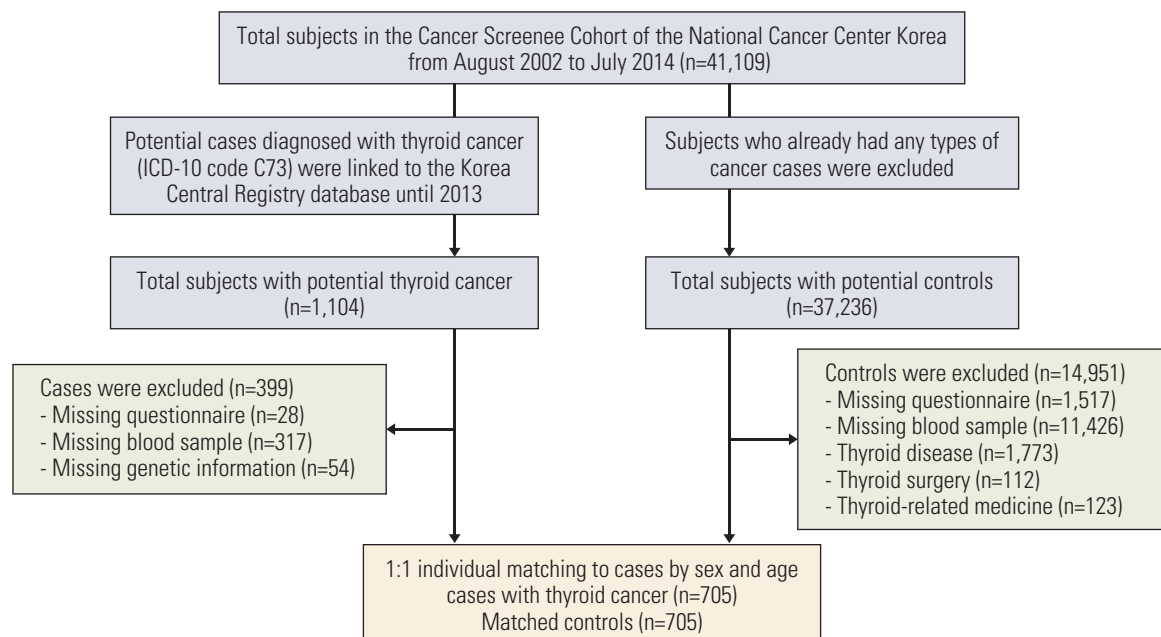
Fig. 1. Flowchart of selecting study subjects. ICD-10, International Classification of Diseases, 10th revision.

FTO is associated with obesity and obesity is associated with thyroid cancer, a comprehensive investigation of the genetic-environmental interactions between *FTO* and obesity may provide important insights into the role of obesity in thyroid carcinogenesis and the variability of thyroid cancer trends in different environmental settings. Therefore, this study examined the independent association between Body mass index (BMI) and single nucleotide polymorphisms (SNPs) in *FTO* and thyroid cancer risk and their combined effect on modifying the risk of thyroid cancer.

Materials and Methods

1. Study selection and data collection

All eligible cases and controls were selected from the Cancer Screenee Cohort, which is a large hospital-based population of 41,109 subjects screened in National Cancer Center, Korea from August 2002 to July 2014. All the patients were asked to complete a self-administered questionnaire about their demographic characteristics and lifestyle factors.

The height and weight of each subject were measured using an Inbody 3.0 (Biospace, Seoul, Korea) body composition analyzer or an X-SCAN PLUS II Body Composition Analyzer (Jawon Medical, Gyeongsan, Korea). BMI was calculated as follows: weight (kg)/(height [m])². The BMI values were stratified into three groups according to the Asian BMI Classification Index of the World Health Organization:

normal (< 23 kg/m²), overweight (23-24.9 kg/m²), and obese (≥ 25 kg/m²) [14].

2. Case and control selection

Thyroid cancer cases were identified according to the International Classification of Diseases for Oncology (ICD-10). Patients with an ICD-10 Code of C73 were identified as thyroid cancer cases. The classification data were obtained from the 2013 Korea Central Cancer Registry database, which provides information on cancer incidence according to case classifications in Korea. Thyroid cancer cases were not analyzed in subgroups according to histological types because most cases (97%) were papillary thyroid cancer (PTC) (data not shown).

Among the 41,109 subjects in the Cancer Screenee Cohort, 1,104 thyroid cancer cases were eligible for enrollment. A total of 705 subjects were enrolled after the subjects who were missing questionnaires (n=28), blood samples (n=317), and genetic information (n=54) were excluded (Fig. 1). Control patients who were not diagnosed with any cancer, including thyroid cancer, were selected from the same cohort. Among the 37,236 potential controls, participants with missing questionnaires, missing blood samples, a history of thyroid-related disease, surgery, medicine usage, and a diagnosis of any type of cancer were excluded from the study. Controls were selected by 1:1 case matching for sex and age. The final analysis included 705 thyroid cancer cases and 705 controls.

Table 1. Distributions of demographic and risk factors of study population

Variable	All			Male			Female		
	Control (n=705)	Case (n=705)	p-value[a)]	Control (n=214)	Case (n=214)	p-value[a)]	Control (n=491)	Case (n=491)	p-value[a)]
Age (yr)	48.7±8.4	48.7±8.4	> 0.99	47.8±8.0	47.8±8.0	> 0.99	49.1±8.5	49.1±8.5	> 0.99
Age group (yr)									
≤ 39	94 (13.3)	94 (13.3)	> 0.99	33 (15.4)	33 (15.4)	> 0.99	61 (12.4)	61 (12.4)	> 0.99
40-49	292 (41.4)	292 (41.4)		91 (42.5)	91 (42.5)		201 (40.9)	201 (40.9)	
50-59	241 (34.2)	241 (34.2)		74 (34.6)	74 (34.6)		167 (34.0)	167 (34.0)	
≥ 60	78 (11.1)	78 (11.1)		16 (7.5)	16 (7.5)		62 (12.6)	62 (12.6)	
Sex									
Male	214 (30.4)	214 (30.4)	> 0.99						
Female	491 (69.6)	491 (69.6)							
Family history of thyroid cancer									
No	676 (95.9)	646 (91.6)	< 0.001	207 (96.7)	197 (92.1)	0.05	469 (95.5)	449 (91.4)	0.01
Yes	15 (2.1)	43 (6.1)		2 (0.9)	10 (4.7)		13 (2.6)	33 (6.7)	
Missing	14 (2.0)	16 (2.3)		5 (2.3)	7 (3.3)		9 (1.8)	9 (1.8)	
Marital status									
Married	606 (86.0)	596 (84.5)	0.65	189 (88.3)	190 (88.8)	0.89	417 (84.9)	406 (82.7)	0.62
Others	74 (10.5)	85 (12.1)		14 (6.5)	15 (7.0)		60 (12.2)	70 (14.3)	
Missing	25 (3.5)	24 (3.4)		11 (5.1)	9 (4.2)		14 (2.9)	15 (3.1)	
Educational level									
Middle school or less	92 (13.0)	105 (14.9)	0.21	16 (7.5)	21 (9.8)	0.43	76 (15.5)	84 (17.1)	0.25
High school	241 (34.2)	205 (29.1)		53 (24.8)	44 (20.6)		188 (38.3)	161 (32.8)	
College or more	326 (46.2)	344 (48.8)		129 (60.3)	138 (64.5)		197 (40.1)	206 (42.0)	
Missing	46 (6.5)	51 (7.2)		16 (7.5)	11 (5.1)		30 (6.1)	40 (8.1)	
Occupation									
Professions, office workers, housewives	463 (65.7)	496 (70.4)	0.12	111 (51.9)	119 (55.6)	0.49	352 (71.7)	377 (76.8)	0.18
Sales, service	134 (19.0)	101 (14.3)		53 (24.8)	41 (19.2)		81 (16.5)	60 (12.2)	
Agriculture, laborer, unemployed, others	72 (10.2)	71 (10.1)		37 (17.3)	43 (20.1)		35 (7.1)	28 (5.7)	
Missing	36 (5.1)	37 (5.2)		13 (6.1)	11 (5.1)		23 (4.7)	26 (5.3)	
Income[b)] (US $/mo)									
< $1,667	97 (13.8)	80 (11.3)	0.34	22 (10.3)	11 (5.1)	0.05	75 (15.3)	69 (14.1)	0.43
$1,667-$3,333	177 (25.1)	196 (27.8)		46 (21.5)	64 (29.9)		131 (26.7)	132 (26.9)	
> $3,333	317 (45.0)	304 (43.1)		113 (52.8)	114 (53.3)		204 (41.5)	190 (38.7)	
Missing	114 (16.2)	125 (17.7)		33 (15.4)	25 (11.7)		81 (16.5)	100 (20.4)	
Smoking status									
Never	464 (65.8)	496 (70.4)	0.09	36 (16.8)	45 (21.0)	0.40	428 (87.2)	451 (91.9)	0.06
Ever	220 (31.2)	197 (27.9)		174 (81.3)	167 (78.0)		46 (9.4)	30 (6.1)	
Missing	21 (3.0)	12 (1.7)		4 (1.9)	2 (0.9)		17 (3.5)	10 (2.0)	
Alcohol consumption									
Never	301 (42.7)	322 (45.7)	0.53	31 (14.5)	32 (15.0)	0.99	270 (55.0)	290 (59.1)	0.43
Ever	393 (55.7)	372 (52.8)		180 (84.1)	179 (83.6)		213 (43.4)	193 (39.3)	
Missing	11 (1.6)	11 (1.6)		3 (1.4)	3 (1.4)		8 (1.6)	8 (1.6)	
Body mass index (kg/m²)	23.5±3.0	24.0±3.1	0.01	24.7±2.9	25.7±2.5	< 0.001	23.0±2.9	23.3±3.0	0.25

(Continued to the next page)

Table 1. Continued

Variable	All			Male			Female		
	Control (n=705)	Case (n=705)	p-value[a]	Control (n=214)	Case (n=214)	p-value[a]	Control (n=491)	Case (n=491)	p-value[a]
Body mass index group (kg/m²)									
Normal (< 23.0)	325 (46.1)	265 (37.6)	0.01	64 (29.9)	28 (13.1)	< 0.001	261 (53.2)	237 (48.3)	0.26
Overweight (23.0-24.9)	161 (22.8)	184 (26.1)		52 (24.3)	65 (30.4)		109 (22.2)	119 (24.2)	
Obese (≥ 25.0)	214 (30.4)	253 (35.9)		98 (45.8)	120 (56.1)		116 (23.6)	133 (27.1)	
Missing	5 (0.7)	3 (0.4)		0	1 (0.5)		5 (1.0)	2 (0.4)	

Values are presented as mean±standard deviation or number (%). [a]Data were analyzed using chi-square test (for categorical variables) and t test (for continuous variables), [b]Income was converted from Korean Won (KRW) to US dollar (US $) with currency rate of 2020 (1,200 KRW is approximately equal to one US $).

3. Genetic analysis

Given that several complex mechanisms for the link between BMI and thyroid cancer have been proposed, including insulin resistance, hyperinsulinemia, and abnormalities in hormone biosynthesis and hormonal pathways, we searched for up-to-date potential variants in the *FTO* gene for BMI, diabetes, polycystic ovary syndrome, and thyroid functions [7]. The keywords to search PubMed for publications until October 5, 2020 were used as follows: "(variants OR polymorphism OR GWAS OR genome-wide association studies) AND (obesity OR body mass index OR diabetes OR polycystic ovary syndrome OR hyperandrogenemia OR thyroid) AND FTO," and limited to titles and abstracts. As a result, 36 candidate SNPs of the *FTO* gene were selected for genetic analysis: rs8047395, rs9939609, rs8044769, rs8053740, rs1421085, rs17817499, rs1121980, rs8050136, rs13405728, rs9930506, rs7195539, rs62048379, rs56094641, rs7185735, rs3751812, rs11642015, rs62048402, rs62033400, rs9940128, rs55872725, rs1558902, rs7202116, rs17817288, rs11642841, rs1477196, rs1861867, rs763967273, rs759031579, rs141115189, rs9926289, rs76804286, rs8043757, rs1861868, rs9937053, rs9930333, and rs12149832.

To determine genetic variations in *FTO*, study participants' DNA was extracted from isolated peripheral blood leukocytes obtained from whole-blood samples. Genotyping was performed using an Infinium OncoArray-500K BeadChip (Illumina Inc., San Diego, CA) with 499 170 SNPs. After applying the quality-control criteria, which included monomorphic variants, minor allele frequencies < 0.01, call rates < 95%, and deviations from Hardy-Weinberg equilibrium (p < 1×10^{-6}), a total of 345,675 SNPs were available for further analysis. Among the 345,675 tags that passed the quality-control criteria, 27 SNPs were selected for further analysis. The linkage disequilibrium (LD) and tagging SNPs were accessed by using Haploview [15].

4. Statistical analysis

All statistical analyses were performed using R software ver. 3.6.0 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria). T tests and chi-square tests were performed to compare the distribution of continuous and categorical variables in cases and controls, respectively, among the total participants and subgroups of males and females. The association between *FTO* variants and BMI was examined by conducting a genome association analysis for variants in chromosome 16 in the log-additive model. To evaluate the association of covariates, BMI, and *FTO* variants with thyroid cancer risk, a conditional logistic regression model was used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs). The conditional logistic regression model was adjusted for first-degree family history of thyroid cancer, marital status, educational level, occupation, monthly income, smoking status, alcohol consumption, and BMI group. Additionally, the package 'SNPassoc' was used to identify variants associated with BMI and perform the haplotype analysis of tagging SNPs [16]. The codominant, dominant, and recessive models for the association between SNPs and thyroid cancer risk were applied to obtain robust findings.

Results

1. Demographic characteristics and their associations with thyroid cancer

Table 1 provides the sociodemographic characteristics of 705 cases and 705 controls from the Korean National Cancer Center Screenee Cohort. Because of the 1:1 frequency-matched design, the age and sex distributions were equal for the cases and controls. In the total population, the average BMI was slightly higher in the cases than in the controls

Table 2. Demographic and risk factors in the association with thyroid cancer risk

Variable	All		Male		Female	
	Univariable	Multivariable[a]	Univariable	Multivariable[a]	Univariable	Multivariable[a]
Family history of thyroid cancer						
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	3.00 (1.64-5.49)[b]	2.97 (1.60-5.55)[b]	9.00 (1.14-71.0)[b]	8.76 (1.01-75.9)[b]	2.54 (1.34-4.82)[b]	2.49 (1.28-4.81)[b]
Marital status						
Married	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Others	1.16 (0.83-1.63)	1.39 (0.96-2.00)	1.08 (0.49-2.37)	1.20 (0.50-2.88)	1.18 (0.81-1.72)	1.44 (0.95-2.19)
Educational level						
Middle school or less	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
High school	0.71 (0.51-0.93)	0.73 (0.50-1.06)	0.61 (0.28-1.34)	0.49 (0.19-1.27)	0.73 (0.49-1.10)	0.78 (0.51-1.18)
College or more	0.86 (0.60-1.23)	0.90 (0.62-1.33)	0.77 (0.37-1.60)	0.58 (0.22-1.49)	0.88 (0.58-1.33)	0.98 (0.63-1.51)
Occupation						
Professions, office workers, housewives	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Sales, service	0.69 (0.51-0.93)[b]	0.69 (0.50-0.94)[b]	0.76 (0.47-1.24)	0.73 (0.41-1.30)	0.66 (0.45-0.97)	0.68 (0.46-1.02)
Agriculture, laborer, unemployed, others	0.93 (0.64-1.36)	0.85 (0.57-1.26)	1.14 (0.65-2.00)	1.17 (0.59-2.33)	0.78 (0.46-1.33)	0.70 (0.40-1.21)
Income[c] (US $/mo)						
< $1,667	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
$1,667-$3,333	1.28 (0.86-1.90)	1.51 (1.03-2.23)[b]	3.53 (1.41-8.81)[b]	3.21 (1.24-8.32)[b]	0.95 (0.60-1.49)	1.24 (0.80-1.93)
> $3,333	1.15 (0.78-1.68)	1.22 (0.83-1.79)	2.45 (1.01-5.94)[b]	2.31 (0.90-5.97)	0.97 (0.62-1.50)	1.03 (0.67-1.60)
Smoking status						
Never	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Ever	0.72 (0.51-1.02)	0.75 (0.52-1.07)	0.82 (0.51-1.31)	0.88 (0.51-1.51)	0.63 (0.38-1.05)	0.63 (0.37-1.08)
Alcohol consumption						
Never	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Ever	0.86 (0.68-1.08)	0.90 (0.71-1.15)	0.93 (0.56-1.56)	1.03 (0.57-1.84)	0.84 (0.65-1.09)	0.88 (0.67-1.16)
Body mass index group (kg/m²)						
Normal (< 23.0)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Overweight (23.0-24.9)	1.46 (1.10-1.93)[b]	1.50 (1.12-2.00)[b]	2.68 (1.50-4.78)[b]	2.66 (1.42-4.97)[b]	1.21 (0.88-1.68)	1.28 (0.91-1.81)
Obese (≥ 25.0)	1.54 (1.18-2.01)[b]	1.62 (1.23-2.14)[b]	2.62 (1.56-4.38)[b]	2.78 (1.57-4.92)[b]	1.28 (0.92-1.76)	1.30 (0.93-1.84)

Values are presented as odds ratios and their 95% confidence intervals from a conditional logistic regression model. [a]Mutually adjusted for family history of thyroid cancer, marital status, educational level, occupation, monthly income, smoking status, alcohol consumption, and body mass index group, [b]Significant difference, [c]Income was converted from Korean Won (KRW) to US dollar (US $) with currency rate of 2020 (1,200 KRW is approximately equal to one US $).

(p=0.01). In addition, the proportion of individuals with a first-degree family history of thyroid cancer was higher in the cases than in the controls (p < 0.001). However, differences between the cases and controls were not observed for marital status, educational level, occupation, monthly income, alcohol consumption, or smoking status. When classified by sex, BMI (p < 0.001) was higher in the male cases than in the male controls, whereas female cases were more likely to have a family history of thyroid cancer than female controls (p=0.01).

In the multivariate conditional logistic regression analyses, associations were observed between the demographic characteristics and thyroid cancer risk (Table 2). A family history of thyroid cancer was associated with an increased risk of thyroid cancer in the total population (adjusted OR, 2.97; 95% CI, 1.60 to 5.55). In contrast, the odds of thyroid cancer in sales and service participants were significantly lower than those in professions, office workers, and housewives (adjust-

Table 3. Characteristics of *FTO* variants included in the analysis

Variant	Position	Minor/Major allele	All		Male		Female	
			MAF (%)	HWE (p-value)	MAF (%)	HWE (p-value)	MAF (%)	HWE (p-value)
rs1861868	53790402	A/G	18.0	0.59	19.3	0.28	17.4	0.91
rs8047395	53798523	G/A	40.1	1.00	41.4	0.92	39.6	0.95
rs9937053	53799507	A/G	16.6	0.21	17.4	0.61	16.3	0.29
rs9930333	53799977	C/A	16.6	0.25	17.3	0.62	16.2	0.29
rs9940128	53800754	A/G	16.6	0.25	17.3	0.62	16.2	0.29
rs1421085	53800954	G/A	13.1	0.56	13.1	1.00	13.1	0.49
rs11642015	53802494	A/G	13.0	0.64	13.1	1.00	12.9	0.57
rs62048402	53803223	A/G	13.0	0.56	13.1	1.00	13.0	0.57
rs1558902	53803574	T/A	13.0	0.56	13.1	1.00	13.0	0.57
rs56094641	53806453	G/A	13.2	0.49	13.4	1.00	13.1	0.49
rs17817288	53807764	A/G	43.2	0.19	44.5	0.33	42.6	0.40
rs1477196	53808258	A/G	31.1	0.66	31.9	0.32	30.8	0.94
rs55872725	53809123	A/G	13.0	0.64	13.1	1.00	12.9	0.57
rs1121980	53809247	A/G	16.6	0.25	17.3	0.62	16.2	0.29
rs8043757	53813450	T/A	12.6	0.81	13.0	1.00	12.4	0.88
rs8050136	53816275	A/C	13.1	0.56	13.2	1.00	13.0	0.57
rs3751812	53818460	A/C	13.2	0.49	13.2	1.00	13.2	0.49
rs9926289	53820503	A/G	13.2	0.49	13.2	1.00	13.2	0.49
rs9939609	53820527	A/T	13.2	0.49	13.2	1.00	13.2	0.49
rs7202116	53821615	G/A	13.2	0.49	13.2	1.00	13.2	0.49
rs7185735	53822651	G/A	13.2	0.49	13.2	1.00	13.2	0.49
rs9930506	53830465	G/A	17.2	0.11	18.2	0.20	16.8	0.36
rs8044769	53839135	A/G	40.0	0.74	40.9	1.00	39.6	0.74
rs12149832	53842908	A/G	13.6	0.07	14.1	0.23	13.4	0.27
rs11642841	53845487	A/C	3.7	0.44	4.0	0.49	3.6	0.36
rs1861867	53848561	A/G	31.2	1.00	32.5	0.66	30.9	0.76
rs7195539	53859158	G/A	8.3	1.00	9.2	0.78	7.9	0.83

FTO, fat mass and obesity-associated; HWE, Hardy-Weinberg equilibrium; MAF, minor allele frequency.

ed OR, 0.69; 95% CI, 0.50 to 0.94), whereas the odds in those with moderate income were higher than in those with low income (adjusted OR, 1.51; 95% CI, 1.03 to 2.23). An association was not observed among family history of cancer, marital status, educational level, monthly income, smoking status, and alcohol consumption in the total population. When classified by sex, the male population did not show any associations between occupation and thyroid cancer (Table 2).

BMI was associated with an increased risk of thyroid cancer in the overweight group (adjusted OR, 1.50; 95% CI, 1.12 to 2.00) and the obese group (adjusted OR, 1.62; 95% CI, 1.23 to 2.14) compared with the risk in the normal group. When stratified by sex, BMI was also associated with an increased risk of thyroid cancer in males in the overweight group (adjusted OR, 2.66; 95% CI, 1.42 to 4.97) and the obese group (adjusted OR, 2.78; 95% CI, 1.57 to 4.92) when the normal group was used as a reference, but the association in the females was not significantly different.

2. Genetic characteristics and their associations with body mass index and thyroid cancer

Table 3 presents the summary statistics of 27 SNPs included in the analysis. Additionally, there were differences in the distribution of genotypes of rs1861868 (p < 0.001) and rs8044769 (p=0.04) between total cases and controls, whereas unequal distribution was observed for rs8044769 (p=0.02) in females only (Table 4).

Table 5 shows the association between single *FTO* variants and thyroid cancer risk in the codominant, dominant, and recessive models. Variant rs1861868 was found to be associated with a decreased risk of thyroid cancer, with adjusted ORs (95% CIs) of 0.73 (0.57-0.92) for A/G vs. G/G, 0.48 (0.25-0.95) for A/A vs. G/G, and 0.70 (0.56-0.89) for A/G-A/A vs. G/G. In contrast, variants rs8047395 and rs8044769 were found to be associated with an increased risk of thyroid cancer, with ORs (95% CIs) of 1.39 (1.02-1.89) and 1.44 (1.05-1.97) in the recessive model.

Table 4. Distribution of *FTO* variants in study population

	All			Male			Female		
	Control (n=705)	Case (n=705)	p-value[a)]	Control (n=214)	Case (n=214)	p-value[a)]	Control (n=491)	Case (n=491)	p-value[a)]
rs1861868									
G/G	438 (62.1)	507 (71.9)	< 0.001	128 (59.8)	147 (68.7)	0.12	310 (63.1)	360 (73.3)	< 0.001
A/G	239 (33.9)	184 (26.1)		78 (36.4)	63 (29.4)		161 (32.8)	121 (24.6)	
A/A	28 (4.0)	14 (2.0)		8 (3.7)	4 (1.9)		20 (4.1)	10 (2.0)	
rs8047395									
A/A	256 (36.3)	249 (35.3)	0.05	75 (35.0)	73 (34.1)	0.96	181 (36.9)	176 (35.8)	0.02
G/A	352 (49.9)	326 (46.2)		103 (48.1)	103 (48.1)		249 (50.7)	223 (45.4)	
G/G	97 (13.8)	130 (18.4)		36 (16.8)	38 (17.8)		61 (12.4)	92 (18.7)	
rs9937053									
G/G	481 (68.2)	492 (69.8)	0.81	145 (67.8)	145 (67.8)	0.95	336 (68.4)	347 (70.7)	0.75
A/G	208 (29.5)	197 (27.9)		64 (29.9)	63 (29.4)		144 (29.3)	134 (27.3)	
A/A	16 (2.3)	16 (2.3)		5 (2.3)	6 (2.8)		11 (2.2)	10 (2.0)	
rs9930333									
A/A	482 (68.4)	493 (69.9)	0.81	145 (67.8)	146 (68.2)	0.94	337 (68.6)	347 (70.7)	0.78
C/A	207 (29.4)	196 (27.8)		64 (29.9)	62 (29.0)		143 (29.1)	134 (27.3)	
C/C	16 (2.3)	16 (2.3)		5 (2.3)	6 (2.8)		11 (2.2)	10 (2.0)	
rs9940128									
G/G	482 (68.4)	493 (69.9)	0.81	145 (67.8)	146 (68.2)	0.94	337 (68.6)	347 (70.7)	0.78
A/G	207 (29.4)	196 (27.8)		64 (29.9)	62 (29.0)		143 (29.1)	134 (27.3)	
A/A	16 (2.3)	16 (2.3)		5 (2.3)	6 (2.8)		11 (2.2)	10 (2.0)	
rs1421085									
A/A	524 (74.3)	538 (76.3)	0.47	161 (75.2)	162 (75.7)	0.91	363 (73.9)	376 (76.6)	0.47
G/A	172 (24.4)	155 (22.0)		50 (23.4)	48 (22.4)		122 (24.8)	107 (21.8)	
G/G	9 (1.3)	12 (1.7)		3 (1.4)	4 (1.9)		6 (1.2)	8 (1.6)	
rs11642015									
G/G	526 (74.6)	539 (76.5)	0.50	161 (75.2)	162 (75.7)	0.91	365 (74.3)	377 (76.8)	0.51
A/G	170 (24.1)	154 (21.8)		50 (23.4)	48 (22.4)		120 (24.4)	106 (21.6)	
A/A	9 (1.3)	12 (1.7)		3 (1.4)	4 (1.9)		6 (1.2)	8 (1.6)	
rs62048402									
G/G	526 (74.6)	538 (76.3)	0.53	161 (75.2)	162 (75.7)	0.91	365 (74.3)	376 (76.6)	0.55
A/G	170 (24.1)	155 (22.0)		50 (23.4)	48 (22.4)		120 (24.4)	107 (21.8)	
A/A	9 (1.3)	12 (1.7)		3 (1.4)	4 (1.9)		6 (1.2)	8 (1.6)	
rs1558902									
A/A	526 (74.6)	538 (76.3)	0.53	161 (75.2)	162 (75.7)	0.91	365 (74.3)	376 (76.6)	0.55
T/A	170 (24.1)	155 (22.0)		50 (23.4)	48 (22.4)		120 (24.4)	107 (21.8)	
T/T	9 (1.3)	12 (1.7)		3 (1.4)	4 (1.9)		6 (1.2)	8 (1.6)	
rs56094641									
A/A	523 (74.2)	535 (75.9)	0.54	161 (75.2)	159 (74.3)	0.92	362 (73.7)	376 (76.6)	0.44
G/A	173 (24.5)	158 (22.4)		50 (23.4)	51 (23.8)		123 (25.1)	107 (21.8)	
G/G	9 (1.3)	12 (1.7)		3 (1.4)	4 (1.9)		6 (1.2)	8 (1.6)	
rs17817288									
G/G	234 (33.2)	233 (33.0)	0.06	67 (31.3)	70 (32.7)	0.78	167 (34.0)	163 (33.2)	0.05
A/G	350 (49.6)	318 (45.1)		104 (48.6)	97 (45.3)		246 (50.1)	221 (45.0)	
A/A	121 (17.2)	154 (21.8)		43 (20.1)	47 (22.0)		78 (15.9)	107 (21.8)	

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Table 4. Continued

	All			Male			Female		
	Control (n=705)	Case (n=705)	p-value[a]	Control (n=214)	Case (n=214)	p-value[a]	Control (n=491)	Case (n=491)	p-value[a]
rs1477196									
G/G	340 (48.2)	333 (47.2)	0.14	104 (48.6)	99 (46.3)	0.88	236 (48.1)	234 (47.7)	0.08
A/G	306 (43.4)	291 (41.3)		87 (40.7)	90 (42.1)		219 (44.6)	201 (40.9)	
A/A	59 (8.4)	81 (11.5)		23 (10.7)	25 (11.7)		36 (7.3)	56 (11.4)	
rs55872725									
G/G	526 (74.6)	539 (76.5)	0.50	161 (75.2)	162 (75.7)	0.91	365 (74.3)	377 (76.8)	0.51
A/G	170 (24.1)	154 (21.8)		50 (23.4)	48 (22.4)		120 (24.4)	106 (21.6)	
A/A	9 (1.3)	12 (1.7)		3 (1.4)	4 (1.9)		6 (1.2)	8 (1.6)	
rs1121980									
G/G	482 (68.4)	493 (69.9)	0.81	145 (67.8)	146 (68.2)	0.94	337 (68.6)	347 (70.7)	0.78
A/G	207 (29.4)	196 (27.8)		64 (29.9)	62 (29.0)		143 (29.1)	134 (27.3)	
A/A	16 (2.3)	16 (2.3)		5 (2.3)	6 (2.8)		11 (2.2)	10 (2.0)	
rs8043757									
A/A	534 (75.7)	542 (76.9)	0.65	163 (76.2)	161 (75.2)	0.92	371 (75.6)	381 (77.6)	0.58
T/A	162 (23.0)	151 (21.4)		48 (22.4)	49 (22.9)		114 (23.2)	102 (20.8)	
T/T	9 (1.3)	12 (1.7)		3 (1.4)	4 (1.9)		6 (1.2)	8 (1.6)	
rs8050136									
C/C	526 (74.6)	536 (76.0)	0.60	161 (75.2)	161 (75.2)	0.93	365 (74.3)	375 (76.4)	0.59
A/C	170 (24.1)	157 (22.3)		50 (23.4)	49 (22.9)		120 (24.4)	108 (22.0)	
A/A	9 (1.3)	12 (1.7)		3 (1.4)	4 (1.9)		6 (1.2)	8 (1.6)	
rs3751812									
C/C	525 (74.5)	534 (75.7)	0.63	161 (75.2)	161 (75.2)	0.93	364 (74.1)	373 (76.0)	0.63
A/C	171 (24.3)	159 (22.6)		50 (23.4)	49 (22.9)		121 (24.6)	110 (22.4)	
A/A	9 (1.3)	12 (1.7)		3 (1.4)	4 (1.9)		6 (1.2)	8 (1.6)	
rs9926289									
G/G	525 (74.5)	534 (75.7)	0.63	161 (75.2)	161 (75.2)	0.93	364 (74.1)	373 (76.0)	0.63
A/G	171 (24.3)	159 (22.6)		50 (23.4)	49 (22.9)		121 (24.6)	110 (22.4)	
A/A	9 (1.3)	12 (1.7)		3 (1.4)	4 (1.9)		6 (1.2)	8 (1.6)	
rs9939609									
T/T	525 (74.5)	534 (75.7)	0.63	161 (75.2)	161 (75.2)	0.93	364 (74.1)	373 (76.0)	0.63
A/T	171 (24.3)	159 (22.6)		50 (23.4)	49 (22.9)		121 (24.6)	110 (22.4)	
A/A	9 (1.3)	12 (1.7)		3 (1.4)	4 (1.9)		6 (1.2)	8 (1.6)	
rs7202116									
A/A	525 (74.5)	534 (75.7)	0.63	161 (75.2)	161 (75.2)	0.93	364 (74.1)	373 (76.0)	0.63
G/A	171 (24.3)	159 (22.6)		50 (23.4)	49 (22.9)		121 (24.6)	110 (22.4)	
G/G	9 (1.3)	12 (1.7)		3 (1.4)	4 (1.9)		6 (1.2)	8 (1.6)	
rs7185735									
A/A	525 (74.5)	534 (75.7)	0.63	161 (75.2)	161 (75.2)	0.93	364 (74.1)	373 (76.0)	0.63
G/A	171 (24.3)	159 (22.6)		50 (23.4)	49 (22.9)		121 (24.6)	110 (22.4)	
G/G	9 (1.3)	12 (1.7)		3 (1.4)	4 (1.9)		6 (1.2)	8 (1.6)	
rs9930506									
A/A	471 (66.8)	487 (69.1)	0.66	136 (63.6)	146 (68.2)	0.58	335 (68.2)	341 (69.5)	0.91
G/A	217 (30.8)	202 (28.7)		73 (34.1)	63 (29.4)		144 (29.3)	139 (28.3)	
G/G	17 (2.4)	16 (2.3)		5 (2.3)	5 (2.3)		12 (2.4)	11 (2.2)	

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Table 4. Continued

	All			Male			Female		
	Control (n=705)	Case (n=705)	p-value[a]	Control (n=214)	Case (n=214)	p-value[a]	Control (n=491)	Case (n=491)	p-value[a]
rs8044769									
G/G	253 (35.9)	251 (35.6)	0.04	74 (34.6)	75 (35.0)	0.90	179 (36.5)	176 (35.8)	0.02
A/G	358 (50.8)	326 (46.2)		106 (49.5)	102 (47.7)		252 (51.3)	224 (45.6)	
A/A	94 (13.3)	128 (18.2)		34 (15.9)	37 (17.3)		60 (12.2)	91 (18.5)	
rs12149832									
G/G	516 (73.2)	528 (74.9)	0.72	152 (71.0)	160 (74.8)	0.66	364 (74.1)	368 (74.9)	0.93
A/G	179 (25.4)	169 (24.0)		59 (27.6)	52 (24.3)		120 (24.4)	117 (23.8)	
A/A	10 (1.4)	8 (1.1)		3 (1.4)	2 (0.9)		7 (1.4)	6 (1.2)	
rs11642841									
C/C	653 (92.6)	655 (92.9)	0.81	200 (93.5)	195 (91.1)	0.46	453 (92.3)	460 (93.7)	0.68
A/C	51 (7.2)	48 (6.8)		14 (6.5)	18 (8.4)		37 (7.5)	30 (6.1)	
A/A	1 (0.1)	2 (0.3)		0	1 (0.5)		1 (0.2)	1 (0.2)	
rs1861867									
G/G	340 (48.2)	324 (46.0)	0.40	103 (48.1)	94 (43.9)	0.68	237 (48.3)	230 (46.8)	0.36
A/G	303 (43.0)	305 (43.3)		88 (41.1)	96 (44.9)		215 (43.8)	209 (42.6)	
A/A	62 (8.8)	76 (10.8)		23 (10.7)	24 (11.2)		39 (7.9)	52 (10.6)	
rs7195539									
A/A	581 (82.4)	604 (85.7)	0.09	171 (79.9)	182 (85.0)	0.36	410 (83.5)	422 (85.9)	0.06
G/A	117 (16.6)	99 (14.0)		41 (19.2)	30 (14.0)		76 (15.5)	69 (14.1)	
G/G	7 (1.0)	2 (0.3)		2 (0.9)	2 (0.9)		5 (1.0)	0	

FTO, fat mass and obesity-associated. [a]Data were analyzed using chi-square test (for categorical variables) and t test (for continuous variables).

Genome association analysis revealed that none of the 27 SNPs included in the study were significantly associated with overweight and obesity (p > 0.1) (Fig. 2). Furthermore, Fig. 3 shows the LD block structure with the high correlation among 27 variants in the FTO gene. Then, Haploview identified seven tagging SNPs including rs1861868, rs8047395, rs56094641, rs1477196, rs9930506, rs11642841, and rs7195539. Compared to the haplotype GAAGACA, AAAGACA (adjusted OR, 0.55; 95% CI, 0.36 to 0.84), and GGAAACA (adjusted OR, 0.43; 95% CI, 0.25 to 0.72) were found to be associated with significantly lower odds of thyroid cancer in the total population and female subgroup, respectively (Table 6).

3. Combined effect of body mass index and variants on thyroid cancer risk

The adjusted ORs and 95% CIs for the combined effect of BMI and SNP on thyroid cancer are presented in Tables 7-9. When using G/G carriers with normal BMI as the reference, overweight and obesity were significantly associated with thyroid cancer risks in all genotype groups of rs17817288, with adjusted ORs (95% CIs) of 1.77 (1.07-2.91), 1.66 (1.06-2.62), and 2.15 (1.18-3.95) for overweight participants carrying G/G, A/G, and A/A, respectively; and 2.68 (1.65-4.34),

1.67 (1.08-2.58), and 1.71 (1.01-2.90) for obese participants carrying A/A, G/A, and G/G, respectively, in the codominant model (Table 7). Neither overweight nor obesity was associated with thyroid cancer risks in all genotype groups of other variants.
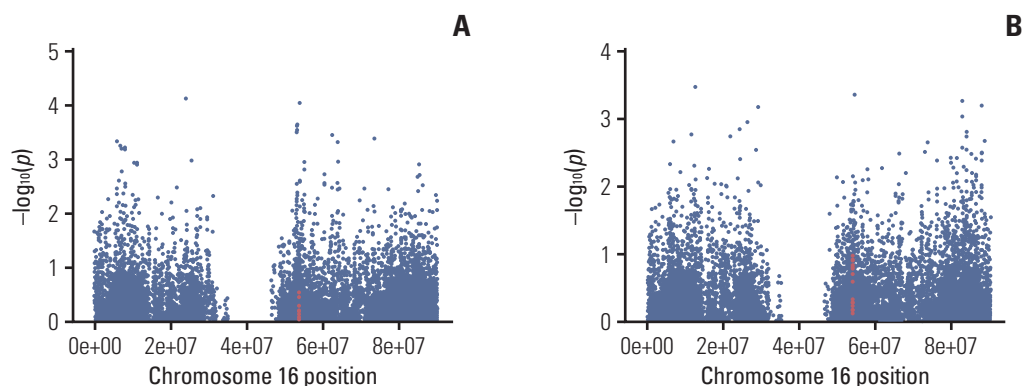
In the dominant model, when using G/G-A/G carriers with normal BMI as the reference, overweight and obesity were significantly associated with thyroid cancer risks in A/G-A/A genotype carriers of rs9937053, rs12149832, and rs1861867 (Table 8). The adjusted ORs (95% CIs) for rs9937053 were 1.66 (1.04-2.67) and 1.71 (1.13-2.58) for overweight participants; and 2.20 (1.39-3.49) and 1.65 (1.12-2.45) for obese participants carrying G/G and A/G-A/A, respectively. The adjusted ORs (95% CIs) for rs12149832 were 1.81 (1.13-2.89) and 1.69 (1.11-2.57) for overweight participants and 2.30 (1.45-3.66) and 1.68 (1.13-2.49) for obese participants carrying G/G and A/G-A/A, respectively. The adjusted ORs (95% CIs) for rs1861867 were 1.40 (1.04-1.90) and 2.69 (1.06-6.83) for overweight participants and 1.56 (1.17-2.07) and 2.09 (1.02-4.27) for obese participants carrying G/G and A/G-A/A, respectively. When using A/A carriers with normal BMI as the reference, overweight and obesity were significantly associated with thyroid cancer risks in G/A-G/G

Table 5. Association between *FTO* genetic variants and thyroid cancer

Variant	Codominant model				Dominant model		Recessive model	
	Het vs. hom1 genotypes		Hom2 vs. hom1 genotypes		Het+hom2 vs. hom1 genotypes		Hom2 vs. het+hom1 genotypes	
	Univariable	Multivariable[a]	Univariable	Multivariable[a]	Univariable	Multivariable[a]	Univariable	Multivariable[a]
rs1861868	0.68 (0.54-0.85)[b]	0.73 (0.57-0.92)[b]	0.44 (0.23-0.84)[b]	0.48 (0.25-0.95)[b]	0.66 (0.53-0.82)[b]	0.70 (0.56-0.89)[b]	0.50 (0.26-0.95)[b]	0.54 (0.28-1.06)
rs8047395	0.95 (0.76-1.20)	0.90 (0.71-1.16)	1.39 (1.01-1.92)[b]	1.31 (0.93-1.84)	1.05 (0.84-1.30)	0.99 (0.78-1.25)	1.43 (1.07-1.91)[b]	1.39 (1.02-1.89)[b]
rs9937053	0.93 (0.74-1.16)	1.00 (0.79-1.27)	0.98 (0.49-1.97)	1.05 (0.51-2.17)	0.93 (0.75-1.16)	1.00 (0.80-1.26)	1.00 (0.50-2.00)	1.05 (0.51-2.16)
rs9930333	0.93 (0.74-1.16)	1.00 (0.79-1.27)	0.98 (0.49-1.97)	1.06 (0.51-2.17)	0.93 (0.75-1.16)	1.01 (0.80-1.27)	1.00 (0.50-2.00)	1.05 (0.51-2.16)
rs9940128	0.93 (0.74-1.16)	1.00 (0.79-1.27)	0.98 (0.49-1.97)	1.06 (0.51-2.17)	0.93 (0.75-1.16)	1.01 (0.80-1.27)	1.00 (0.50-2.00)	1.05 (0.51-2.16)
rs1421085	0.88 (0.68-1.12)	0.97 (0.75-1.27)	1.30 (0.55-3.09)	1.45 (0.59-3.57)	0.90 (0.71-1.15)	1.00 (0.77-1.29)	1.33 (0.56-3.16)	1.46 (0.59-3.59)
rs11642015	0.88 (0.69-1.13)	0.98 (0.75-1.28)	1.30 (0.55-3.10)	1.45 (0.59-3.58)	0.91 (0.71-1.15)	1.00 (0.78-1.30)	1.33 (0.56-3.16)	1.46 (0.59-3.59)
rs62048402	0.89 (0.69-1.14)	0.99 (0.76-1.29)	1.30 (0.55-3.10)	1.46 (0.59-3.58)	0.91 (0.72-1.16)	1.01 (0.78-1.31)	1.33 (0.56-3.16)	1.46 (0.59-3.59)
rs1558902	0.89 (0.69-1.14)	0.99 (0.76-1.29)	1.30 (0.55-3.10)	1.46 (0.59-3.58)	0.91 (0.72-1.16)	1.01 (0.78-1.31)	1.33 (0.56-3.16)	1.46 (0.59-3.59)
rs56094641	0.89 (0.70-1.14)	0.99 (0.76-1.29)	1.30 (0.55-3.10)	1.46 (0.59-3.59)	0.91 (0.72-1.16)	1.02 (0.79-1.31)	1.33 (0.56-3.16)	1.46 (0.59-3.59)
rs17817288	0.92 (0.73-1.17)	0.87 (0.68-1.11)	1.28 (0.94-1.73)	1.21 (0.87-1.67)	1.01 (0.80-1.26)	0.95 (0.75-1.20)	1.35 (1.03-1.76)[b]	1.32 (1.00-1.75)
rs1477196	0.97 (0.78-1.21)	0.91 (0.72-1.14)	1.41 (0.97-2.05)	1.32 (0.89-1.95)	1.04 (0.85-1.28)	0.97 (0.78-1.21)	1.43 (1.00-2.05)	1.38 (0.94-2.01)
rs55872725	0.88 (0.69-1.13)	0.98 (0.75-1.28)	1.30 (0.55-3.10)	1.45 (0.59-3.58)	0.91 (0.71-1.15)	1.00 (0.78-1.30)	1.33 (0.56-3.16)	1.46 (0.59-3.59)
rs1121980	0.93 (0.74-1.16)	1.00 (0.79-1.27)	0.98 (0.49-1.97)	1.06 (0.51-2.17)	0.93 (0.75-1.16)	1.01 (0.80-1.27)	1.00 (0.50-2.00)	1.05 (0.51-2.16)
rs8043757	0.92 (0.71-1.18)	1.00 (0.77-1.31)	1.32 (0.55-3.13)	1.46 (0.59-3.59)	0.94 (0.74-1.20)	1.03 (0.80-1.34)	1.33 (0.56-3.16)	1.46 (0.59-3.59)
rs8050136	0.91 (0.71-1.16)	1.00 (0.77-1.30)	1.31 (0.55-3.11)	1.46 (0.59-3.60)	0.93 (0.73-1.18)	1.03 (0.79-1.33)	1.33 (0.56-3.16)	1.46 (0.59-3.59)
rs3751812	0.91 (0.71-1.17)	1.01 (0.78-1.32)	1.31 (0.55-3.11)	1.46 (0.60-3.61)	0.93 (0.73-1.19)	1.04 (0.80-1.34)	1.33 (0.56-3.16)	1.46 (0.59-3.59)
rs9926289	0.91 (0.71-1.17)	1.01 (0.78-1.32)	1.31 (0.55-3.11)	1.46 (0.60-3.61)	0.93 (0.73-1.19)	1.04 (0.80-1.34)	1.33 (0.56-3.16)	1.46 (0.59-3.59)
rs9939609	0.91 (0.71-1.17)	1.01 (0.78-1.32)	1.31 (0.55-3.11)	1.46 (0.60-3.61)	0.93 (0.73-1.19)	1.04 (0.80-1.34)	1.33 (0.56-3.16)	1.46 (0.59-3.59)
rs7202116	0.91 (0.71-1.17)	1.01 (0.78-1.32)	1.31 (0.55-3.11)	1.46 (0.60-3.61)	0.93 (0.73-1.19)	1.04 (0.80-1.34)	1.33 (0.56-3.16)	1.46 (0.59-3.59)
rs7185735	0.91 (0.71-1.17)	1.01 (0.78-1.32)	1.31 (0.55-3.11)	1.46 (0.60-3.61)	0.93 (0.73-1.19)	1.04 (0.80-1.34)	1.33 (0.56-3.16)	1.46 (0.59-3.59)
rs9930506	0.91 (0.73-1.13)	0.97 (0.77-1.22)	0.92 (0.46-1.82)	1.01 (0.50-2.05)	0.91 (0.73-1.13)	0.97 (0.77-1.22)	0.94 (0.48-1.86)	1.02 (0.50-2.06)
rs8044769	0.92 (0.73-1.16)	0.88 (0.69-1.12)	1.39 (1.00-1.92)	1.34 (0.95-1.88)	1.01 (0.81-1.26)	0.97 (0.77-1.22)	1.46 (1.09-1.96)[b]	1.44 (1.05-1.97)[b]
rs12149832	0.92 (0.72-1.18)	1.02 (0.79-1.32)	0.79 (0.31-1.99)	0.90 (0.34-2.37)	0.92 (0.72-1.16)	1.01 (0.79-1.30)	0.80 (0.32-2.03)	0.90 (0.34-2.36)
rs11642841	0.94 (0.63-1.40)	1.07 (0.70-163)	2.00 (0.18-22.1)	4.01 (0.29-55.8)	0.96 (0.65-1.43)	1.11 (0.73-1.68)	2.00 (0.18-22.1)	4.01 (0.29-55.7)
rs1861867	1.06 (0.85-1.32)	1.01 (0.80-1.27)	1.29 (0.89-1.88)	1.23 (0.83-1.83)	1.10 (0.89-1.35)	1.04 (0.83-1.30)	1.25 (0.88-1.79)	1.23 (0.84-1.78)
rs7195539	0.81 (0.61-1.09)	0.80 (0.59-1.09)	0.28 (0.06-1.34)	0.24 (0.05-1.20)	0.78 (0.59-1.04)	0.77 (0.57-1.04)	0.29 (0.06-1.38)	0.24 (0.05-1.23)

Values are presented as odds ratios and their 95% confidence intervals from a conditional logistic regression model. *FTO*, fat mass and obesity-associated; het, heterozygous genotype; hom1, homozygous genotype of major allele; hom2, homozygous genotype of minor allele. [a]Adjusted for family history of thyroid cancer, marital status, educational level, occupation, monthly income, smoking status, alcohol consumption, and body mass index group, [b]Significant difference.

Fig. 2. Linkage disequilibrium plot for single nucleotide polymorphisms within the fat mass and obesity-associated (*FTO*) gene in chromosome 16. The numbers in the squares are r² values (×100) between the loci, with red shades indicating greater r² values.

Fig. 3. Genome association analysis for variants related to overweight (A) and obesity (B) in chromosome 16. Included variants in this study are presented in the red color.

Table 6. Association between *FTO* haplotypes and thyroid cancer

Haplotype	Total		Male		Female	
	Univariable	Multivariable[a]	Univariable	Multivariable[a]	Univariable	Multivariable[a]
GAAGACA	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
AAAGACA	0.56 (0.37-0.84)[b]	0.55 (0.36-0.84)[b]	0.94 (0.63-1.38)	0.88 (0.59-1.30)	1.07 (0.84-1.36)	1.06 (0.83-1.36)
GGAAACA	1.03 (0.84-1.27)	1.01 (0.82-1.24)	0.88 (0.43-1.80)	0.83 (0.40-1.71)	0.43 (0.26-0.72)[b]	0.43 (0.25-0.72)[b]
GGAGACA	1.22 (0.82-1.80)	1.16 (0.78-1.73)	1.07 (0.53-2.13)	0.98 (0.49-1.97)	1.30 (0.81-2.08)	1.26 (0.78-2.04)

Values are presented as odds ratios and their 95% confidence intervals. *FTO*, fat mass and obesity-associated. [a] Adjusted for family history of thyroid cancer, marital status, educational level, occupation, monthly income, smoking status, alcohol consumption, and body mass index group, [b] Significant difference.

genotype carriers of rs7195539, with ORs (95% CIs) of 1.70 (1.12-2.57) and 1.64 (1.09-2.47) for overweight participants and 1.90 (1.27-2.86) and 1.75 (1.19-2.56) for obese participants carrying A/A and G/A-G/G, respectively.

In the recessive model, when using G/G carriers with normal BMI as the reference, overweight and obesity were significantly associated with thyroid cancer risks in A/A genotype carriers of rs17817288 and rs8044769 (Table 9). The adjusted ORs (95% CIs) for rs17817288 were 1.64 (1.19-2.25) and 2.11 (1.21-3.67) for overweight participants and 1.95 (1.43-2.67) and 1.66 (1.04-2.65) for obese participants carrying G/G-A/G and A/A, respectively. The adjusted ORs (95% CIs) for rs8044769 were 1.53 (1.12-2.10) and 2.55 (1.35-4.81) for overweight participants and 2.30 (1.45-3.66) and 1.68 (1.13-2.49) for obese participants carrying G/G-A/G and A/A, respectively.

Discussion

Our study examined the main effects of BMI and *FTO* in thyroid carcinogenesis and the effect of their combined interactions on thyroid cancer susceptibility. Our findings

suggest that high BMI subclasses are positively associated with thyroid cancer risk, which is consistent with the results of several epidemiologic studies. In a systemic review of 36 studies, BMI was positively associated with thyroid cancer risk in both male and female populations [17]. In another systematic review of 21 articles that included 12,199 thyroid cancer cases, the risk of thyroid cancer was increased by 25% in overweight individuals and by 55% in obese individuals compared with the risk in normal weight individuals [18]. The findings were similar in a Korean hospital-based case-control study, which observed a positive association between BMI and thyroid cancer [12]. A multicenter prospective cohort study from the Korean Cancer Prevention Study-II also reported that an increased risk of thyroid cancer was associated with BMI [13]. Our findings support the association between BMI and an increased risk of thyroid cancer and indicate that the role of obesity-related *FTO* in thyroid cancer risk should be further evaluated.

FTO is an obesity-susceptibility gene that was identified in a previous study [19]. In addition, the association was observed across populations with diverse ethnicities, and it was found to have the largest impact in young adulthood [13]. In a study of 38,759 Europeans performed to identify

Table 7. Combined effect of body mass index and each polymorphism on thyroid cancer risk in the codominant model

Variant	Hom1 normal	Hom1 overweight	Hom1 obese	Het normal	Het overweight	Het obese	Hom2 normal	Hom2 overweight	Hom2 obese
rs1861868	1.00 (reference)	1.36 (0.97-1.91)	1.46 (1.05-2.04)[a]	0.63 (0.43-0.92)[a]	1.05 (0.65-1.72)	1.16 (0.77-1.75)	0.47 (0.18-1.22)	0.87 (0.22-3.52)	0.60 (0.15-2.47)
rs8047395	1.00 (reference)	1.67 (1.04-2.69)[a]	2.20 (1.39-3.49)[a]	1.02 (0.70-1.48)	1.50 (0.96-2.34)	1.70 (1.12-2.58)[a]	2.13 (1.23-3.67)[a]	2.39 (1.24-4.57)[a]	1.62 (0.92-2.84)
rs9937053	1.00 (reference)	1.25 (0.88-1.77)	1.53 (1.10-2.14)[a]	0.80 (0.56-1.16)	2.07 (1.25-3.43)[a]	1.48 (0.98-2.24)	1.26 (0.34-4.74)	0.76 (0.21-2.76)	2.54 (0.71-9.02)
rs9930333	1.00 (reference)	1.27 (0.90-1.79)	1.54 (1.10-2.15)[a]	0.82 (0.57-1.19)	2.05 (1.23-3.40)[a]	1.49 (0.98-2.25)	1.27 (0.34-4.76)	0.77 (0.21-2.79)	2.56 (0.72-9.10)
rs9940128	1.00 (reference)	1.27 (0.90-1.79)	1.54 (1.10-2.15)[a]	0.82 (0.57-1.19)	2.05 (1.23-3.40)[a]	1.49 (0.98-2.25)	1.27 (0.34-4.76)	0.77 (0.21-2.79)	2.56 (0.72-9.10)
rs1421085	1.00 (reference)	1.23 (0.89-1.71)	1.39 (1.01-1.91)[a]	0.64 (0.43-0.96)[a]	2.01 (1.14-3.53)[a]	1.64 (1.04-2.58)[a]	1.46 (0.35-5.99)	1.05 (0.17-6.61)	3.76 (0.70-20.3)
rs11642015	1.00 (reference)	1.23 (0.89-1.71)	1.40 (1.02-1.93)[a]	0.65 (0.43-0.97)[a]	2.08 (1.17-3.68)[a]	1.63 (1.03-2.56)[a]	1.47 (0.36-6.04)	1.06 (0.17-6.68)	3.76 (0.70-20.3)
rs62048402	1.00 (reference)	1.23 (0.89-1.71)	1.40 (1.02-1.92)[a]	0.65 (0.43-0.98)[a]	2.08 (1.18-3.68)[a]	1.65 (1.05-2.59)[a]	1.47 (0.36-6.04)	1.06 (0.17-6.69)	3.76 (0.70-20.3)
rs1558902	1.00 (reference)	1.23 (0.89-1.71)	1.40 (1.02-1.92)[a]	0.65 (0.43-0.98)[a]	2.08 (1.18-3.68)[a]	1.65 (1.05-2.59)[a]	1.47 (0.36-6.04)	1.06 (0.17-6.69)	3.76 (0.70-20.3)
rs56094641	1.00 (reference)	1.22 (0.88-1.69)	1.39 (1.01-1.91)[a]	0.65 (0.43-0.97)[a]	2.11 (1.20-3.69)[a]	1.64 (1.04-2.58)[a]	1.46 (0.36-6.01)	1.06 (0.17-6.70)	3.73 (0.69-20.1)
rs17817288	1.00 (reference)	1.77 (1.07-2.91)[a]	2.68 (1.65-4.34)[a]	1.07 (0.72-1.57)	1.66 (1.06-2.62)[a]	1.67 (1.08-2.58)[a]	2.25 (1.33-3.80)[a]	2.15 (1.18-3.95)[a]	1.71 (1.01-2.90)[a]
rs1477196	1.00 (reference)	1.81 (1.20-2.74)[a]	1.95 (1.30-2.91)[a]	1.03 (0.72-1.46)	1.38 (0.90-2.12)	1.69 (1.13-2.52)[a]	2.60 (1.31-5.14)[a]	2.28 (1.04-5.02)[a]	1.54 (0.83-2.85)
rs55872725	1.00 (reference)	1.23 (0.89-1.71)	1.40 (1.02-1.93)[a]	0.65 (0.43-0.97)[a]	2.08 (1.17-3.68)[a]	1.63 (1.03-2.56)[a]	1.47 (0.36-6.04)	1.06 (0.17-6.68)	3.76 (0.70-20.3)
rs1121980	1.00 (reference)	1.27 (0.90-1.79)	1.54 (1.10-2.15)[a]	0.82 (0.57-1.19)	2.05 (1.23-3.40)[a]	1.49 (0.98-2.25)	1.27 (0.34-4.76)	0.77 (0.21-2.79)	2.56 (0.72-9.10)
rs8043757	1.00 (reference)	1.18 (0.85-1.64)	1.38 (1.00-1.89)	0.60 (0.40-0.92)[a]	2.47 (1.37-4.48)[a]	1.68 (1.06-2.66)[a]	1.36 (0.33-5.64)	1.09 (0.17-6.92)	3.65 (0.68-19.7)
rs8050136	1.00 (reference)	1.20 (0.87-1.67)	1.39 (1.01-1.91)[a]	0.64 (0.42-0.96)[a]	2.27 (1.28-4.01)[a]	1.65 (1.05-2.60)[a]	1.48 (0.36-6.09)	1.07 (0.17-6.80)	3.70 (0.69-20.0)
rs3751812	1.00 (reference)	1.20 (0.86-1.67)	1.38 (1.01-1.91)[a]	0.64 (0.42-0.96)[a]	2.29 (1.29-4.05)[a]	1.69 (1.07-2.64)[a]	1.48 (0.36-6.11)	1.08 (0.17-6.84)	3.70 (0.69-20.0)
rs9926289	1.00 (reference)	1.20 (0.86-1.67)	1.38 (1.01-1.91)[a]	0.64 (0.42-0.96)[a]	2.29 (1.29-4.05)[a]	1.69 (1.07-2.64)[a]	1.48 (0.36-6.11)	1.08 (0.17-6.84)	3.70 (0.69-20.0)
rs9939609	1.00 (reference)	1.20 (0.86-1.67)	1.38 (1.01-1.91)[a]	0.64 (0.42-0.96)[a]	2.29 (1.29-4.05)[a]	1.69 (1.07-2.64)[a]	1.48 (0.36-6.11)	1.08 (0.17-6.84)	3.70 (0.69-20.0)
rs7202116	1.00 (reference)	1.20 (0.86-1.67)	1.38 (1.01-1.91)[a]	0.64 (0.42-0.96)[a]	2.29 (1.29-4.05)[a]	1.69 (1.07-2.64)[a]	1.48 (0.36-6.11)	1.08 (0.17-6.84)	3.70 (0.69-20.0)
rs7185735	1.00 (reference)	1.20 (0.86-1.67)	1.38 (1.01-1.91)	0.64 (0.42-0.96)	2.29 (1.29-4.05)[a]	1.69 (1.07-2.64)[a]	1.48 (0.36-6.11)	1.08 (0.17-6.84)	3.70 (0.69-20.0)
rs9930506	1.00 (reference)	1.36 (0.96-1.92)	1.58 (1.13-2.21)	0.87 (0.60-1.26)	1.74 (1.08-2.80)[a]	1.44 (0.95-2.18)	1.08 (0.31-3.84)	0.81 (0.22-2.90)	2.61 (0.73-9.31)
rs8044769	1.00 (reference)	1.82 (1.13-2.91)	2.32 (1.45-3.69)	1.07 (0.73-1.56)	1.45 (0.92-2.28)	1.70 (1.12-2.59)[a]	2.16 (1.25-3.73)[a]	2.63 (1.34-5.14)[a]	1.77 (1.00-3.13)
rs12149832	1.00 (reference)	1.32 (0.95-1.84)	1.44 (1.05-1.99)	0.75 (0.50-1.13)	1.87 (1.11-3.15)[a]	1.67 (1.07-2.61)[a]	0.96 (0.23-3.97)	0 (0-6.0e+75)	2.89 (0.52-16.2)
rs11642841	1.00 (reference)	1.41 (1.04-1.90)	1.56 (1.17-2.07)	0.58 (0.28-1.20)	2.68 (1.05-6.80)[a]	1.97 (0.96-4.05)	2.12 (0.09-48.0)		
rs1861867	1.00 (reference)	1.73 (1.14-2.62)	1.90 (1.27-2.87)	1.11 (0.78-1.59)	1.52 (0.99-2.34)	1.83 (1.23-2.73)[a]	1.96 (1.03-3.73)[a]	2.38 (1.05-5.37)[a]	1.45 (0.76-2.77)
rs7195539	1.00 (reference)	1.65 (1.20-2.28)	1.83 (1.35-2.49)	1.18 (0.75-1.88)	1.11 (0.60-2.05)	1.02 (0.58-1.79)	0 (0-3.2e+53)	0.46 (0.04-5.76)	0.58 (0.06-5.76)

Values are presented as odds ratios and their 95% confidence intervals from a multivariable conditional logistic regression model, adjusted for family history of thyroid cancer, marital status, educational level, occupation, monthly income, smoking status, alcohol consumption, and body mass index group. het, heterozygous genotype; hom1, homozygous genotype of major allele; hom2, homozygous genotype of minor allele. [a]Significant difference.

Table 8. Combined effect of body mass index and each polymorphism on thyroid cancer risk in the dominant model

Variant	Hom1 normal	Hom1 overweight	Hom1 obese	Het+hom2 normal	Het+hom2 overweight	Het+hom2 obese
rs1861868	1.00 (reference)	1.65 (1.20-2.28)[a]	1.83 (1.35-2.49)[a]	1.18 (0.75-1.88)	1.11 (0.60-2.05)	1.02 (0.58-1.79)
rs8047395	1.00 (reference)	1.37 (0.97-1.91)	1.47 (1.06-2.06)[a]	0.61 (0.43-0.88)	1.04 (0.65-1.68)	1.12 (0.75-1.69)
rs9937053	1.00 (reference)	1.66 (1.04-2.67)[a]	2.20 (1.39-3.49)[a]	1.20 (0.84-1.71)	1.71 (1.13-2.58)[a]	1.65 (1.12-2.45)[a]
rs9930333	1.00 (reference)	1.25 (0.89-1.77)	1.52 (1.09-2.13)[a]	0.83 (0.58-1.19)	1.86 (1.15-3.00)[a]	1.52 (1.01-2.27)[a]
rs9940128	1.00 (reference)	1.27 (0.90-1.80)	1.54 (1.10-2.14)[a]	0.84 (0.59-1.21)	1.84 (1.14-2.98)[a]	1.53 (1.02-2.28)[a]
rs1421085	1.00 (reference)	1.27 (0.90-1.80)	1.54 (1.10-2.14)[a]	0.84 (0.59-1.21)	1.84 (1.14-2.98)[a]	1.53 (1.02-2.28)[a]
rs11642015	1.00 (reference)	1.23 (0.89-1.71)	1.39 (1.01-1.90)[a]	0.67 (0.45-1.00)	1.93 (1.12-3.34)[a]	1.72 (1.11-2.66)[a]
rs62048402	1.00 (reference)	1.23 (0.89-1.71)	1.40 (1.02-1.92)[a]	0.68 (0.46-1.01)	2.00 (1.15-3.47)[a]	1.70 (1.10-2.64)[a]
rs1558902	1.00 (reference)	1.23 (0.89-1.71)	1.39 (1.02-1.91)[a]	0.68 (0.46-1.01)	2.00 (1.15-3.47)[a]	1.73 (1.11-2.68)[a]
rs56094641	1.00 (reference)	1.23 (0.89-1.71)	1.39 (1.02-1.91)[a]	0.68 (0.46-1.01)	2.00 (1.15-3.47)[a]	1.73 (1.11-2.68)[a]
rs17817288	1.00 (reference)	1.21 (0.87-1.69)	1.39 (1.01-1.90)[a]	0.68 (0.46-1.01)	2.03 (1.18-3.49)[a]	1.71 (1.10-2.66)[a]
rs1477196	1.00 (reference)	1.73 (1.05-2.85)[a]	2.66 (1.65-4.30)[a]	1.28 (0.88-1.85)	1.79 (1.17-2.73)[a]	1.64 (1.09-2.45)[a]
rs55872725	1.00 (reference)	1.76 (1.17-2.66)[a]	1.93 (1.29-2.87)[a]	1.17 (0.83-1.64)	1.52 (1.02-2.27)[a]	1.64 (1.12-2.38)[a]
rs1121980	1.00 (reference)	1.23 (0.89-1.71)	1.40 (1.02-1.92)[a]	0.68 (0.46-1.01)	2.00 (1.15-3.47)[a]	1.70 (1.10-2.64)[a]
rs8043757	1.00 (reference)	1.27 (0.90-1.80)	1.54 (1.10-2.14)[a]	0.84 (0.59-1.21)	1.84 (1.14-2.98)[a]	1.53 (1.02-2.28)[a]
rs8050136	1.00 (reference)	1.17 (0.85-1.63)	1.37 (1.00-1.88)[a]	0.63 (0.42-0.95)	2.37 (1.34-4.20)[a]	1.75 (1.12-2.74)[a]
rs3751812	1.00 (reference)	1.20 (0.86-1.66)	1.39 (1.01-1.91)[a]	0.67 (0.45-1.00)	2.16 (1.24-3.76)[a]	1.72 (1.11-2.68)[a]
rs9926289	1.00 (reference)	1.20 (0.86-1.66)	1.38 (1.00-1.90)	0.67 (0.45-1.00)	2.18 (1.26-3.79)[a]	1.76 (1.13-2.72)[a]
rs9939609	1.00 (reference)	1.20 (0.86-1.66)	1.38 (1.00-1.90)	0.67 (0.45-1.00)	2.18 (1.26-3.79)[a]	1.76 (1.13-2.72)[a]
rs7202116	1.00 (reference)	1.20 (0.86-1.66)	1.38 (1.00-1.90)	0.67 (0.45-1.00)	2.18 (1.26-3.79)[a]	1.76 (1.13-2.72)[a]
rs7185735	1.00 (reference)	1.20 (0.86-1.66)	1.38 (1.00-1.90)	0.67 (0.45-1.00)	2.18 (1.26-3.79)[a]	1.76 (1.13-2.72)[a]
rs9930506	1.00 (reference)	1.20 (0.86-1.66)	1.38 (1.00-1.90)	0.67 (0.45-1.00)	2.18 (1.26-3.79)[a]	1.76 (1.13-2.72)[a]
rs8044769	1.00 (reference)	1.36 (0.96-1.92)	1.58 (1.13-2.21)[a]	0.88 (0.61-1.27)	1.62 (1.02-2.55)[a]	1.49 (1.00-2.23)[a]
rs12149832	1.00 (reference)	1.81 (1.13-2.89)[a]	2.30 (1.45-3.66)[a]	1.24 (0.87-1.79)	1.69 (1.11-2.57)[a]	1.68 (1.13-2.49)[a]
rs11642841	1.00 (reference)	1.31 (0.94-1.83)	1.43 (1.04-1.97)[a]	0.75 (0.51-1.12)	1.71 (1.03-2.83)[a]	1.70 (1.10-2.64)[a]
rs1861867	1.00 (reference)	1.40 (1.04-1.90)[a]	1.56 (1.17-2.07)[a]	0.62 (0.31-1.25)	2.69 (1.06-6.83)[a]	2.09 (1.02-4.27)[a]
rs7195539	1.00 (reference)	1.70 (1.12-2.57)[a]	1.90 (1.27-2.86)[a]	1.22 (0.87-1.71)	1.64 (1.09-2.47)[a]	1.75 (1.19-2.56)

Values are presented as odds ratios and their 95% confidence intervals from a multivariable conditional logistic regression model, adjusted for family history of thyroid cancer, marital status, educational level, occupation, monthly income, smoking status, alcohol consumption, and body mass index group. het, heterozygous genotype; hom1, homozygous genotype of major allele; hom2, homozygous genotype of minor allele. [a]Significant difference.

an obesity risk allele in *FTO*, carriers harboring one copy of the risk allele weighed on average 1.2 kg more than people without the allele. Adults who were homozygous for the risk allele weighed 3 kg more and had a 1.67-fold higher rate of obesity than those without the allele [20]. Although the *FTO* gene is not associated with changes in fetal growth, it has a critical impact in young adults and is associated with changes in BMI and obesity in children aged seven and older. Studies have suggested that SNPs located within the first intron of *FTO* are strongly associated with obesity [19]. In vitro studies have shown that reducing the functional activity of *FTO* in a mouse model resulted in reduced fat mass and body weight, elevated energy expenditure and unchanged physical activity, whereas the overexpression of *FTO* in a mouse model caused increased adiposity and did not impact

the energy expenditure; this mouse model provides evidence that *FTO* directly affects fat mass and is linked with obesity [21]. However, the exact molecular mechanisms underlying the effect of *FTO* on obesity are not fully understood.

This study has shown that the genetic variants rs8047395 and rs8044769 in the *FTO* gene are associated with thyroid cancer. Based on our findings, individuals who carry the minor G/G allele of rs8047395 have a higher risk of thyroid cancer than those carrying the A/A and G/A alleles, and individuals who carry the minor A/A allele of rs8044769 have a higher risk of thyroid cancer than those carrying the G/G and A/G alleles. Studies have observed an association between *FTO* and an increased risk of different types of cancers, which suggests that *FTO* has a role in carcinogenesis [22,23]. A study examining the SNPs rs7206790, rs8047395,

Table 9. Combined effect of body mass index and each polymorphism on thyroid cancer risk in the recessive model

Variant	Hom1+het normal	Hom1+het overweight	Hom1+het obese	Hom2 normal	Hom2 overweight	Hom2 obese
rs1861868	1.00 (reference)	1.47 (1.09-1.97)[a]	1.58 (1.19-2.10)[a]	0.54 (0.21-1.39)	1.13 (0.28-4.46)	0.69 (0.17-2.81)
rs8047395	1.00 (reference)	1.55 (1.13-2.12)[a]	1.88 (1.38-2.54)[a]	2.10 (1.28-3.45)[a]	2.38 (1.29-4.40)[a]	1.62 (0.97-2.70)
rs9937053	1.00 (reference)	1.54 (1.14-2.06)[a]	1.62 (1.22-2.14)[a]	1.33 (0.36-4.99)	0.83 (0.23-2.97)	2.79 (0.78-9.93)
rs9930333	1.00 (reference)	1.54 (1.14-2.06)[a]	1.62 (1.22-2.14)[a]	1.33 (0.36-4.99)	0.83 (0.23-2.97)	2.79 (0.78-9.93)
rs9940128	1.00 (reference)	1.54 (1.14-2.06)[a]	1.62 (1.22-2.14)[a]	1.33 (0.36-4.99)	0.83 (0.23-2.97)	2.79 (0.78-9.93)
rs1421085	1.00 (reference)	1.52 (1.14-2.04)[a]	1.61 (1.21-2.13)[a]	1.58 (0.39-6.40)	1.03 (0.16-6.42)	4.21 (0.77-22.9)
rs11642015	1.00 (reference)	1.52 (1.14-2.04)[a]	1.61 (1.21-2.13)[a]	1.58 (0.39-6.40)	1.03 (0.16-6.42)	4.21 (0.77-22.9)
rs62048402	1.00 (reference)	1.52 (1.14-2.04)[a]	1.61 (1.21-2.13)[a]	1.58 (0.39-6.40)	1.03 (0.16-6.42)	4.21 (0.77-22.9)
rs1558902	1.00 (reference)	1.52 (1.14-2.04)[a]	1.61 (1.21-2.13)[a]	1.58 (0.39-6.40)	1.03 (0.16-6.42)	4.21 (0.77-22.9)
rs56094641	1.00 (reference)	1.52 (1.14-2.04)[a]	1.61 (1.21-2.13)[a]	1.58 (0.39-6.40)	1.03 (0.16-6.42)	4.21 (0.77-22.9)
rs17817288	1.00 (reference)	1.64 (1.19-2.25)[a]	1.95 (1.43-2.67)[a]	2.17 (1.37-3.43)[a]	2.11 (1.21-3.67)[a]	1.66 (1.04-2.65)[a]
rs1477196	1.00 (reference)	1.57 (1.15-2.13)[a]	1.79 (1.34-2.41)[a]	2.51 (1.30-4.84)[a]	2.25 (1.04-4.86)[a]	1.54 (0.85-2.78)
rs55872725	1.00 (reference)	1.52 (1.14-2.04)[a]	1.61 (1.21-2.13)[a]	1.58 (0.39-6.40)	1.03 (0.16-6.42)	4.21 (0.77-22.9)
rs1121980	1.00 (reference)	1.54 (1.14-2.06)[a]	1.62 (1.22-2.14)[a]	1.33 (0.36-4.99)	0.83 (0.23-2.97)	2.79 (0.78-9.93)
rs8043757	1.00 (reference)	1.52 (1.14-2.04)[a]	1.61 (1.21-2.13)[a]	1.58 (0.39-6.40)	1.03 (0.16-6.42)	4.21 (0.77-22.9)
rs8050136	1.00 (reference)	1.52 (1.14-2.04)[a]	1.61 (1.21-2.13)[a]	1.58 (0.39-6.40)	1.03 (0.16-6.42)	4.21 (0.77-22.9)
rs3751812	1.00 (reference)	1.52 (1.14-2.04)[a]	1.61 (1.21-2.13)[a]	1.58 (0.39-6.40)	1.03 (0.16-6.42)	4.21 (0.77-22.9)
rs9926289	1.00 (reference)	1.52 (1.14-2.04)[a]	1.61 (1.21-2.13)[a]	1.58 (0.39-6.40)	1.03 (0.16-6.42)	4.21 (0.77-22.9)
rs9939609	1.00 (reference)	1.52 (1.14-2.04)[a]	1.61 (1.21-2.13)[a]	1.58 (0.39-6.40)	1.03 (0.16-6.42)	4.21 (0.77-22.9)
rs7202116	1.00 (reference)	1.52 (1.14-2.04)[a]	1.61 (1.21-2.13)[a]	1.58 (0.39-6.40)	1.03 (0.16-6.42)	4.21 (0.77-22.9)
rs7185735	1.00 (reference)	1.52 (1.14-2.04)[a]	1.61 (1.21-2.13)[a]	1.58 (0.39-6.40)	1.03 (0.16-6.42)	4.21 (0.77-22.9)
rs9930506	1.00 (reference)	1.53 (1.14-2.05)[a]	1.61 (1.21-2.13)[a]	1.14 (0.33-4.03)	0.84 (0.24-3.00)	2.78 (0.78-9.88)
rs8044769	1.00 (reference)	1.53 (1.12-2.10)[a]	1.87 (1.38-2.53)[a]	2.06 (1.26-3.38)[a]	2.55 (1.35-4.81)[a]	1.71 (1.02-2.88)[a]
rs12149832	1.00 (reference)	1.53 (1.14-2.06)[a]	1.61 (1.22-2.14)[a]	1.04 (0.26-4.23)	0 (0-7.4e+75)	3.18 (0.57-17.8)
rs11642841	1.00 (reference)	1.51 (1.13-2.02)[a]	1.61 (1.22-2.13)[a]	2.10 (0.09-48.8)		
rs1861867	1.00 (reference)	1.54 (1.14-2.09)[a]	1.76 (1.31-2.36)[a]	1.84 (1.00-3.40)	2.25 (1.02-4.97)[a]	1.37 (0.74-2.54)
rs7195539	1.00 (reference)	1.49 (1.12-2.00)[a]	1.63 (1.23-2.16)[a]	0 (0-7.6e+53)	0.50 (0.04-6.01)	0.53 (0.05-5.22)

Values are presented as odds ratios and their 95% confidence intervals from a multivariable conditional logistic regression model, adjusted for family history of thyroid cancer, marital status, educational level, occupation, monthly income, smoking status, alcohol consumption, and body mass index group. het, heterozygous genotype; hom1, homozygous genotype of major allele; hom2, homozygous genotype of minor allele. [a]Significant difference.

rs9939609, and rs1477196 on intron 1 of *FTO* found that all of the SNPs were associated with an increased risk of breast cancer [24]. Similarly, a study conducted in a German population showed a positive association between the rs8047395 SNP of the *FTO* gene and PTC [25]. These findings provide primary evidence that *FTO* may play an important role in carcinogenesis. Moreover, a study conducted in the United States found that nine of the 10 top-ranking SNPs ($p_{trend} <$ 0.010) investigated for thyroid cancer risk were located in *FTO*; however, none of these SNPs were associated with thyroid cancer risk after controlling for the false discovery rate. This study showed an association between BMI and increased PTC risk (OR, 1.18; 95% CI, 1.02 to 1.37), although additional adjustments for BMI did not change the SNP-PTC association [26]. However, the association between rs8044769

and thyroid cancer risk has not been examined. Different findings for these associations between studies may be related to the complex role of *FTO* in the molecular mechanisms of carcinogenesis, which remain unknown. The diverse roles of *FTO* in adiposity, energy balance, type 2 diabetes and metabolism may also play a role in carcinogenesis, which would result in inconsistent associations [27,28].

This study investigated the effect of interactions between BMI and genetic variants of *FTO* on thyroid cancer risk using a gene-environment interaction analysis method. We found a positive effect of BMI subclasses on thyroid cancer in all groups of different genotypes of rs17817288 in the codominant model, rs9937053, rs12149832, rs1861867, and rs7195539 in the dominant model, and rs17817288 and rs8044769 in the recessive model. Although the mechanism

of this interaction remains unclear, *FTO* may interact with BMI in several ways. First, the association could be explained by the role of *FTO* in regulating energy homeostasis, body size, and fat accumulation [29]. Thus, genetic variants of this gene are associated with obesity, diabetes, and metabolic syndromes, which are cancer risk factors [30]. Second, previous studies have claimed that *FTO* is associated with DNA methylation [25], and genetic polymorphisms of *FTO* may impact the normal pattern of DNA synthesis and methylation, which are factors in carcinogenesis [31] and affect both body mass and tumor suppression. For BMI, recent studies have suggested that adiposity may also influence DNA methylation. A recent GWAS showed that BMI is associated with widespread changes in DNA methylation, which is a key regulator of gene expression and molecular phenotypes [32]. Thus, the influence of BMI and *FTO* on DNA methylation may explain the combined interaction effect on susceptibility to thyroid cancer.

This study makes a significant contribution to our understanding of how genetic variants of *FTO* affect the risk of thyroid cancer. Only one other study of a German population has investigated the association between thyroid cancer and the *FTO* genetic variant rs8047395. However, that study population was exclusively Caucasian, and few studies have been conducted in Asian populations [25]. Another strength of this study is the analysis of both socioeconomic status and lifestyle risk factors for thyroid cancer, including smoking status, alcohol consumption, and reproductive factors. This study has several limitations. First, this study is a hospital-based case-control study, and the controls may not be sufficiently representative of the general population because their genetic variants or lifestyle habits may be similar or related to cancer cases. However, the large number of controls in this study should eliminate any potential problem with similarities in the characteristics of participants. Second, this study may have a recall bias because the demographic information was based solely on self-conducted questionnaires dependent on the memory of the participants. However, data collected from the questionnaire were not a crucial component of the information analyzed for this study and likely did not affect our findings.

In summary, the interactions observed in this study suggest that the effect of subclasses of BMI on thyroid cancer risk may differ according to individual genetic variants of *FTO*. Although the underlying mechanism requires further investigation, this study improves our understanding of the role of BMI and *FTO* as indicators of thyroid cancer risk and their role in thyroid cancer carcinogenesis. In the future, additional epidemiological studies with larger sample sizes should be performed to support and extend our findings on the role of genetic risk factors.

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