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Common obesity-related genetic variants and papillary thyroid cancer risk

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Abstract

Background—Epidemiologic studies have shown consistent associations between obesity and increased thyroid cancer risk, but, to date, no studies have investigated the relationship between thyroid cancer risk and obesity-related single nucleotide polymorphisms (SNPs).

Methods—We evaluated 575 tag SNPs in 23 obesity-related gene regions in a case-control study of 341 incident papillary thyroid cancer (PTC) cases and 444 controls of European ancestry. Logistic regression models, adjusted for attained age, year of birth, and sex were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) with SNP genotypes, coded as 0, 1, and 2 and modeled continuously to calculate *P*-trends.

Results—Nine out of 10 top-ranking SNPs (P_{trend}<0.01) were located in the *FTO* (fat mass and obesity associated) gene region, while the other was located in *INSR* (insulin receptor). None of the associations were significant after correcting for multiple testing.

Conclusions—Our data do not support an important role of obesity-related genetic polymorphisms in determining the risk of PTC.

Impact—Factors other than selected genetic polymorphisms may be responsible for the observed associations between obesity and increased PTC risk.

Keywords

single nucleotide polymorphisms; case-control study; obesity; body mass index; thyroid neoplasms

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INTRODUCTION

Obesity has consistently been associated with increased risk of thyroid cancer in epidemiologic studies [1], but the biological mechanisms underlying this association remain poorly understood. Evaluating genetic variation in obesity-related genes may help to identify pathways involved in thyroid cancer etiology, independent of, or mediated by, body size.

We examined associations between single nucleotide polymorphisms (SNPs) in 23 obesity-related candidate genes and papillary thyroid cancer (PTC), the most common histological type of thyroid cancer. These genes were chosen because of their role in body energy homeostasis and metabolism or previous associations with obesity or type 2 diabetes [2–5].

METHODS

The study population has been previously described [6]. In brief, cases included individuals diagnosed with incident, histologically confirmed PTC during follow-up of the US Radiologic Technologists (USRT) cohort (n=202) and individuals diagnosed and treated for PTC at the University of Texas M. D. Anderson Cancer Center (UTMDACC) (n=142). In USRT, controls (n=452) were frequency matched by race, year of birth (± two years), and sex to cases. Controls from USRT were then selected to match cases from UTMDACC. Analyses were restricted to non-Hispanic whites. Three cases and eight controls were excluded due to missing height or weight. The institutional review boards approved the use of these data, and all subjects provided written informed consent.

The 23 genes chosen for this analysis (listed in Supplemental Table 1) were selected *a priori*. Tag SNPs (n=575) were selected from the common SNPs (minor allele frequency >5%) genotyped by the HapMap Project in the Caucasian population using TagZilla, part of the GLU software package, with a binning threshold of r^2>0.8. Genotyping was performed at the NCI Core Genotyping Facility using a custom-designed iSelect Infinium assay. SNPs were excluded if they failed quality-control measures: <95% concordance, <90% completion, or had evidence of a departure from Hardy-Weinberg equilibrium in controls (P<0.00001). Allele frequencies were largely similar between USRT and UTMDACC cases; thus, these groups were combined for analyses.

Data on demographics, medical history, anthropometry, and other health-related characteristics were collected by self-administered questionnaires or telephone interview in USRT and self-administered questionnaire at time of blood collection in UTMDACC.

We computed SNP-specific P-values for trend and odds ratios (ORs) and 95% confidence intervals (CIs) for each genotype, using logistic regression models adjusted for sex, attained age, and year of birth. Separate models additionally adjusted for body mass index (BMI). We also examined 138,605 two-way SNP-SNP interactions using allelic-based gene-gene interactions in models adjusted for sex, attained age, year of birth, and BMI [7]. We combined SNP-specific P-values of trend into region-based P-values using the adaptive rank truncated method [8]. P-values <0.05 were considered statistically significant, and tests were two-sided. While tables show uncorrected P-values, we also conducted correction for multiple comparisons controlling the false discovery rate (FDR). Statistical analyses were conducted using Stata/SE version 11.0 and R software.

RESULTS

Compared to controls, PTC cases were more likely to have a family history of thyroid cancer among first-degree relatives and less likely to be current smokers (Table 1). Cases had higher BMI compared to controls.

Of the ten SNPs identified with the lowest SNP-level *P*-values (Table 2), nine were located in *FTO* (fat mass and obesity associated) and one was located in *INSR* (insulin receptor). However, none remained statistically significant after FDR correction. Although BMI was associated with increased PTC risk (per 5 kg/m^2, OR=1.18, 95% CI: 1.02–1.37), additional adjustment for BMI did not appreciably change the SNP-PTC associations. We did not observe statistically-significant SNP-SNP interactions after FDR correction. Also, at gene region level none was significantly associated with PTC risk (all region-based *P*-values >0.2).

DISCUSSION

In general, our results do not suggest an important role of selected obesity-related genetic variants in determining PTC risk. Certain polymorphisms in the *FTO* and *INSR* genes were weakly linked to PTC risk independent of BMI, but these associations were no longer significant after multiple comparisons correction.

Genes chosen for this analysis were *a priori*-selected based on their known functions or observed associations with obesity, thereby reducing the possibility that our findings were due solely to chance. Nonetheless, there may be other obesity-related genes that were not considered in our genotyping platform but may play an important role in papillary thyroid carcinogenesis. More agnostic approaches may be needed to discover important genetic risk factors for this disease. Additionally, while most individual SNPs and none of the two-way interactions were not significantly associated with PTC risk, certain combination of SNPs may have stronger effects, although larger studies are necessary to detect SNP-SNP interactions.

As the biological mechanisms underlying the observed obesity-thyroid cancer relationship remain unclear, the results of this study underscore the need to evaluate, directly, levels of various adipocytokines and other obesity-related biomarkers, as well as modifiable determinants of obesity, including over-nutrition and physical inactivity, as possible risk factors for this disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Select characteristics of the cases and controls

	Cases		Controls	
	Women (n=272)	**Men (n=69)**	**Women (n=415)**	**Men (n=29)**
Study, n (%)				
U.S. Radiologic Technologists	182 (67)	18 (26)	415 (100)	29 (100)
M. D. Anderson Cancer Center	90 (33)	51 (74)	0	0
Attained age, n (%)				
19–25	23 (8)	2 (3)	30 (7)	0
26–35	58 (21)	15 (22)	95 (23)	5 (17)
36–45	89 (33)	24 (35)	142 (34)	13 (45)
46–55	65 (24)	11 (16)	99 (24)	6 (21)
56–65	29 (11)	13 (19)	43 (10)	5 (17)
66–79	8 (3)	4 (6)	6 (1)	0
Smoking status, n (%)				
Never	167 (62)	38 (55)	218 (53)	12 (41)
Former	67 (25)	20 (29)	89 (22)	10 (34)
Current	37 (14)	11 (16)	104 (25)	7 (24)
Family history of thyroid cancer, n (%)	13 (4.8)	4 (5.8)	5 (1.2)	1 (3.5)
Body mass index (BMI)[a], median (interquartile range)	23.9 (21.1–28.3)	28.8 (25.6–32.6)	23.2 (21.0–25.8)	25.0 (23.1–27.5)

[a]Weight in kilograms divided by height in meters squared

Table 2

Associations between obesity-related SNPs and papillary thyroid cancer risk

SNP	Region	Location	Variant	Cases	Controls	OR[a]	OR[b]
RS17817288	*FTO*	52365265	GG	60	114	1.00 (Reference)	1.00 (Reference)
			AG	181	235	1.57 (1.06–2.32)	1.60 (1.08–2.38)
			AA	99	95	2.08 (1.33–3.25)	2.14 (1.36–3.36)
						P-trend=0.001[*]	*P-trend=0.001*[*]
RS11642841	*FTO*	52402988	CC	156	154	1.00 (Reference)	1.00 (Reference)
			AC	140	217	0.65 (0.47–0.90)	0.65 (0.47–0.91)
			AA	45	73	0.53 (0.34–0.84)	0.52 (0.33–0.83)
						P-trend=0.002	*P-trend=0.002*
RS8047395	*FTO*	52356024	AA	71	120	1.00 (Reference)	1.00 (Reference)
			AG	170	234	1.27 (0.87–1.85)	1.28 (0.88–1.88)
			GG	100	86	1.97 (1.28–3.05)	2.03 (1.31–3.16)
						P-trend=0.002	*P-trend=0.002*
RS1121980	*FTO*	52366748	GG	136	137	1.00 (Reference)	1.00 (Reference)
			AG	155	223	0.72 (0.52–1.01)	0.70 (0.50–0.97)
			AA	49	82	0.54 (0.35–0.85)	0.52 (0.33–0.82)
						P-trend=0.005	*P-trend=0.003*
RS8050136	*FTO*	52373776	CC	144	150	1.00 (Reference)	1.00 (Reference)
			AC	156	222	0.77 (0.55–1.07)	0.75 (0.54–1.04)
			AA	41	72	0.51 (0.32–0.81)	0.49 (0.30–0.79)
						P-trend=0.005	*P-trend=0.003*
RS9939609	*FTO*	52378028	TT	144	151	1.00 (Reference)	1.00 (Reference)
			AT	155	220	0.77 (0.56–1.07)	0.75 (0.54–1.05)
			AA	41	72	0.51 (0.32–0.82)	0.49 (0.30–0.80)
						P-trend=0.005	*P-trend=0.003*
RS1477196	*FTO*	52365759	GG	115	182	1.00 (Reference)	1.00 (Reference)
			AG	164	203	1.33 (0.95–1.86)	1.33 (0.95–1.86)
			AA	60	54	1.98 (1.24–3.13)	2.00 (1.26–3.19)
						P-trend=0.003	*P-trend=0.003*

SNP	Region	Location	Variant	Cases	Controls	OR[a]	OR[b]
RS7202116	*FTO*	52379116	AA	144	151	1.00 (Reference)	1.00 (Reference)
			AG	156	220	0.78 (0.56–1.08)	0.76 (0.55–1.06)
			GG	41	72	0.51 (0.32–0.82)	0.49 (0.31–0.80)
						P-trend=0.005	*P-trend=0.004*
RS1861867	*FTO*	52406062	GG	109	183	1.00 (Reference)	1.00 (Reference)
			AG	163	187	1.61 (1.15–2.26)	1.60 (1.13–2.25)
			AA	68	74	1.68 (1.09–2.59)	1.73 (1.12–2.68)
						P-trend=0.006	*P-trend=0.005*
RS919275	*INSR*	7212441	TT	118	116	1.00 (Reference)	1.00 (Reference)
			CT	165	242	0.68 (0.48–0.96)	0.69 (0.49–0.97)
			CC	53	82	0.54 (0.34–0.86)	0.57 (0.36–0.91)
						P-trend=0.006	*P-trend=0.011*

[*] SNP-based linear *P*-trends (unadjusted for multiple comparisons) based on modeling the three-level genotype (0, 1, 2) as continuous in logistic regression models

[a] Adjusted for attained age (age at diagnosis for cases and referent age for controls; continuous), year of birth (<1940, 1940–1949, 1950+), and sex

[b] Adjusted for attained age, year of birth, sex, and BMI (per 5 kg/m^2)

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