Common Genetic Variants in Sex Hormone Pathway Genes and Papillary Thyroid Cancer Risk

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Background: Hormonal differences are hypothesized to contribute to the approximately ≥ 2 -fold higher thyroid cancer incidence rates among women compared with men worldwide. Although thyroid cancer cells express estrogen receptors and estrogen has a proliferative effect on papillary thyroid cancer (PTC) cells *in vitro*, epidemiologic studies have not found clear associations between thyroid cancer and female hormonal factors. We hypothesized that polymorphic variation in hormone pathway genes is associated with the risk of developing papillary thyroid cancer.

Methods: We evaluated the association between PTC and 1151 tag single nucleotide polymorphisms (SNPs) in 58 candidate gene regions involved in sex hormone synthesis and metabolism, gonadotropins, and prolactin in a case-control study of 344 PTC cases and 452 controls, frequency matched on age and sex. Odds ratios and *p*-values for the linear trend for the association between each SNP genotype and PTC risk were estimated using unconditional logistic regression. SNPs in the same gene region or pathway were aggregated using adaptive rank-truncated product methods to obtain gene region-specific or pathway-specific *p*-values. To account for multiple comparisons, we applied the false discovery rate method.

Results: Seven SNPs had *p*-values for linear trend < 0.01 , including four in the *CYP19A1* gene, but none of the SNPs remained significant after correction for multiple comparisons. Results were similar when restricting the dataset to women. *p*-values for examined gene regions and for all genes combined were ≥ 0.09 .

Conclusions: Based on these results, SNPs in selected hormone pathway genes do not appear to be strongly related to PTC risk. This observation is in accord with the lack of consistent associations between hormonal factors and PTC risk in epidemiologic studies.

Introduction

THYROID CANCER is one of the few cancers for which female incidence rates far exceed those among men (1). Worldwide, the overall female-to-male incidence rate ratio is at least twofold (2). This ratio is particularly high (5.4) during ado-

lescent years and monotonically decreases with age reaching about 1.1 at age ≥ 80 (3). Sex steroid hormones are hypothesized to contribute to the observed female predominance of thyroid cancer in reproductive years, and *in vitro* studies have demonstrated that estradiol stimulates the proliferation of papillary thyroid cancer (PTC) cells (4). Unlike cancers of

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established hormonal etiology such as breast cancer, however, hormonal and reproductive factors have not been consistently associated with thyroid cancer risk in epidemiologic studies, as previously summarized (5,6). Thus, the female predominance of thyroid cancer remains largely unexplained.

Studies of germline variation in genes related to sex steroid hormones and reproductive function may provide clues about thyroid cancer etiology and potential insight into the higher incidence rates observed among women compared with men. We hypothesized that polymorphic variation in hormone pathway genes is associated with the risk of developing PTC. To test this hypothesis, we evaluated the associations between PTC and 1151 tag single nucleotide polymorphisms (SNPs) in 58 candidate gene regions involved in sex hormone synthesis and metabolism, germ cell development and gonadotropins, and prolactin using data from a common genotyping platform designed to examine the associations between germline polymorphisms and a variety of rare cancers (7,8), including thyroid cancer (9).

Materials and Methods

A detailed description of the study population, laboratory methods, and statistical analyses for this case-control study was previously published (9). Briefly, we conducted a case-control analysis based on 344 confirmed PTC cases and 452 controls. There were 202 cases ascertained within the U.S. Radiologic Technologists (USRT) cohort (10) and 142 serially recruited cases with PTC diagnosed and treated at the University of Texas M.D. Anderson Cancer Center (UTMDACC) between 1999 and 2005 (11). All controls were from the USRT study, and had been selected for an earlier thyroid cancer study, matched to cases on gender and year of birth (± 2 years) (12). Controls were assigned a referent age to correspond to the time of a case's diagnosis. Only cases and controls of self-reported European ancestry were included in this analysis. Both studies were reviewed and approved by their respective Institutional Review Boards, and all subjects provided informed consent.

Variable collection and data harmonization

Participant demographics and information about health history, family history of cancer, and other risk factors occurring before thyroid cancer diagnosis or the referent date for controls were collected by self-administered mailed questionnaires (1984–1989, 1994–1998, and 2003–2005) or telephone interview in the USRT study or a self-administered questionnaire at the time of blood collection in the UTMDACC study. Self-reported race/ethnicity (United States Office of Management and Budget Categories) and histological type of thyroid cancer were defined similarly in both studies. Other variables (cigarette smoking, alcohol consumption, previous exposure to therapeutic radiation, and family history of any cancer or specifically of thyroid cancer) were harmonized to enable comparable analysis across the two studies.

Laboratory methods

DNA extraction. In the USRT study, venipuncture whole blood samples were shipped with a temperature stabilizing pack overnight to the processing laboratory in Frederick, MD.

At UTMDACC, venipuncture whole blood samples were collected and processed in the clinic. Both studies extracted DNA from peripheral blood leucocytes using Qiagen Mini Kits (Qiagen, Inc., Valencia, CA) according to the manufacturer's instructions.

Genotyping. After exclusion of SNPs with $<95\%$ concordance, SNPs with $<90\%$ completion among the randomly inserted quality control replicates, and SNPs that failed Hardy-Weinberg Equilibrium test (p -value < 0.00001), there were 1151 tag SNPs in 58 candidate gene regions broadly related to hormonal and reproductive function genotyped at the National Cancer Institute's Core Genotyping Facility (Advanced Technology Center, Gaithersburg, MD; <http://cgf.nci.nih.gov>) using the custom-designed iSelect Infinium assay (Illumina, San Diego, CA; www.illumina.com). This platform was designed before the publication of the two thyroid cancer GWAS studies (13,14) conducted to date. Tag SNPs were selected from the common SNPs (minor allele frequency, MAF $> 5\%$) genotyped by the HapMap Project (Data Release 20/Phase II, NCBI Build 36.1, assembly dbSNPb126) in the Caucasian population (CEU) using TagZilla, which is a part of the Genotype Library and Utilities software package (<http://code.google.com/p/glu-genetics>) with a binning threshold of $r^2 > 0.8$ following the method of Carlson *et al.* (15).

Allele frequencies for PTC cases were largely similar between the USRT and the UTMDACC study sites and between men and women, so these groups were combined for genetic analyses.

Statistical analysis

Analyses were conducted first at the individual SNP level and then at the gene region and pathway levels. Statistical analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC) and in R.

SNP-based associations. Unconditional logistic regression models were used to estimate odds ratios and to calculate p -values for the linear trend for the association between each tag SNP genotype and PTC risk. We calculated the linear P_{trend} for SNP genotype in crude models and models adjusted for sex, attained age in four categories (< 35 , 35–44, 45–54, and 55+ years), and year of birth (< 1940 , 1940–1949, and 1950+) as an ordinal variable. Correction for multiple comparisons was made using the false discovery rate (FDR) control method (16).

Gene region- and pathway-based analyses. We combined SNP specific p -values for linear trends within the same gene region using an adaptive rank truncated product method (17). This method accounts for the linkage disequilibrium (LD) structure within a gene region and allows for flexibility in assumptions about the number of SNPs to include in the p -value calculation ($P_{\text{gene region}}$). Gene region-level p -values were combined into the p -values associated with the three pathways (P_{pathway}): (1) sex hormone synthesis and metabolism, (2) gonadotropins and germ cell development, and (3) prolactin. Lastly, we evaluated the significance of the overall group of hormone-related pathways combining all gene region-level-based p -values (P_{overall}).

TABLE 1. SELECTED CHARACTERISTICS OF CASES AND CONTROLS

	Cases, n (%)	Controls, n (%)	p-value ^a
Total Study	344 (100.0)	452 (100.0)	
Radiologic Technologists	202 (58.7)	452 (100.0)	
M. D. Anderson Cancer Center	142 (41.3)	0	NA
Gender			
Female	274 (79.7)	423 (93.6)	
Male	70 (20.3)	29 (6.4)	<0.001
Attained/referent age ^b , year			
19–25	26 (7.6)	30 (6.6)	
26–35	73 (21.2)	103 (22.8)	
36–45	113 (32.8)	159 (35.2)	
46–55	77 (22.4)	105 (23.2)	
56–65	43 (12.5)	49 (10.8)	
66–79	12 (3.5)	6 (1.3)	0.360
Number of relatives with thyroid cancer			
None	319 (92.7)	442 (97.8)	
At least one	15 (4.4)	6 (1.3)	
Unknown	10 (2.9)	4 (0.9)	<0.001

^ap-value calculated using Chi-square or Yates' chi-square test.

^bControls were assigned a referent age to correspond to the time of a case's diagnosis.

NA, not applicable.

Results

Table 1 presents selected demographic and risk factor information for the 344 PTC cases and 452 controls included in this analysis. The proportion of women was lower among cases compared with controls (79.7% vs. 93.6%) reflecting the fact that controls were selected from the USRT cohort originally to match the USRT cases (90.6% women). The age distribution of cases and controls was similar. Cases were more likely to report a family history of thyroid cancer than controls ($p < 0.001$).

There were seven SNPs with a $P_{\text{trend}} < 0.01$ (Table 2). Among these, four were in the *CYP19A1* gene (rs4774585, rs1004984, rs752760, and rs1004982). The top two SNPs appeared to be in LD ($D' = 0.97$ and $r^2 = 0.72$ for rs4774585 and rs1004984), but the maximum pairwise r^2 value for all other combinations of these four SNPs was 0.16 suggesting that these represent three distinct hits. The other SNPs included rs2881766 in *ESR1*, rs10739847 in *HSD17B3*, and rs6472462 in *SULF1*. None of the SNPs remained significant after FDR correction for multiple comparisons. Restricting the dataset to women, the results were largely similar. There were six SNPs with P_{trend} value < 0.01 including four in *CYP19A1* (rs4774585, rs7163193, rs2414099, and rs1004984), one in *HSD17B3* (rs10739847), and one in *GNRH2* (rs4815558) (Table 3). Again, none of the SNPs remained significant after correction for multiple comparisons. The lowest p -value for the examined gene-region and pathway analyses was 0.09 for

TABLE 2. ODDS RATIOS AND 95% CONFIDENCE INTERVALS FOR THE TAG SINGLE NUCLEOTIDE POLYMORPHISMS ASSOCIATED WITH PAPILLARY THYROID CANCER RISK AT $P_{\text{TREND}} < 0.01$

Target gene	SNP	Genotype	Cases/controls	Odds ratio	95% Confidence interval	$P_{\text{trend}}^a/P_{\text{trend}}^b \text{ FDR}^b$
<i>CYP19A1</i> ^c	rs4774585	GG	198/309	1.00	Referent	
		GA	129/130	1.63	1.19, 2.25	
		AA	17/13	1.61	0.73, 3.57	0.0036/0.9191
<i>CYP19A1</i> ^c	rs1004984	GG	117/194	1.00	Referent	
		GA	158/191	1.41	1.02, 1.96	
		AA	55/45	1.91	1.18, 3.09	0.0041/0.9191
<i>CYP19A1</i> ^c	rs752760	CC	94/167	1.00	Referent	
		CT	177/216	1.47	1.05, 2.07	
		TT	72/69	1.75	1.13, 2.72	0.0072/0.9191
<i>CYP19A1</i> ^c	rs1004982	TT	120/200	1.00	Referent	
		TC	167/201	1.43	1.04, 1.98	
		CC	57/51	1.70	1.07, 2.72	0.0094/0.9191
<i>ESR1</i> ^d	rs2881766	TT	200/300	1.00	Referent	
		TG	122/136	1.48	1.07, 2.04	
		GG	20/16	1.94	0.95, 3.94	0.0056/0.9191
<i>HSD17B3</i> ^e	rs10739847	AA	91/141	1.00	Referent	
		AT	158/219	1.21	0.85, 1.72	
		TT	90/92	1.75	1.15, 2.66	0.0095/0.9191
<i>SULF1</i> ^f	rs6472462	GG	63/113	1.00	Referent	
		GA	174/223	1.61	1.09, 2.38	
		AA	106/114	1.80	1.17, 2.76	0.0097/0.9191

^aSNP-based linear P_{trend} calculated based on the three-level genotype (0, 1, and 2) in logistic regression models adjusted for sex, attained age in four categories (<35, 35–44, 45–54, and 55+ years), and year of birth (<1940, 1940–1949, and 1950+) as an ordinal variable.

^bFalse discovery rate (FDR) corrected linear P_{trend} .

^c*CYP19A1* contained 59 tagging SNPs.

^d*ESR1* contained 55 tagging SNPs.

^e*HSD17B3* contained 41 tagging SNPs.

^f*SULF1* contained 65 tagging SNPs.

SNPs, single nucleotide polymorphisms.

TABLE 3. ODDS RATIOS (AND 95% CONFIDENCE INTERVALS) FOR THE TAG SNPs ASSOCIATED WITH PAPILLARY THYROID CANCER RISK AT $P_{\text{TREND}} < 0.01$, RESTRICTED TO WOMEN

Target gene	SNP	Genotype	Cases/controls	Odds ratio	95% Confidence interval	$P_{\text{trend}}^a/P_{\text{trend FDR}}^b$
CYP19A1 ^c	rs4774585	GG	156/290	1.00	Referent	0.0047/0.9066
		GA	108/121	1.71	1.22, 2.39	
		AA	10/12	1.42	0.59, 3.45	
CYP19A1 ^c	rs7163193	GG	139/256	1.00	Referent	0.0091/0.9066
		GA	111/144	1.42	1.02, 1.98	
		AA	24/23	1.91	1.01, 3.58	
CYP19A1 ^c	rs2414099	TT	168/303	1.00	Referent	0.0092/0.9066
		TC	97/109	1.62	1.15, 2.28	
		CC	8/9	1.47	0.54, 3.99	
CYP19A1 ^c	rs1004984	GG	94/181	1.00	Referent	0.0094/0.9066
		GA	128/177	1.42	1.00, 2.01	
		AA	43/43	1.82	1.10, 3.02	
HSD17B3 ^d	rs10739847	AA	70/133	1.00	Referent	0.0064/0.9066
		AT	126/204	1.27	0.87, 1.85	
		TT	76/86	1.85	1.19, 2.88	
GNRH2 ^e	rs4815558	CC	213/297	1.00	Referent	0.008/0.9066
		CA	58/113	0.66	0.46, 0.96	
		AA	3/13	0.33	0.09, 1.21	

^aSNP-based linear P_{trend} calculated based on the three-level genotype (0, 1, and 2) in logistic regression models adjusted for sex, attained age in four categories (<35, 35–44, 45–54, and 55+ years), and year of birth (<1940, 1940–1949, and 1950+) as an ordinal variable.

^bFDR corrected linear P_{trend} .

^cCYP19A1 contained 59 tagging SNPs.

^dHSD17B3 contained 41 tagging SNPs.

^eGNRH2 contained 14 tagging SNPs.

the CYP21A2 gene (not shown). The P_{overall} for all hormonal pathway genes was 0.95 (Table 4).

Discussion

The results of this study of 344 PTC cases and 452 controls do not provide strong evidence for an association between PTC risk and the SNPs in hormone pathway genes examined. There were seven SNPs with $P_{\text{trend}} < 0.01$, but none of these SNPs remained significant after FDR correction for multiple comparisons.

The seven SNPs included four SNPs in the CYP19A1 gene and one in each of the ESR1, HSD17B3, and SULF1 genes. With the exception of one SNP in ESR1 (18), there have been no previous findings associating these genes with thyroid cancer etiology to our knowledge. We identified one report of

a significant association between a candidate SNP (rs2228480) in ESR1 and thyroid cancer in a case-control study of 106 thyroid cancer cases (18). This SNP was not one of our top hits, but the P_{trend} value was 0.05 (Supplementary Table S1; Supplementary Data are available online at www.liebertonline.com/thy). Further exploration of the ESR1 gene may be warranted in future genotyping studies. In the two relatively small GWAS studies of thyroid cancer conducted to date, hormone pathway genes have not emerged among the top hits (13,14).

Sample size is a recognized limitation of this study and one shared with most other candidate SNP studies of thyroid cancer as discussed in a recent review of polymorphic variation and thyroid cancer risk (19). While we had sufficient statistical power to detect strong associations, our power to detect weak-to-moderate associations, particularly for less

TABLE 4. LISTING OF GENES WITHIN PATHWAYS AND P-VALUES FOR PATHWAYS

Pathway	Genes	Number of SNPs	P_{pathway}
Sex hormone synthesis and metabolism	SULT1A2/SULT1A1, AKR1C1/AKR1C2, AKR1C3, AKR1C4, AKR1D1, CYP11A1, CYP11B1, CYP11B2, CYP17A1, CYP19A1, CYP1A1/CYP1A2, CYP1B1, CYP21A2, ESR1, ESR2, HAO2/HSD3B2, HSD17B1, HSD17B2, HSD17B3, HSD17B4, HSD3B1, PGR, SHBG, SRD5A1, SRD5A2, STAR, SULT1B1, SULT1E1, TXNRD2/COMT, UGT1A8/UGT1A10/UGT1A9/UGT1A7/UGT1A6/UGT1A5/UGT1A4/UGT1A3/UGT1A1/UGT2B11, AR, CYP3A5/CYP3A7/CYP3A4, HSD11B1, GREB1, NCOA3/SULF2, SULF1, NR1I2/GSK3B, TSPAN31/CDK4/CYP27B1	842	0.8501
Gonadotropins and germ cell development	DAZL, DMRT1, ACR, INHA, INHBB, LHB, GNRHR, FSHB, GNRH1, GNRH2, AMH, INSL3/JAK3, LGR8, LHCGR	208	0.7818
Prolactin	PRLH, PRLHR, PRL, PRLR, GHI	84	0.9731
All pathways		1134	0.9502

common variants, was limited. While the proportion of men was significantly lower among controls than cases owing to the gender composition of the USRT study, similar allele frequencies among men and women permitted combined analysis, in which we adjusted for sex. Analysis restricted to women only yielded similar results and interpretation suggesting that sex was adequately controlled for in our combined analysis. A greater limitation was that there were too few male cases to examine the associations between sex hormone pathway SNPs in men separately or to investigate interactions by sex. Since controls were not required to undergo ultrasound or other imaging tests to verify that they were indeed disease free, misclassification of cases as controls could attenuate a true association between the examined SNPs and PTC risk. It will be important to confirm our generally null results in populations receiving uniform screening.

Despite these limitations, with 344 PTC cases, it is one of the largest studies conducted to date. We minimized potential for population stratification and phenotypic heterogeneity of thyroid cancer cases by restricting the study population to Caucasians and the cases with confirmed PTC. Good gene coverage is also one of the strengths of this study. Comparison of loci coverage of the iSelect assay compared with the platforms used for the published GWAS revealed greater coverage for a representative group of gene regions.

In summary, our evaluation of 1151 tag SNPs in 58 candidate genes does not provide strong evidence that polymorphic variation in hormone pathway genes is strongly associated with PTC risk. This observation is in agreement with the lack of consistent associations between hormonal and reproductive factors and PTC risk in epidemiologic studies (5,6). Nonetheless, future genome-wide association studies in very large populations are needed to provide additional insights on genetic susceptibility to thyroid cancer and its excess in women.

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Disclosure Statement

The authors declare that no competing financial interests exist.

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