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Germline variants in DNA repair genes, diagnostic radiation and risk of thyroid cancer

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Abstract

Background: Radiation exposure is a well-documented risk factor for thyroid cancer; diagnostic imaging represents an increasing source of exposure. Germline variations in DNA repair genes could increase risk of developing thyroid cancer following diagnostic radiation exposure. No studies have directly tested for interaction between germline mutations and radiation exposure.

Methods: Using data and DNA samples from a Connecticut population-based case-control study performed in 2010–2011, we genotyped 440 cases of incident thyroid cancer and 465 population-based controls for 296 single-nucleotide polymorphisms (SNPs) in 52 DNA repair genes. We used multivariate unconditional logistic regression models to estimate associations between each SNP and thyroid cancer risk, as well as to directly estimate the genotype-environment interaction between each SNP and ionizing radiation.

Results: Three SNPs were associated with increased risk of thyroid cancer and with thyroid microcarcinoma: HUS rs2708896, HUS rs10951937, and MGMT rs12769288. No SNPs were associated with increased risk of larger tumor (>10mm) in the additive-model. The gene-environment interaction analysis yielded 24 SNPs with $P_{interaction}$<0.05 for all thyroid cancer, 12

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Authors' Contributions

YZ and RU conceived and designed the research; JS designed the SNP panel; HH, NZ, WW, and FL prepared DNA samples; MS designed the statistical analysis plan; JS, HH, and WW performed statistical analysis; JS wrote the first draft; TC and all authors contributed to the final draft and approved the manuscript.

Conflicts of interest: none declared.

Disclaimer

The authors assume full responsibility for analyses and interpretation of these results.

SNPs with $P_{interaction}$<0.05 for thyroid microcarcinoma, and 5 SNPs with $P_{interaction}$<0.05 for larger tumor.

Conclusions: Germline variants in DNA repair genes are associated with thyroid cancer risk, and are differentially associated with thyroid microcarcinoma and large tumor size. Our study provides the first evidence that germline genetic variations modify the association between diagnostic radiation and thyroid cancer risk.

Impact: Thyroid microcarcinoma may represent a distinct subset of thyroid cancer. The effect of diagnostic radiation on thyroid cancer risk varies by germline polymorphism.

Keywords

thyroid cancer; DNA repair polymorphisms; case-control study

Introduction

The link between ionizing radiation and thyroid cancer, particularly papillary thyroid carcinoma (PTC), has been well-characterized in the literature. Given the rapidly-increasing use of diagnostic radiation in healthcare settings, iatrogenic PTC is a potential sequela of routine medical workups (1) that should be mitigated as much as possible through primary prevention efforts.

DNA repair pathways work to protect the body from DNA damage caused by ionizing radiation and other mutagenic sources in the environment. These pathways include non-homologous end-joining, homologous recombination, nucleotide excision repair, and base excision repair, as well as direct reversal of DNA damage. Mutations in any of these pathways – whether acquired during life or inherited at birth – might alter an individual's lifetime risk of carcinogenesis, especially for individuals who have been exposed to higher lifetime doses of ionizing radiation.

The literature of recent years has started to examine the role of somatic mutations in PTC carcinogenesis, such as RET/PTC and other chromosomal arrangements (2, 3). However, the role of germline mutations in PTC development remains poorly-documented. Furthermore, no studies to date have examined the role that such germline mutations might have in modifying the risk of PTC due to ionizing radiation. Here we test the hypothesis that germline variations in DNA repair genes are associated with risk of PTC and, furthermore, that these variations further-modify the effects of ionizing radiation on PTC risk. We do so by evaluating 299 single-nucleotide polymorphisms (SNPs) in 52 genes related to DNA repair, using data from the Connecticut population-based case-control study.

Materials and methods

Study participants

Details of the population-based case-control study were described in previous publications (1, 4). We identified cases of histologically-confirmed, incident thyroid cancer via the Yale Cancer Center's Rapid Case Ascertainment Shared Resource. 462 of the eligible cases (65.9% of all eligible cases) completed in-person interviews and were included in our study.

Connecticut residents who had no lifetime history of cancer of any type were recruited via random-digit dialing as population-based controls. 498 individuals participated as controls in the study. Cases and controls were frequency-matched by age (± 5 years). The study was approved by the Human Investigations Committee at Yale and the Connecticut Department of Public Health. Written informed consent was obtained from each participant.

SNP genotyping

After undergoing the standardized interview process described previously, a total of 448 thyroid cancer cases and 465 controls donated samples of venipuncture whole blood. Peripheral blood leukocyte DNA was extracted using the Qiagen phenol-chloroform extraction kit (Qiagen, N.V.) according to standard manufacturer protocol. DNA was then genotyped using a custom-made Golden Gate Illumina assay. Genotyping data were successfully obtained for 440 thyroid carcinoma cases and 465 controls. The GoldenGate assay included analysis of 299 single-nucleotide polymorphisms (SNPs) in 52 gene regions involved in DNA repair, based on statistical significance previously-demonstrated at the SNP and gene levels in the 2011 analysis by Neta et al. (5). (Included in our analysis were all individual SNPs that had demonstrated a significance of $p_{snp}<0.1$ in the study by Neta et al., as well as all additional SNPs associated with gene regions with $p_{gene}<0.1$ in the same study.) Quality-control duplicate samples were also included in the genotyping platform. All duplicate samples yielded a concordance rate of ≥99%. Hardy-Weinberg equilibrium (HWE) was assessed in controls for each SNP using a chi-square test. SNPs with a p-value >0.00001 from the chi-squared test were considered to be in HWE. Of the 299 SNPs tested, 3 SNPs were not in HWE and were excluded from the final analyses.

Statistical analysis

Unconditional logistic regression models were employed to estimate risk and to calculate odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for age, gender, and race. For each SNP of interest, the common homozygote was treated as the reference. We tested for linear trend using an additive model that assigned a value of 0 to common heterozygotes, 1 to heterozygotes (single-variant) and 2 to rare homozygotes (double-variant). We also compared the sum of heterozygotes and rare homozygotes to the common allele homozygote for each SNP to test for the collective significance of variation compared to the common allele. To control for race, sub-group analysis was performed using only Caucasian participants as the cases and controls. Further subgroup analysis was performed for PTC, PTC microcarcinoma (n=163), and PTC large tumor size (n=168). A final subgroup analysis used “PTC microcarcinoma” as cases and “PTC large tumor size” as controls.

Gene-environment interaction analysis

For the gene-environment interaction analysis, exposure to diagnostic radiation was defined as exposure to any of the following procedures: a) upper gastrointestinal series, b) lower gastrointestinal series, c) chest x-rays, d) head and neck CT scans, e) chest CT scans, f) abdominal CT scans, g) pelvic CT scans, h) nuclear cardiology tests, i) thyroid uptake studies using I-131 or another radioactive agent, j) nuclear medicine tests including bone, brain, liver scans, or other studies that utilize pre-test injection of a radioactive agent, k) kidney x-rays involving dye injection into a vein or artery, and l) mammograms. Non-

exposure was defined as lack of exposure to any of these 12 procedures. An unconditional logistic regression model was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for association between exposure to diagnostic x-rays and risk of thyroid cancer and its subtypes in different genotypic strata. To increase statistical power, the heterozygous and homozygous variant genotypes were combined for each SNP and compared to the "common homozygous" genotype. The significance of gene-exposure interaction was assessed by adding an interaction term in the logistic models. Results were adjusted for age (continuous), gender, race, and BMI.

We used an a priori significance level of 0.01 for each test rather than a Bonferroni correction because the Bonferroni correction is overly-conservative when hypothesis tests are correlated (6, 7). A significance level of 0.01 will increase the type I error rate to the point of certainly identifying some false positives findings. However, it will also reduce the number of false negative findings, and thus the actual α is likely to be substantially-less than the nominal α in this case. All p-values presented were two-sided. All analyses were performed using Statistical Analysis Software, version 9.3 (SAS Institute, Cary, NC).

Results

Table 1 displays selected demographic characteristics of cases and controls. Distribution of these characteristics was similar to that obtained for the original population (1). Supplementary Table 1 lists the genes represented in our analysis, grouped by category and displaying the number of analyzed SNPs per gene.

The results of the additive-model SNP analysis were similar for thyroid cancer and for papillary thyroid cancer. HUS1 rs2708896 genotypes (P_{trend} = 0.0057), HUS1 rs10951937 genotypes (P_{trend} = 0.0070), and MGMT rs12769288 genotypes (P_{trend}=0.0023) were associated with PTC risk (Table 2). A number of other SNPs yielded statistically-significant odds ratios for the heterozygous or the homozygous rare genotypes, but did not meet statistical significance in the additive model. These SNPs include EME2 rs2076431, MGMT rs10764901, RAD54B rs2046666, MBD4 rs4273365, and ATR rs10804682.

In the PTC subtype analysis, the variations in HUS1 rs2708896, HUS1 rs10951937, and MGMT rs12769288 all demonstrated statistically-significant associations with PTC microcarcinoma in the additive model (Table 3). MGMT rs10764901, MBD4 rs4273365, and ATR rs10804682, along with RECQL rs12312710, yielded statistically-significant odds ratios for the heterozygous or the homozygous rare genotypes, but did not meet statistical significance in the additive model. No SNPs displayed statistically-significant associations with PTC large tumor size in the additive model. However, a number of SNPs did yield statistically-significant odds ratios for the less-common genotypes. These SNPs include EME2 rs2076431, OGG1 rs159154, OGG1 rs159153, XAB2 rs1674034, XAB2 rs794078, and ATR rs10804682. None of the SNPs listed above met statistical significance in the case-control analysis of microcarcinoma versus large tumor size. We performed a post-hoc analysis of the results for PTC large tumor size stratified by tumor size (11–15mm, 16–30mm, and >30mm). This analysis revealed one SNP – rs1674034 in XAB2 – that was significantly-associated with PTC 16–30mm (P_{trend} = 0.0009 for all races, P_{trend} = 0.0059

for Caucasians). No other SNPs remained significantly-associated with any of the subgroups of PTC large tumor size after adjusting for race.

Supplementary Table 2 displays associations between diagnostic radiation exposure and risk of thyroid cancer among genotyped cases and controls. The results were similar to those obtained in the original 2015 analysis (1). The initial GxE analysis of thyroid cancer (Table 4) yielded23 total SNPs with $P_{interaction}<0.05$. Only 3 of these SNPs reached *a priori* significance of $P_{interaction}<0.01$: ALKBH3 rs10768994 ($P_{interaction} = 0.0086$), LIG1 rs2163619 ($P_{interaction} = 0.0060$), and LIG1 rs10421339 ($P_{interaction} = 0.0081$). Three more SNPs only achieved $p<0.05$ but yielded large odds ratios: MGMT rs4750763 (OR 3.79, CI 1.44–9.98, $P_{interaction} = 0.015$), MGMT rs1762444 (OR 3.36, CI 1.37–8.27, $P_{interaction} = 0.024$), and RPA3 rs4720751 (OR 2.91, CI 1.39–6.09, $P_{interaction} = 0.034$). When cases were restricted to PTC (Table 5), only LIG1 rs2163619 and LIG1 rs10421339 reached $P_{interaction}<0.01$. In total, the SNPs with $P_{interaction}<0.05$ for thyroid cancer included mutations in ALKBH3 (7), LIG1 (7), TOPBP1 (3), RPA3 (2), MGMT (2), PARP4 (1), and UBE2A (1). The thyroid microcarcinoma subanalysis (Table 6) yielded 12 SNPs with $P_{interaction}<0.05$, but only 1 SNP that reached *a priori* significance, XRCC2 rs10234749 (OR 7.82, CI 2.20–27.78, $P_{interaction} = 0.0041$). Of the other 11 SNPs with $P_{interaction}<0.05$, 4 were associated with ALKBH3, 4 were associated with ERCC5, and one was associated with PARP4. The sub-analysis of PTC microcarcinoma (Supplementary Table 3) yielded similar results. The sub-analysis of thyroid cancer with large tumor size yielded 5 SNPs with $P_{interaction}<0.05$ (Supplementary Table 4). Three of these SNPs reached *a priori* significance: LIG1 rs251693 (OR 2.20, CI 1.02–4.73, $P_{interaction} = 0.0056$), LIG1 rs2288878 (OR 2.19, CI 1.02–4.70, $P_{interaction} = 0.0040$), and LIG1 rs274897 (OR 2.26, CI 1.05–4.87, $P_{interaction} = 0.0038$). When cases were restricted to PTC, none of the SNPs remained significant.

Discussion

The role of germline mutations in thyroid cancer and PTC has thus far received limited investigation. Gudmundsson et al. (8) performed a GWAS study to search for PTC susceptibility loci and uncovered two candidate SNPs. Individuals homozygous for both variant SNPs carried an estimated thyroid cancer risk more than five times greater than that of non-carriers. The authors replicated these results in two populations of European descent. Further studies have identified additional susceptibility loci (9, 10)

Most extant candidate gene studies of PTC have only examined up to 5–10 SNPs each (11–15). However, the study performed by Neta et al. in 2011 tested 5,077 SNPs from 340 candidate genes involved in genomic integrity (5). This study revealed 9 genomic integrity SNPs associated with PTC risk with $p_{trend}<0.0005$, as well as 7 gene regions associated with PTC risk with $p_{trend}<0.01$, although none of these SNPs remained statistically-significant after adjustment for false discovery rate. Three of the identified SNPs (HUS1 rs2708906, ALKBH3 rs10838192, and MGMT rs4751109), and 2 of the identified gene regions (HUS1 and ALKBH3), correspond to genes involved in DNA repair. These promising results have merited validation.

Our study identifies a number of SNPs in DNA repair genes statistically-significant associated with PTC. Among these genes are the three identified by Neta et al.: HUS1, MGMT, and ALKBH3. The HUS1 protein forms a complex with two other proteins, RAD1 and RAD9, and deposits in regions of damaged DNA. This activates the ATR kinase signaling cascade and thus the overall cellular response to DNA damage (16). MGMT repairs mutagenic methylguanine lesions generated by alkylating agents; decreased expression has been linked to increased incidence of gliomas (17) and testicular germ cell tumors (18). ALKBH3 plays a similar role by removing 1-methyladenine and 3-methylcytosine lesions from DNA (19).

Interestingly, our sub-analysis reveals SNPs being differentially associated with PTC microcarcinoma and PTC larger tumor. For example, significant mutations in HUS1 and MGMT were identified in microcarcinoma but not in larger tumor. Other mutations such as those in XAB2 and OGG1 only showed association with larger tumor. None of these SNPs yielded significant values in the head-to-head comparison of microcarcinoma versus larger tumor. (One possible explanation could be that some “microcarcinoma” cases in fact represent a misclassification of larger tumors in their early stages of development.) The differential association of SNPs with tumor sizes suggests that there might be underlying biological differences between microcarcinomas and larger tumors, which would merit further genomic investigation.

Our study is the first to examine interaction between SNPs and lifetime exposure to ionizing radiation. The GxE analyses revealed significant SNPs linked to MGMT and ALKBH3 (described previously) as well as in four additional genes: ERCC5, PARP1, XRCC2, and LIG1. The ERCC5 endonuclease makes the 3’ incision in DNA excision repair following UV-induced damage (20). Genetic variation in ERCC5 has been associated with risk of lung cancer (21), gastric cancer (22), and xerodermapigmentosum (23). XRCC2 and PARP1 are both involved in homologous recombination. XRCC2-deficient cells appear more sensitive to PARP1 inhibitors than XRCC2-expressing cells, suggesting that XRCC2 and PARP1 share a DNA repair pathway (24). The LIG1 ligase is involved in DNA replication, recombination, and base excision repair (25); LIG1 germline polymorphisms have been associated with non-small cell lung cancer (26, 27). SNPs in LIG1 appeared to be most strongly associated with larger tumor in this study, whereas the SNPs in ERCC5, PARP1, and XRCC2 displayed association with microcarcinoma.

None of our significant SNPs were in protein-coding regions. SNPs within introns might affect RNA splicing patterns and thus upregulate or downregulate key DNA repair protein products (28). In particular, SNPs that alter the usual pattern of exonic splicing enhancers (ESEs) could affect spliceosome assembly and lead to exon skipping (29). To investigate this hypothesis, we used ESEFinder (Cold Spring Harbor Laboratory) to test 43 of our most significant SNP “hits” for changes in their pattern of ESEs. Thirty-three SNPs demonstrated the potential to modify at least one ESE (Supplementary Table 5). SNPs located upstream of genes could be involved with promotor or regulator sequences, influencing the amount of RNA transcribed in various biological circumstances (30). Mounting evidence suggests that a majority of gene-environment interaction is determined by distant regulatory sequences

(31). We did not directly test for cellular RNA or protein content, but further biological experiments could test for evidence differential gene transcription and RNA modification.

An important limitation of the present study is the sample size, which, although larger than those of previous candidate SNP studies, still proved insufficient to detect SNPs with unequivocal statistical significance after Bonferroni correction for multiple comparison. SNP validation would require an even larger pool of cases and controls. A larger sample size would also increase confidence in certain “significant” results that are based on very small sample sizes. Finally, although our post-hoc analysis of large tumor size subsets suggests that additional SNP associations might exist, the present study was not powered to detect such associations.

Recall bias must be considered in this study. Data on diagnostic radiography exposure relied upon self-reporting by cases and controls, rather than health record documentation. However, as described in our previous publication, other studies (32–34) have suggested nondifferential reporting error between thyroid cancer cases and controls. Even if differential recall bias were a possibility for subjects in a particular age range (35), our age-stratified analysis of the original data described previously was unable to uncover evidence of such bias in our own findings. Furthermore, our significant findings are limited to thyroid microcarcinoma. Additionally, diverse types of diagnostic radiation exposure were combined, which might cause potential exposure misclassification. In gene-environment interaction studies, both differential and nondifferential misclassification of a binary environmental factor biases a multiplicative interaction effect toward the null (36).

As previously discussed, our candidate gene approach likely misses many potentially-significant regions of the genome. A fruitful future direction for this work would be performing a genome-wide association study (GWAS) using a randomly-selected subset of our cases and controls, to identify novel regions of genomic significance.

Conclusion

This study provides further evidence that germline mutations in DNA repair genes are significantly associated with risk of thyroid cancer and PTC. It suggests that microcarcinoma, which is particularly associated with diagnostic radiation exposure, represents a distinct subset of thyroid cancer and PTC with its own biological signature. Finally, our study provides novel evidence to suggest a significant interaction between germline mutations in DNA repair genes and ionizing radiation in the pathogenesis of thyroid cancer. These results merit replication with larger sample sizes and alternative study methods to establish statistical significance, and to further explore the basis of the molecular biology behind them.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1.

Distribution of selected characteristics among thyroid cancer cases and controls.

	Cases (n=440)		Controls (n=465)		P
	Number	%	Number	%	
Age (years)					0.0001
<40	84	19.1	61	13.1	
40–49	112	25.5	117	25.2	
50–59	140	31.8	126	27.1	
60–69	78	17.7	94	20.2	
≥70	26	5.9	67	14.4	
Gender					<0.0001
Male	84	19.1	145	31.2	
Female	356	80.9	320	68.8	
Race					0.21
White	396	90.0	427	91.8	
Black	16	3.6	20	4.3	
Other	28	6.4	18	3.9	
BMI (kg/m^2)					0.0005
<25	140	31.8	185	39.8	
25–29.9	138	31.4	160	34.3	
≥30	159	36.1	112	24.1	
Missing	3	0.7	8	1.7	
Family history of thyroid cancer					0.0051
Yes	71	16.1	46	9.9	
No	369	83.9	419	90.1	
Benign thyroid disease					<0.0001
Yes	56	12.7	12	2.6	
No	384	87.3	453	97.4	

Table 2.

Statistically significant association between genotypes and risk of papillary thyroid cancer among whites (n=760).

Chromosome	Gene name	SNP	Genotype	Cases	Controls	OR (95% CI)	P-value
7	HUS1	rs2708896	GG	99	108	1	
			TG	171	199	0.92(0.65–1.30)	0.641180875
			TT	63	120	0.55(0.36–0.83)	0.004611807
			P for trend				**0.00570544**
			TG & TT	234	319	0.78(0.56–1.08)	0.133937371
7	HUS1	rs10951937	TT	126	142	1	
			TG	161	185	0.98(0.70–1.35)	0.886392195
			GG	46	100	0.51(0.33–0.79)	0.002373343
			P for trend				**0.00704081**
			GG & TG	207	285	0.81(0.60–1.10)	0.182937296
10	MGMT	rs12769288	CC	276	317	1	
			TC	55	101	0.62(0.43–0.90)	0.012889857
			TT	2	9	0.23(0.05–1.10)	0.065342142
			P for trend				**0.0023066**
			TC & TT	57	110	0.59(0.41–0.85)	0.004426897

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Table 3.

Statistically significant association between genotypes and risk of papillary thyroid microcarcinoma among whites (n=590).

Chromosome	Gene name	SNP	Genotype	Cases	Controls	OR (95% CI)	P-value
7	HUS1	rs2708896	GG	53	108	1	
			TG	81	199	0.78(0.51–1.21)	0.269937173
			TT	29	120	0.46(0.27–0.79)	0.004725606
			P for trend				0.005150922
			TG & TT	110	319	0.66(0.44–0.99)	0.047220849
7	HUS1	rs10951937	TT	68	142	1	
			TG	78	185	0.86(0.57–1.28)	0.447883484
			GG	17	100	0.35(0.19–0.65)	0.000708759
			P for trend				0.001602607
			GG & TG	95	285	0.68(0.47–1.00)	0.048742011
10	MGMT	rs12769288	CC	141	317	1	
			TC	20	101	0.43(0.25–0.73)	0.001710087
			TT	2	9	0.47(0.10–2.26)	0.347352446
			P for trend				0.002130931
			TC & TT	22	110	0.43(0.26–0.72)	0.001229464

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Table 4.

Statistically significant effect modification of genotypes between diagnostic radiation exposure and risk of thyroid cancer (n=905).

Chromosome	Gene name	Genotype	Non-exposed			Exposed		
			Cases	Controls	OR* (95% CI)	Cases	Controls	OR* (95% CI)
3	TOPBP1_06	rs17301766						
		CC	21	40	1.00	269	260	1.96 (1.06–3.66)
		TC or TT	15	12	1.00	134	152	0.81 (0.33–1.98)
		P for interaction						*0.028*
3	TOPBP1_09	rs11706586						
		CC	20	40	1.00	267	262	2.06 (1.10–3.86)
		TC or TT	15	12	1.00	135	151	0.85 (0.35–2.08)
		P for interaction						*0.025*
3	TOPBP1_10	rs7349558						
		AA	22	40	1.00	270	257	1.94 (1.05–3.59)
		AC or CC	14	12	1.00	133	156	0.79 (0.32–1.95)
		P for interaction						*0.039*
7	RPA3_01	rs4720751						
		TT	20	24	1.00	175	217	0.85 (0.43–1.71)
		TC or CC	15	28	1.00	227	196	2.91 (1.39–6.09)
		P for interaction						*0.034*
7	RPA3_02	rs17136898						
		AA	22	41	1.00	301	292	2.11 (1.15–3.88)
		AG or GG	13	11	1.00	101	121	0.78 (0.29–2.07)
		P for interaction						*0.050*
7	XRCC2_01	rs10234749						
		CC	19	36	1.00	279	251	2.51 (1.32–4.75)
		AC or AA	16	16	1.00	122	162	0.59 (0.25–1.44)
		P for interaction						*0.025*
10	MGMT_02	rs1762444						
		GG	8	25	1.00	158	161	3.36 (1.37–8.27)
		AG or AA	27	27	1.00	244	252	0.98 (0.52–1.85)

Chromosome	Gene name	Genotype	Non-exposed			Exposed		
			Cases	Controls	OR* (95% CI)	Cases	Controls	OR* (95% CI)
		P for interaction						*0.024*
10	MGMT_32	rs12219606						
		CC	8	21	1.00	139	143	2.55 (0.98–6.65)
		AC or AA	27	31	1.00	265	270	1.19 (0.65–2.16)
		P for interaction						*0.049*
10	MGMT_36	rs4750763						
		AA	7	26	1.00	165	171	3.79 (1.44–9.98)
		AC or CC	28	26	1.00	237	242	0.99 (0.54–1.85)
		P for interaction						*0.015*
11	ALKBH3_03	rs11037690						
		GG	14	32	1.00	203	193	2.43 (1.15–5.14)
		AG or AA	21	20	1.00	198	220	0.99 (0.48–2.02)
		P for interaction						*0.029*
11	ALKBH3_14	rs10768994						
		TT	8	26	1.00	137	131	2.88 (1.13–7.29)
		TC or CC	28	26	1.00	267	282	0.99 (0.53–1.84)
		P for interaction						*0.0086*
11	ALKBH3_15	rs10768995						
		GG	21	19	1.00	146	158	0.97 (0.45–2.09)
		GC or CC	14	33	1.00	256	255	2.37 (1.16–4.86)
		P for interaction						*0.012*
11	ALKBH3_19	rs868784						
		CC	11	29	1.00	169	155	2.66 (1.16–6.12)
		TC or TT	24	23	1.00	233	258	1.06 (0.54–2.05)
		P for interaction						*0.018*
11	ALKBH3_20	rs3893853						
		CC	20	38	1.00	275	247	2.01 (1.06–3.82)
		TC or TT	16	14	1.00	128	166	0.85 (0.36–1.98)
		P for interaction						*0.014*
11	ALKBH3_21	rs4755217						

Chromosome	Gene name	Genotype	Non-exposed			Exposed		
			Cases	Controls	OR* (95% CI)	Cases	Controls	OR* (95% CI)
		TT	8	26	1.00	137	133	2.86 (1.13–7.24)
		TC or CC	27	25	1.00	259	275	1.03 (0.55–1.95)
		P for interaction						*0.014*
11	ALKBH3_22	rs1973717						
		CC	20	20	1.00	155	165	1.10 (0.52–2.34)
		TC or TT	15	32	1.00	245	247	2.09 (1.03–4.26)
		P for interaction						*0.045*
13	PARP4_04	rs4770687						
		GG	14	13	1.00	99	121	0.62 (0.23–1.65)
		AG or AA	22	39	1.00	303	291	2.28 (1.24–4.19)
		P for interaction						*0.043*
19	LIG1_01	rs251693						
		TT	16	18	1.00	112	138	0.71 (0.32–1.61)
		TC or CC	19	34	1.00	291	275	2.51 (1.30–4.83)
		P for interaction						*0.024*
19	LIG1_02	rs2288878						
		GG	16	18	1.00	108	137	0.72 (0.32–1.61)
		AG or AA	20	34	1.00	294	276	2.36 (1.23–4.50)
		P for interaction						*0.024*
19	LIG1_03	rs274897						
		CC	16	18	1.00	109	138	0.69 (0.30–1.55)
		GC or GG	19	34	1.00	293	274	2.55 (1.32–4.91)
		P for interaction						*0.020*
19	LIG1_04	rs2386523						
		CC	14	15	1.00	86	103	0.73 (0.30–1.80)
		TC or TT	21	37	1.00	317	309	2.34 (1.25–4.38)
		P for interaction						*0.025*
19	LIG1_05	rs2163619						
		GG	13	13	1.00	73	95	0.57 (0.22–1.50)
		AG or AA	22	39	1.00	330	316	2.40 (1.30–4.42)

Chromosome	Gene name	Genotype	Non-exposed			Exposed		
			Cases	Controls	OR* (95% CI)	Cases	Controls	OR* (95% CI)
		P for interaction						*0.0060*
19	LIG1_07	rs274873						
		AA	14	16	1.00	95	111	0.59 (0.24–1.46)
		AG or GG	22	36	1.00	308	302	2.24 (1.21–4.15)
		P for interaction						*0.035*
19	LIG1_10	rs10421339						
		GG	15	15	1.00	94	113	0.45 (0.18–1.16)
		GC or CC	20	37	1.00	308	300	2.50 (1.34–4.69)
		P for interaction						*0.0081*
X	UBE2A_01	rs5910616						
		GG	33	43	1.00	309	328	1.28 (0.75–2.19)
		AG or GG	2	9	1.00	91	85	6.82 (1.08–43.08)
		P for interaction						*0.043*

*Adjusted for age (continuous), gender, race, and BMI.

OR: Odds Ratio; CI: Confidence Interval

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Table 5.

Statistically significant effect modification of genotypes between diagnostic radiation exposure and risk of papillary thyroid cancer (n=838).

Chromosome	Gene name	Genotype	Non-exposed			Exposed		
			Cases	Controls	OR* (95% CI)	Cases	Controls	OR* (95% CI)
3	TOPBP1_06	rs17301766						
		CC	21	40	1.00	221	260	1.62 (0.86–3.06)
		TC or TT	14	12	1.00	116	152	0.79 (0.32–1.96)
		P for interaction						*0.044*
3	TOPBP1_09	rs11706586						
		CC	20	40	1.00	221	262	1.73 (0.91–3.27)
		TC or TT	14	12	1.00	115	151	0.81 (0.33–2.01)
		P for interaction						*0.035*
7	RPA3_01	rs4720751						
		TT	19	24	1.00	141	217	0.69 (0.33–1.41)
		TC or CC	15	28	1.00	196	196	2.73 (1.29–5.75)
		P for interaction						*0.024*
7	HUS1_03	rs3176595						
		GG	31	36	1.00	261	328	1.03 (0.59–1.82)
		AG or AA	4	16	1.00	74	84	4.20 (1.09–16.23)
		P for interaction						*0.033*
7	XRCC2_01	rs10234749						
		CC	18	36	1.00	231	251	2.24 (1.16–4.32)
		AC or AA	16	16	1.00	104	162	0.50 (0.20–1.24)
		P for interaction						*0.026*
10	MGMT_02	rs1762444						
		GG	8	25	1.00	131	161	2.86 (1.15–7.11)
		AG or AA	26	27	1.00	205	252	0.84 (0.44–1.62)
		P for interaction						*0.025*
10	MGMT_36	rs4750763						
		AA	7	26	1.00	137	171	3.49 (1.30–9.39)
		AC or CC	27	26	1.00	199	242	0.85 (0.45–1.59)

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Chromosome	Gene name	Genotype	Non-exposed			Exposed		
			Cases	Controls	OR* (95% CI)	Cases	Controls	OR* (95% CI)
		P for interaction						*0.016*
11	ALKBH3_03	rs11037690						
		GG	13	32	1.00	171	193	2.16 (0.99–4.72)
		AG or AA	21	20	1.00	164	220	0.88 (0.43–1.81)
		P for interaction						*0.026*
11	ALKBH3_14	rs10768994						
		TT	8	26	1.00	115	131	2.40 (0.93–6.17)
		TC or CC	27	26	1.00	223	282	0.87 (0.46–1.63)
		P for interaction						*0.010*
11	ALKBH3_15	rs10768995						
		GG	21	19	1.00	124	158	0.83 (0.38–1.80)
		GC or CC	13	33	1.00	212	255	2.21 (1.05–4.64)
		P for interaction						*0.011*
11	ALKBH3_19	rs868784						
		CC	10	29	1.00	144	155	2.40 (1.01–5.72)
		TC or TT	24	23	1.00	193	258	0.92 (0.47–1.80)
		P for interaction						*0.014*
11	ALKBH3_20	rs3893853						
		CC	19	38	1.00	231	247	1.72 (0.89–3.34)
		TC or TT	16	14	1.00	106	166	0.74 (0.31–1.74)
		P for interaction						*0.013*
11	ALKBH3_21	rs4755217						
		TT	8	26	1.00	116	133	2.47 (0.96–6.32)
		TC or CC	26	25	1.00	214	275	0.90 (0.47–1.72)
		P for interaction						*0.015*
11	ALKBH3_22	rs1973717						
		CC	20	20	1.00	133	165	0.95 (0.44–2.04)
		TC or TT	14	32	1.00	201	247	1.89 (0.91–3.96)
		P for interaction						*0.048*
13	PARP4_04	rs4770687						

Chromosome	Gene name	Genotype	Non-exposed			Exposed		
			Cases	Controls	OR* (95% CI)	Cases	Controls	OR* (95% CI)
		GG	13	13	1.00	80	121	0.56 (0.20–1.55)
		AG or AA	22	39	1.00	256	291	1.92 (1.04–3.54)
		P for interaction						*0.042*
19	LIG1_01	rs251693						
		TT	16	18	1.00	93	138	0.55 (0.24–1.28)
		TC or CC	18	34	1.00	244	275	2.33 (1.19–4.56)
		P for interaction						*0.019*
19	LIG1_02	rs2288878						
		GG	16	18	1.00	90	137	0.55 (0.24–1.28)
		AG or AA	19	34	1.00	246	276	2.20 (1.13–4.27)
		P for interaction						*0.020*
19	LIG1_03	rs274897						
		CC	16	18	1.00	90	138	0.52 (0.22–1.21)
		GC or GG	18	34	1.00	246	274	2.38 (1.22–4.67)
		P for interaction						*0.015*
19	LIG1_04	rs2386523						
		CC	14	15	1.00	72	103	0.56 (0.22–1.43)
		TC or TT	20	37	1.00	265	309	2.16 (1.14–4.10)
		P for interaction						*0.020*
19	LIG1_05	rs2163619						
		GG	13	13	1.00	61	95	0.39 (0.14–1.12)
		AG or AA	21	39	1.00	276	316	2.19 (1.17–4.09)
		P for interaction						*0.0044*
19	LIG1_07	rs274873						
		AA	14	16	1.00	79	111	0.43 (0.16–1.11)
		AG or GG	21	36	1.00	258	302	2.07 (1.10–3.90)
		P for interaction						*0.026*
19	LIG1_10	rs10421339						
		GG	15	15	1.00	79	113	0.34 (0.12–0.91)
		GC or CC	19	37	1.00	257	300	2.29 (1.20–4.36)

Chromosome	Gene name	Genotype	Non-exposed			Exposed		
			Cases	Controls	OR* (95% CI)	Cases	Controls	OR* (95% CI)
		P for interaction						*0.0066*
X	UBE2A_01	rs5910616						
		GG	32	43	1.00	256	328	1.11 (0.64–1.92)
		AG or AA	2	9	1.00	80	85	6.35 (1.00–40.40)
		P for interaction						*0.034*

*Adjusted for age (continuous), gender, race, and BMI.

OR: Odds Ratio; CI: Confidence Interval

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Table 6.

Statistically significant effect modification of genotypes between diagnostic radiation exposure and risk of thyroid microcarcinoma (n=672).

Chromosome	Gene name	Genotype	Non-exposed			Exposed		
			Cases	Controls	OR* (95% CI)	Cases	Controls	OR* (95% CI)
7	XRCC2_01	rs10234749						
		CC	3	36	1.00	135	251	7.82 (2.20–27.78)
		AC or AA	6	16	1.00	60	162	0.65 (0.20–2.11)
		P for interaction						*0.0041*
10	MGMT_33	rs10829618						
		GG	3	41	1.00	122	264	7.16 (2.02–25.39)
		GC or CC	6	11	1.00	75	149	0.99 (0.32–3.12)
		P for interaction						*0.036*
10	MGMT_39	rs4751112						
		AA	3	39	1.00	118	256	6.78 (1.89–24.30)
		AG or GG	7	13	1.00	79	157	1.01 (0.34–2.99)
		P for interaction						*0.045*
11	ALKBH3_01	rs12804822						
		AA	2	33	1.00	109	232	8.92 (1.96–40.55)
		AC or CC	7	19	1.00	88	181	1.23 (0.44–3.46)
		P for interaction						*0.022*
11	ALKBH3_07	rs3740983						
		TT	2	32	1.00	104	224	9.52 (2.07–43.81)
		TG or GG	7	20	1.00	93	189	1.29 (0.47–3.53)
		P for interaction						*0.030*
11	ALKBH3_08	rs7482199						
		TT	2	34	1.00	103	231	8.97 (1.97–40.92)
		TC or CC	8	18	1.00	94	182	1.15 (0.43–3.07)
		P for interaction						*0.018*
11	ALKBH3_11	rs11037726						
		AA	2	34	1.00	106	233	9.01 (1.97–41.15)
		TA or TT	8	18	1.00	91	179	1.17 (0.44–3.15)

Chromosome	Gene name	Genotype	Non-exposed			Exposed		
			Cases	Controls	OR* (95% CI)	Cases	Controls	OR* (95% CI)
		P for interaction						*0.017*
13	PARP4_04	rs4770687						
		GG	6	13	1.00	48	121	0.62 (0.18–2.16)
		AG or AA	4	39	1.00	148	291	5.73 (1.89–17.40)
		P for interaction						*0.020*
13	ERCC5_07	rs4150355						
		GG	7	22	1.00	77	173	1.35 (0.49–3.69)
		AG or AA	2	30	1.00	120	240	8.01 (1.72–37.23)
		P for interaction						*0.033*
13	ERCC5_11	rs17655						
		GG	9	29	1.00	102	244	0.95 (0.39–2.35)
		CG or CC	1	23	1.00	95	169	21.97 (2.74–176.47)
		P for interaction						*0.030*
13	ERCC5_13	rs9586002						
		GG	2	31	1.00	120	243	8.88 (1.96–40.16)
		TG or TT	7	21	1.00	77	170	1.11 (0.40–3.10)
		P for interaction						*0.033*
13	ERCC5_14	rs1886087						
		AA	6	16	1.00	52	111	1.47 (0.47–4.62)
		TA or TT	3	36	1.00	145	302	5.77 (1.62–20.54)
		P for interaction						*0.036*

*Adjusted for age (continuous), gender, race, and BMI.

OR: Odds Ratio; CI: Confidence Interval