Environmental Research 182 (2020) 109013

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Genetic susceptibility may modify the association between cell phone use and thyroid cancer: A population-based case-control study in Connecticut

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ARTICLE INFO

Keywords:
Radiofrequency radiation
Thyroid cancer
Cell phone
Genetic susceptible
Genetic-environment interaction

ABSTRACT

Emerging studies have provided evidence on the carcinogenicity of radiofrequency radiation (RFR) from cell phones. This study aims to test the genetic susceptibility on the association between cell phone use and thyroid cancer. Population-based case-control study was conducted in Connecticut between 2010 and 2011 including 440 thyroid cancer cases and 465 population-based controls with genotyping information for 823 single nucleotide polymorphisms (SNPs) in 176 DNA genes. We used multivariate unconditional logistic regression models to estimate the genotype-environment interaction between each SNP and cell phone use and to estimate the association with cell phone use in populations according to SNP variants. Ten SNPs had $P < 0.01$ for interaction in all thyroid cancers. In the common homozygote groups, no association with cell phone use was observed. In the variant group (heterozygotes and rare homozygotes), cell phone use was associated with an increased risk for rs11070256 (odds ratio (OR): 2.36, 95% confidence interval (CI): 1.30–4.30), rs1695147 (OR: 2.52, 95% CI: 1.30–4.90), rs6732673 (OR: 1.59, 95% CI: 1.01–2.49), rs396746 (OR: 2.53, 95% CI: 1.13–5.65), rs12204529 (OR: 2.62, 95% CI: 1.33–5.17), and rs3800537 (OR: 2.64, 95% CI: 1.30–5.36) with thyroid cancers. In small tumors, increased risk was observed for 5 SNPs (rs1063639, rs1695147, rs11070256, rs12204529 and rs3800537), In large tumors, increased risk was observed for 3 SNPs (rs11070256, rs1695147, and rs396746). Our result suggests that genetic susceptibilities modify the associations between cell phone use and risk of thyroid cancer. The findings provide more evidence for RFR carcinogenic group classification.

1. Introduction

The International Agency for Research on Cancer (IARC) classified radiofrequency radiation (RFR) emitted from cell phone as possible human carcinogen (Group 2B) in 2011 based on limited evidence from humans (IARC Working Group, 2013). One cohort study (Schuz et al., 2006) and five case-control studies (Auvinen et al., 2002; Hardell et al., 2011; Inskip et al., 2001; INTERPHONE Study Group, 2010; Muscat et al., 2000) were evaluated by the IARC Working Group. Brain tumors including glioma, acoustic neuroma, and meningioma were evaluated in these studies. Two studies observed an increased risk of brain tumor in people with the highest cumulative cell phone use (Hardell et al., 2011; INTERPHONE Study Group, 2010). Though these studies were vulnerable to methodological limitations and possible biases, such as no appropriate evidence-based metric for cell phone use, the working group stated that positive associations have been observed between exposure to radiofrequency radiation and glioma, and acoustic neuroma (IARC Working Group, 2013). Most group members agreed that positive associations in these studies could not be dismissed and that it was appropriate to classify RFR as a Group 2B carcinogen (Baan et al., 2011).

Since 2011, emerging studies have offered additional evidence on

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https://doi.org/10.1016/j.envres.2019.109013
Received 22 October 2019; Received in revised form 4 December 2019; Accepted 5 December 2019
Available online 06 December 2019
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the carcinogenicity of RFR. An animal experiment published in 2018 by the National Toxicology Program (NTP) concluded that there was clear evidence to support an association between RFR exposure from cell phones and tumors in the hearts and brains of male rats (National Toxicology Program, 2018a; National Toxicology Program, 2018b; Wyde et al., 2018). These findings were confirmed by another animal study from the Ramazzini Institute (Falcioni et al., 2018). Additional population studies have also been published since the IARC classification. Nine articles using data from case-control studies concluded that long-term cell phone use was associated with an increased risk of brain tumor (Aydin et al., 2011; Cardis et al., 2011; Carlberg and Hardell, 2012; Coureau et al., 2014; Grell et al., 2016; Hardell and Carlberg, 2015; Hardell et al., 2013; Momoli et al., 2017). Two cohort studies did not observe an association between cell phone use and brain tumor (Benson et al., 2013; Frei et al., 2011). However, one study (Benson et al., 2013) only provided baseline exposure and another study (Frei et al., 2011) used mobile phone subscription. The limitations of exposure assessment suffered from these two cohort studies might render their null associations uninformative (Söderqvist et al., 2012). These new findings build up researchers' concerns about health effects of cell phone use and support the effort to reclassify RFR as a Group 1 carcinogen (Miller et al., 2018). A new report from IARC advisory group also recommended a re-evaluation of RFR classification (IARC, 2019).

Cell phone technology has changed over the past three decades. The analog cell phone was introduced to the US in 1983 and then digital cell phone in 1993. In 2008, the US Federal Communications Commission officially let American carriers decommission analog network (Scherer, 2018). Cell antennas tend to be located at the bottom of cell phones since the introduction of smartphone around 2010, and thus the peak RFR exposure is more likely to occur in the neck than in the brain (Carlberg et al., 2016). Thyroid gland located in the neck is the most radiation-sensitive organ (Zhang et al., 2015); and the only established exogenous risk factor for thyroid cancer is ionizing radiation (Sinnott et al., 2010). A recent study linked cell phone use with thyroid cancer (Luo et al., 2019), though only borderline significant results were observed. Thyroid cancer incidence rates have been rising substantially over the past several decades, paralleling the increased use of cell phones. Therefore, more studies are needed to investigate whether RFR from cell phones contributes to the increase.

It is suggested that in addition to thermal effects, the energy from RFR is sufficient to alter the structure and function of proteins involved in DNA damage repair (Phillips et al., 2009). Recent studies indicated that exposure to RFR increased DNA damage (Smith-Roe, 2019; Yakymenko et al., 2016). However, genetic factors were not considered in previous epidemiologic studies. To our knowledge, no epidemiologic studies have examined gene-environment interactions.

Given the potential relationships between RFR from cell phone use, thyroid cancer and DNA damage repair, this study aims to investigate the role of DNA repair genes in the association between cell phone use and thyroid cancer using data from a population-based case-control study in Connecticut, USA. We hypothesize that variants of single nucleotide polymorphisms (SNPs) within DNA repair genes can modify the effects of RFR from cell phone use.

2. Method

2.1. Study population

Details of the population-based case-control study were described in previous publications (Luo et al., 2019; Sandler et al., 2018). In brief, the study included 462 histologically confirmed incident thyroid cancers (papillary (ICD-O-3: 8050, 8052, 8130, 8260, 8340–8344, 8450, and 8452), follicular (ICD-O-3: 8290, 8330–8332, and 8335), medullary (ICD-O-3: 8345, 8346, and 8510), or anaplastic (ICD-O-3: 8021)) diagnosed between 2010 and 2011 in Connecticut (375 females and 87 males), and 498 population-based controls (344 females and 154 males). All cases were between 21 and 84 years old, without previous cancer except nonmelanoma skin cancer, and were alive at the time of interview. A total of 701 eligible cases were identified and 462 (65.9%) completed in-person interviews. Controls were recruited through random digit dialing. A total of 498 controls joined the study with a participation rate of 61.5%. All participants, including cases and controls in this study, were interviewed by trained study interviewers using a standardized and structured questionnaire to collect information on demographics, cell phone use, radiation exposure, lifestyle factors, occupation, and diet. 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 all participants.

Table 1
Distribution of selected characteristics of the study population.

	Case (n = 440) n (%)	Controls (n = 465) n (%)	P value[c]
Age (years)			
Mean (SD)	50.9 (12.1)	54.1 (13.1)	< 0.01
< 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)	< 0.01
Sex			
Male	84 (19.1)	145 (31.2)	
Female	356 (80.9)	320 (68.8)	< 0.01
Race			
White	396 (90.0)	427 (91.8)	
Black	16 (3.6)	20 (4.3)	
Other	28 (6.4)	18 (3.9)	0.21
Body mass index (kg/m^2)			
< 25	140 (31.8)	185 (39.8)	
25 to < 30	138 (31.4)	160 (34.3)	
30+	159 (36.1)	112 (24.1)	
Missing	3 (0.7)	8 (1.7)	< 0.01
Years of education			
High school or lower	152 (34.6)	101 (21.7)	
College	176 (40.0)	226 (48.6)	
Graduate school	110 (25.0)	133 (28.6)	
Missing	2 (0.4)	5 (1.1)	< 0.01
Family history of thyroid cancer among first-degree relatives			
Yes	71 (16.1)	46 (9.9)	
No	369 (83.9)	419 (90.1)	0.03
Prior benign thyroid disease[a]			
Yes	56 (12.7)	12 (2.6)	
No	384 (87.3)	453 (97.4)	< 0.01
Alcohol consumption[b]			
Yes	185 (42.0)	251 (54.0)	
No	255 (58.0)	214 (46.0)	< 0.01

SD: standard deviation.

[a] Benign thyroid disease included hyperthyroidism, hypothyroidism, goiter, thyroid nodules, and thyroid adenoma.

[b] Ever alcohol consumption was defined as ever had more than 12 drinks of alcoholic beverages such as beer, wine, or liquor. 1 drink of beer = 1 can or bottle; 1 drink of wine = 14 oz glass; 1 drink of liquor = 1 shot.

[c] p values from chi-square test were used to test the difference between cases and controls.

2.2. Cell phone use assessment

The participants were asked the following questions regarding the frequency, duration, and protective behaviors of cell phone use: (1) Have you ever used a cell phone at least once a week for 6 months prior to one year before diagnosis? (2) What calendar year did you start regularly using a cell phone? (3) What calendar year did you stop regularly using a cell phone? (4) Excluding the time period that you did not use a cell phone, altogether how many years have you regularly used a cell phone? (5) What proportion of the time did you use a hands-free device when you regularly used a cell phone? (6) On average, how

Table 2
Associations between cell phone use and thyroid cancer risk according to SNP variants that had an P < 0.01 for interaction with cell phone use.

Gene	SNP	Cell phone non-user			Cell phone user			P value for interaction[b]	Q value for interaction[c]
		Case	Control	OR[a] (95% CI)	Case	Control	OR[a] (95% CI)		
PAK6	rs11070256								
	AA	72	59	1.00	211	227	0.66 (0.39, 1.12)		
	AC/CC	23	53	1.00	133	125	2.36 (1.30, 4.30)	0.0008	0.0497
MDM2	rs1695147								
	AA	72	69	1.00	212	245	0.76 (0.50, 1.15)		
	AC/CC	23	43	1.00	131	106	2.52 (1.30, 4.90)	0.0027	0.0497
HDAC4	rs6732673								
	TT	46	33	1.00	115	127	0.62 (0.34, 1.14)		
	TC/CC	48	80	1.00	226	224	1.59 (1.01, 2.49)	0.0026	0.0497
HDAC4	rs1063639								
	GG	27	14	1.00	80	86	0.35 (0.11, 1.08)		
	GA/AA	69	98	1.00	264	264	1.46 (0.98, 2.18)	0.0022	0.0497
HDAC4	rs843458								
	AA	48	73	1.00	238	222	1.60 (0.96, 2.67)		
	AC/CC	47	40	1.00	105	130	0.65 (0.37, 1.15)	0.0072	0.0719
GATA4	rs3757949								
	GG	46	78	1.00	204	191	1.70 (0.98, 2.95)		
	GC/CC	47	35	1.00	137	158	0.62 (0.35, 1.09)	0.0066	0.0719
UBE2V1	rs6125888								
	TT	71	100	1.00	274	265	1.41 (0.95, 2.08)		
	TG/GG	24	13	1.00	69	86	0.39 (0.14, 1.08)	0.0077	0.0719
LINC00336	rs396746								
	AA	82	82	1.00	251	275	0.87 (0.59, 1.30)		
	AC/CC	13	31	1.00	93	77	2.53 (1.13, 5.65)	0.0084	0.0719
DACT2	rs12204529								
	CC	73	72	1.00	239	255	0.76 (0.50, 1.17)		
	CG/GG	22	40	1.00	104	97	2.62 (1.33, 5.17)	0.0025	0.0497
DACT2	rs3800537								
	AA	76	75	1.00	248	257	0.81 (0.53, 1.22)		
	AG/GG	19	38	1.00	96	95	2.64 (1.30, 5.36)	0.0046	0.0705

[a] Adjusted for age (continuous), sex (male, female), education (< college, college, > college), family history of thyroid cancer (yes, no), alcohol consumption (yes, no), body mass index (BMI, < 25, 25–29.9, ≥30), and previous benign thyroid diseases (yes, no).
[b] Interaction between cell phone use and SNP variants.
[c] Q values are adaptive P values that control for the positive false discovery rate.

many phone calls did you make or receive per day? (7) On average, how many hours per day did you use a cell phone? If a participant answered "Yes" to question (1), he/she was defined as a "cell phone user" and otherwise a "cell phone non-user". Information on cordless phone use was not collected in our study. Phone use hours per day, phone calls per day and phone use years were calculated from these variables. These variables were categorized into two halves based on the median values.

2.3. SNP genotyping

After undergoing the standardized interview process described previously, a total of 448 thyroid cancer cases (356 females and 84 males) and 465 controls (320 females and 145 males) donated samples of whole blood by venipuncture. 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 Illumina GoldenGate assay. Genotyping data were successfully obtained for 440 thyroid cancer cases and 465 controls. The GoldenGate assay included analysis of 878 SNPs in 177 gene regions involved in DNA repair. Quality control duplicate samples were also included in the genotyping platform. All duplicate samples yielded a concordance rate of ≥99%. The Hardy–Weinberg equilibrium (HWE) was assessed in controls for each SNP using a chi-squared test. SNPs with a P > 0.00001 from the chi-squared test were considered to be in HWE. Of the 878 SNPs tested, 55 SNPs were not in HWE and were excluded from the final analyses.

2.4. Statistical analysis

Unconditional logistic regression models were employed to evaluate the associations of SNP variants and cell phone use. Each SNP was categorized into two groups: common group (common homozygote) and variant group (heterozygote and rare homozygote combined). First, we evaluated the interaction between cell phone use and SNP variants by adding a cross-product term between SNP variant (common/variant) and cell phone use (user/non-user) as well as product terms between SNP variant and all covariates in the model, including cell phone use. SNPs with a P < 0.01 for interaction with cell phone use were selected. A significance level of 0.01 was used for the interaction term rather than a Bonferroni correction because the Bonferroni correction is usually conservative (Bender and Lange, 1999; Perneger, 1998). The Bonferroni correction was used for independent SNP test but rarely for interactions (Conneely and Boehnke, 2007). Currently, there is no consensus on the magnitude of significance level for interaction and a conservative P value may go against the precautionary principle. Additionally, Bonferroni correction fails to simultaneously address type 1 errors as well as the correlated nature in multiple tests (Conneely and Boehnke, 2007). In this case, a significance level of 0.01 can substantially reduce the false claims of significance and thus it is used for interaction. Further, we computed the Q values to control for positive false discovery rate (Storey, 2002; Storey et al., 2004). The Q value is proposed as an alternative to control for multiple tests and reduce false positive.

Second, we stratified the study population according to each selected SNP and re-run the regression to evaluate the associations of cell phone use in each stratum. Odds ratios (OR) and 95% confidence interval (95% CI) of cell phone use were calculated. Considering these

Table 3
Associations of cell phone use on small and large thyroid tumors in populations stratified by SNP variants.

Gene	SNP	Small tumor (≤10 mm)			Large tumor (> 10 mm)		
		Non-user	User		Non-user	User	
		Case[b]	Case[b]	OR[a] (95% CI)	Case[b]	Case[b]	OR[a] (95% CI)
PAK6	rs11070256						
	AA	33	99	0.75 (0.42, 1.32)	39	108	0.53 (0.27, 1.04)
	AC/CC	11	64	2.33 (1.06, 5.12)	12	69	2.48 (1.14, 5.37)
MDM2	rs1695147						
	AA	31	99	0.83 (0.49, 1.42)	41	111	0.69 (0.41, 1.15)
	AC/CC	13	63	2.29 (1.01, 5.19)	10	66	2.64 (1.10, 6.34)
HDAC4	rs6732673						
	TT	20	52	0.67 (0.31, 1.42)	26	62	0.55 (0.26, 1.13)
	TC/CC	24	109	1.64 (0.93, 2.89)	24	114	1.50 (0.85, 2.67)
HDAC4	rs1063639						
	GG	13	40	0.28 (0.08, 1.01)	14	39	0.39 (0.14, 1.04)
	GA/AA	31	123	1.68 (1.00, 2.82)	38	138	1.24 (0.76, 2.03)
HDAC4	rs843458						
	AA	25	112	1.51 (0.86, 2.68)	23	122	1.72 (0.95, 3.12)
	AC/CC	19	50	0.81 (0.40, 1.67)	28	55	0.56 (0.28, 1.10)
GATA4	rs3757949						
	GG	19	95	1.95 (0.97, 3.92)	27	105	1.45 (0.83, 2.54)
	GC/CC	24	66	0.61 (0.31, 1.22)	23	71	0.62 (0.31, 1.26)
UBE2V1	rs6125888						
	TT	34	127	1.39 (0.85, 2.28)	37	143	1.31 (0.81, 2.13)
	TG/GG	10	35	0.58 (0.19, 1.74)	14	34	0.37 (0.13, 1.04)
LINC00336	rs396746						
	AA	35	123	1.06 (0.64, 1.76)	47	126	0.73 (0.45, 1.17)
	AC/CC	9	40	1.42 (0.53, 3.78)	4	51	4.64 (1.40, 15.4)
DACT2	rs12204529						
	CC	36	113	0.79 (0.47, 1.34)	37	123	0.71 (0.42, 1.21)
	CG/GG	8	49	3.52 (1.37, 9.09)	14	54	1.99 (0.90, 4.41)
DACT2	rs3800537						
	AA	38	119	0.83 (0.50, 1.39)	38	126	0.75 (0.44, 1.27)
	AG/GG	6	44	4.10 (1.44, 11.70)	13	51	1.92 (0.85, 4.33)

[a] Adjusted for age (continuous), sex (male, female), education (< college, college, > college), family history of thyroid cancer (yes, no), alcohol consumption (yes, no), body mass index (BMI, < 25, 25–29.9, ≥30), and previous benign thyroid diseases (yes, no).
[b] The number of controls can be found in Table 2.

selected SNPs might be correlated, we used Haploview to analyze the linkage disequilibrium (LD) and haplotype among these SNPs (Barrett et al., 2005).

Because small and large thyroid cancers may represent different disease entities, the cases were further stratified by tumor size into small group (≤10 mm) and large group (> 10 mm). The analysis was performed again in the small and large groups, respectively. Additionally, cell phone users in this study were further stratified based on the median values of daily use hours, daily phone calls and phone use years, aiming to examine the impacts of cell phone use frequency and duration on thyroid cancer. A trend test was performed using stratum-specific median values.

All models were adjusted for age (continuous), sex (male, female), education (< college, college, > college), family history of thyroid cancer (yes, no), alcohol consumption (yes, no), body mass index (BMI, < 25, 25–29.9, ≥30), and previous benign thyroid diseases (yes, no). Additional adjustment for variables, including occupational radiation exposure, radiation treatment, race, smoking, family income, diagnostic radiation exposure, dietary intake of seafood and iodine intake did not substantially change (10%) the observed associations; therefore, these variables were not included in the final models. Less than 2% participants had missing values in education and BMI. Multiple imputation was used to generate missing values in covariates. 10 simulated datasets were generated and standard analytical procedures were performed for complete data as proposed (Yuan, 2010).

A significance level of 0.05 was used for statistical inferences other than interaction in this study. All P values in this study are two-sided. All analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, North Carolina, USA).

3. Results

Table 1 shows the distributions of selected demographic characteristics in cases and controls. The distribution was similar in this subset with blood samples and genotyping compared to those from the full study population (Luo et al., 2019). The independent association of cell phone use in this population can be found in Supplementary Table S1. Supplementary Table S2 lists all SNPs analyzed in this study grouped by genes. The associations between SNPs and thyroid cancer among this population were evaluated and the result can be found in another previous study (Sandler et al., 2018).

Table 2 shows the association between cell phone use and thyroid cancer risk stratified by SNP variants that were observed to have P < 0.01 for interaction. In total, there were 10 SNPs from 7 genes including *PAK6* (rs11070256), *MDM2* (rs1695147), *HDAC4* (rs6732673, rs1063639, rs843458), *GATA4* (rs3757949), *UBE2V1* (rs6125888), LINC00336 (rs396746) and *DACT2* (rs12204529, rs3800537). All these SNPs had a Q value less than 0.10, a threshold value that was widely used for interaction (Brouwers et al., 2013). None of these SNPs was independently associated with thyroid cancer in this study population (Supplementary Table S3). In the common SNP group, no association was observed. In the variant group, cell phone use was observed to be significantly associated with an increased risk of thyroid cancer for 6 SNPs: *PAK6* rs11070256 (OR: 2.36, 95% CI: 1.30–4.30), *MDM2* rs1695147 (OR: 2.52, 95% CI: 1.30–4.90), *HDAC4* rs6732673 (OR: 1.59, 95% CI: 1.01–2.49), *LINC00336 rs396746* (OR: 2.53, 95% CI: 1.13–5.65), *DACT2* rs12204529 (OR: 2.62, 95% CI: 1.33–5.17) and *DACT2* rs3800537 (OR: 2.64, 95% CI: 1.30–5.36). SNPs with an interaction P < 0.10 can be found in Supplementary Table S4.

Table 4
Associations of cell phone use daily use hour on the risk of thyroid cancer in populations stratified by SNP variants.

Gene	SNP	Cell phone non-user			Daily use hour						
					≤1 h/day			> 1 h/day			P value for trend
		Case	Control	OR[a] (95% CI)	Case	Control	OR[a] (95% CI)	Case	Control	OR[a] (95% CI)	
PAK6	rs11070256										
	AA	33	59	1.00	73	88	0.66 (0.38–1.14)	71	61	0.91 (0.51–1.62)	0.8862
	AC/CC	11	53	1.00	48	41	2.67 (1.31–5.42)	44	33	3.01 (1.44–6.30)	0.0041
MDM2	rs1695147										
	AA	31	69	1.00	71	92	0.78 (0.47–1.30)	73	60	1.18 (0.69–2.02)	0.5074
	AC/CC	13	43	1.00	50	37	2.76 (1.26–6.06)	41	34	2.86 (1.30–6.32)	0.0156
HDAC4	rs6732673										
	TT	20	33	1.00	43	48	0.61 (0.29–1.28)	40	32	1.08 (0.50–2.36)	0.7358
	TC/CC	24	80	1.00	76	80	1.63 (0.95–2.78)	74	62	2.00 (1.15–3.46)	0.0154
HDAC4	rs1063639										
	GG	13	14	1.00	27	35	0.25 (0.06–1.02)	26	20	0.54 (0.19–1.54)	0.3825
	GA/AA	31	98	1.00	94	94	1.63 (1.01–2.65)	89	73	1.94 (1.18–3.18)	0.0106
HDAC4	rs843458										
	AA	25	73	1.00	41	46	0.88 (0.44, 1.75)	26	36	0.85 (0.40, 1.81)	0.6847
	AC/CC	19	40	1.00	79	83	1.53 (0.89, 2.63)	89	58	2.28 (1.09, 4.77)	0.1024
GATA4	rs3757949										
	GG	19	78	1.00	48	64	0.62 (0.32, 1.20)	45	37	0.89 (0.43, 1.85)	0.2846
	GC/CC	24	35	1.00	71	63	1.90 (0.90, 4.01)	69	57	2.25 (1.28, 3.96)	0.0853
UBE2V1	rs6125888										
	TT	34	100	1.00	18	30	0.68 (0.42, 1.10)	21	25	0.45 (0.16, 1.23)	0.2951
	TG/GG	10	13	1.00	102	98	1.59 (0.95, 2.66)	94	69	1.89 (0.91, 3.93)	0.1231
LINC00336	rs396746										
	AA	35	82	1.00	83	105	0.80 (0.50–1.30)	87	73	1.23 (0.75–2.02)	0.3380
	AC/CC	9	31	1.00	38	24	4.15 (1.57–11.0)	28	21	3.31 (1.21–9.12)	0.1044
DACT2	rs12204529										
	CC	36	72	1.00	80	92	0.75 (0.45–1.25)	80	67	1.13 (0.67–1.89)	0.5611
	CG/GG	8	40	1.00	41	37	3.11 (1.38–7.00)	34	27	3.37 (1.42–8.03)	0.0074
DACT2	rs3800537										
	AA	38	75	1.00	82	91	0.82 (0.50–1.36)	83	68	1.17 (0.70–1.96)	0.4758
	AG/GG	6	38	1.00	39	38	2.93 (1.28–6.72)	32	26	3.38 (1.39–8.22)	0.0088

[a] Adjusted for age (continuous), sex (male, female), education (< college, college, > college), family history of thyroid cancer (yes, no), alcohol consumption (yes, no), body mass index (BMI, < 25, 25–29.9, ≥30), and previous benign thyroid diseases (yes, no).

Table 3 shows the results between cell phone use and thyroid cancer according to SNP variant groups when the cases are restricted to small or large tumors. In the common SNP group, no increased risk of thyroid cancer was observed, which is consistent with previous findings. In the variant group, the results were interesting. In small tumors, cell phone use was observed to be associated with increased risk of thyroid cancer for *PAK6* rs11070256 (OR: 2.33, 95% CI: 1.06–5.12), *MDM2* rs1695147 (OR: 2.29, 95% CI: 1.01–5.19), *HDAC4* rs1063639 (OR: 1.68, 95% CI: 1.00–2.82), *DACT2* rs12204529 (OR: 3.52, 95% CI: 1.37–9.09), and *DACT2* rs3800537 (OR: 4.10, 95% CI: 1.44–11.70). In large tumors, cell phone use was observed to be associated with increased risk of thyroid cancer for *PAK6* rs11070256 (OR: 2.48, 95% CI: 1.14–5.37), *MDM2* rs1695147 (OR: 2.64, 95% CI: 1.10–6.34), and *LINC00336* rs396746 (OR: 4.64, 95% CI: 1.40–15.4). The associations were observed in both small and large tumors for *PAK6* rs11070256 and *MDM2* rs1695147.

Table 4, 5 and 6 show the associations of cell phone use frequency (daily use hours and daily phone calls) and duration (cell phone use years), respectively. In the variant group, some trends were observed. As the daily use hour increased, the risk of thyroid cancer increased for *PAK6* rs11070256 (P_{trend} = 0.0041), *MDM2* rs1695147 (P_{trend} = 0.0156), *HDAC4* rs6732673 (P_{trend} = 0.0154), *HDAC4* rs1063639 (P_{trend} = 0.0106), *DACT2* rs12204529 (P_{trend} = 0.0074) and *DACT2* rs3800537 (P_{trend} = 0.0088). Similarly, as the number of daily phone call increased, the risk of thyroid cancer increased for *PAK6* rs11070256 (P_{trend} = 0.0016), *MDM2* rs1695147 (P_{trend} = 0.0076) and *LINC00336* rs396746 (P_{trend} = 0.0077). For the phone use duration, as the cell phone use year increased, the risk of thyroid cancer increased for *LINC00336* rs396746 (P_{trend} = 0.0340), *DACT2* rs12204529 (P_{trend} = 0.0099) and *DACT2* rs3800537 (P_{trend} = 0.0164).

In Haplotype analysis, no correlation was observed among the 10 selected SNPs, except for rs12204529 and rs3800537, which are both on gene *DACT2*.

4. Discussion

In this first study examining the combined influence of genetic susceptibility and cell phone use in relation to thyroid cancer, we observed interactions between cell phone use and SNP variants. In the variant groups for 6 SNPs, cell phone use was associated with a higher risk of thyroid cancer. The increased risk varied across tumor sizes depending on the SNPs: the increased risk was observed in both small and large thyroid tumors for *PAK6* rs11070256 and *MDM2* rs1695147, but only in small tumors for *HDAC4* rs1063639, *DACT2* rs12204529 and *DACT2* rs3800537, and only in large tumors for *LINC00336* rs396746. Furthermore, associations of increased thyroid cancer risk within variant groups were also observed for increasing cell phone use frequency and duration. Our results suggest that genetic susceptibilities modify the associations between cell phone use and risk of thyroid cancer and identify potential susceptible subgroups.

Proteins encoded by genes selected in this study play important roles in tumor suppression or growth. The PAK6 protein is a member of the p21-activated kinases family and associated with apoptosis. PAK6 can either promote tumor growth by inhibiting cell apoptosis (Chen et al., 2015), or suppress tumor growth through Ser-578 phosphorylation of the androgen receptor and Thr-158 and Sre-186 phosphorylation of the AR-E3 ligase MDM2 (Liu et al., 2013).

MDM2 protein is a key regulator of cell apoptosis. It controls p53 in an autoregulatory feedback loop (Oliner et al., 1993). Furthermore, p53 is a tumor suppressor and can regulate apoptosis and ferroptosis (Xie et al., 2017), an apoptosis-independent form of cell death. By repressing

Table 5
Associations of daily phone call on the risk of thyroid cancer in populations stratified by SNP variants.

Gene	SNP	Cell phone non-user			Daily phone call						
					≤5 calls/day			> 5 calls/day			P value for trend
		Case	Control	OR[a] (95% CI)	Case	Control	OR[a] (95% CI)	Case	Control	OR[a] (95% CI)	
PAK6	rs11070256										
	AA	33	59	1.00	123	128	0.70 (0.43–1.15)	74	85	0.58 (0.33–1.01)	0.0572
	AC/CC	11	53	1.00	73	83	1.82 (0.96–3.44)	51	40	3.12 (1.53–6.37)	0.0016
MDM2	rs1695147										
	AA	31	69	1.00	124	150	0.75 (0.48–1.18)	74	85	0.72 (0.43–1.20)	0.2249
	AC/CC	13	43	1.00	71	60	2.25 (1.11–4.57)	51	40	2.97 (1.38–6.40)	0.0076
HDAC4	rs6732673										
	TT	20	33	1.00	62	73	0.61 (0.31–1.17)	47	49	0.66 (0.32–1.36)	0.3208
	TC/CC	24	80	1.00	134	138	1.52 (0.94–2.44)	76	75	1.59 (0.93–2.74)	0.1102
HDAC4	rs1063639										
	GG	13	14	1.00	41	55	0.29 (0.12–0.69)	34	24	0.53 (0.20–1.41)	0.4384
	GA/AA	31	98	1.00	155	155	1.46 (0.95–2.24)	91	100	1.35 (0.84–2.18)	0.2638
HDAC4	rs843458										
	AA	25	73	1.00	61	73	0.69 (0.37, 1.27)	35	50	0.63 (0.31, 1.25)	0.7835
	AC/CC	19	40	1.00	135	138	1.47 (0.90, 2.38)	90	75	1.69 (0.98, 2.93)	0.3263
GATA4	rs3757949										
	GG	19	78	1.00	76	97	0.56 (0.30, 1.03)	51	54	0.65 (0.33, 1.29)	0.4335
	GC/CC	24	35	1.00	119	112	1.72 (1.05, 2.81)	73	70	1.67 (0.97, 2.89)	0.6795
UBE2V1	rs6125888										
	TT	34	100	1.00	39	47	0.46 (0.19, 1.11)	25	35	0.45 (0.18, 1.13)	0.8957
	TG/GG	10	13	1.00	157	163	1.34 (0.88, 2.04)	100	90	1.52 (0.95, 2.43)	0.3572
LINC00336	rs396746										
	AA	35	82	1.00	144	163	0.83 (0.55–1.27)	88	102	0.83 (0.52–1.34)	0.4731
	AC/CC	9	31	1.00	52	48	2.43 (1.01–5.86)	37	23	3.81 (1.45–10.0)	0.0077
DACT2	rs12204529										
	CC	36	72	1.00	133	156	0.70 (0.44–1.10)	90	87	0.88 (0.53–1.46)	0.7812
	CG/GG	8	40	1.00	62	55	2.95 (1.43–6.08)	35	38	2.00 (0.89–4.49)	0.1301
DACT2	rs3800537										
	AA	38	75	1.00	141	157	0.75 (0.48–1.18)	90	88	0.91 (0.55–1.49)	0.8120
	AG/GG	6	38	1.00	55	54	2.97 (1.38–6.35)	35	37	2.07 (0.90–4.76)	0.1304

[a] Adjusted for age (continuous), sex (male, female), education (< college, college, > college), family history of thyroid cancer (yes, no), alcohol consumption (yes, no), body mass index (BMI, < 25, 25–29.9, ≥30), and previous benign thyroid diseases (yes, no). s.

p53 (Boyd et al., 2000), MDM2 can promote tumor growth.

HDAC4 protein promotes deacetylation of histone and non-histone proteins, leading to chromatin condensation and transcriptional repression (Glozak and Seto, 2007). HDAC4 upregulation has been reported to promote cancer in many studies (Colarossi et al., 2014) and its inhibitors have also been reported to suppress tumor growth (Ahn et al., 2012).

GATA4 was selected for interaction though no significant association with cell phone use was observed in *GATA4* variant group. *GATA4* can activate the transcription factor NF-κB to initiate the senescence-associated secretory phenotype, a pro-inflammatory response linked to tumor promotion (Kang et al., 2015). It has been reported to promote ovarian tumors and testicular tumors.

UBE2V1 is also selected in the study but no significant association was observed in the variant group. *UBE2V1* mediates degradation of Sirt1 by ubiquitination, inhibiting histone H4 lysine 16 acetylation, and then epigenetically suppresses autophagy gene expression and promotes cancer metastasis (Shen et al., 2018). Meanwhile, it has also been reported to suppress differentiation of carcinoma cell lines by inhibiting CDK1 then altering cell cycle distribution (Sancho et al., 1998).

LINC00336 is under-investigated and its relevant molecular pathways are unknown. *LINC00*336 has been observed to be associated with ferroptosis in a recent study. In lung cancer, overexpression of *LINC00336* inhibits ferroptosis and hence promotes tumor growth (Wang, 2019).

DACT2 protein is regulated by promoter region hypermethylation and serves as a tumor suppressor in various cancers including thyroid cancer (Zhao et al., 2014), through intervention in the Wnt and/or TGF-β signaling pathways (Hou et al., 2013).

We observed significant associations between cell phone use and thyroid cancer in variant groups for some SNPs, though none of the SNPs are involved in gene editing. SNP rs1063639 is a synonymous variant and the other SNPs are within introns. However, genetic variants within introns can also be correlated with variants within exons or other regions that directly affect gene expression. In this study, except for SNPs in gene *HDAC4*, other SNPs are highly correlated (LD $r^2 > 0.90$) with at least one SNP in functional genetic regions within a window size of 500,000 bases (Table S5; Correlations were calculated using Ensembl (Zerbino et al., 2018)). Moreover, SNPs within introns might affect RNA splicing patterns and thus downregulate or upregulate key protein products (Chorev and Carmel, 2012). Overall, though SNPs selected in this study are within introns, they may still imply possible genetic interactions with environmental factors.

When interpreting the study findings, potential limitations must be considered. First, we used a significance level of 0.01 for interaction rather than the conservative Bonferroni correction. However, we used the Q value to control for false discovery rate. All selected SNPs in this study had a Q value less than 0.10, a threshold value that was widely used for interaction (Brouwers et al., 2013), suggesting one false positive be expected in this study. Therefore, false positive is not a major concern in this study. A strong significance test should lie on the biological plausibility and reproduction of our observations in independent cohorts. Given the public health importance, we call for more studies to continue the investigation on the interaction between cell phone use and genetic variants. Second, cell phone use was assessed using questionnaires in this study and thus the exposure classification and recall bias cannot be ruled out. As discussed in the previous article (Luo et al., 2019), there was no evidence linking cell phone use and thyroid cancer that could have influenced participant's risk perception. Additionally, increased risks were only observed in the variant group. If the increased

Table 6
Associations of cell phone use year on the risk of thyroid cancer in populations stratified by SNP variants.

Gene	SNP	Cell phone non-user			Cell phone use year						
					≤13 years			> 13 years			P value for trend
		Case	Control	OR[a] (95% CI)	Case	Control	OR[a] (95% CI)	Case	Control	OR[a] (95% CI)	
PAK6	rs11070256										
	AA	33	59	1.00	131	144	0.62 (0.38–1.01)	76	81	0.71 (0.42–1.21)	0.2982
	AC/CC	11	53	1.00	81	71	2.49 (1.32–4.71)	52	53	2.23 (1.12–4.43)	0.0975
MDM2	rs1695147										
	AA	31	69	1.00	131	154	0.73 (0.46–1.14)	80	90	0.81 (0.49–1.33)	0.4506
	AC/CC	13	43	1.00	81	60	2.77 (1.37–5.59)	47	44	2.19 (1.02–4.69)	0.0870
HDAC4	rs6732673										
	TT	20	33	1.00	69	77	0.56 (0.29–1.08)	44	48	0.70 (0.34–1.42)	0.3820
	TC/CC	24	80	1.00	142	137	1.60 (1.00–2.56)	82	86	1.57 (0.93–2.65)	0.1239
HDAC4	rs1063639										
	GG	13	14	1.00	47	52	0.30 (0.09–1.03)	33	34	0.44 (0.17–1.10)	0.1946
	GA/AA	31	98	1.00	165	162	1.48 (0.97–2.27)	95	99	1.41 (0.88–2.25)	0.1919
HDAC4	rs843458										
	AA	25	73	1.00	65	77	0.64 (0.35, 1.17)	40	53	0.67 (0.34, 1.33)	0.5375
	AC/CC	19	40	1.00	146	138	1.55 (0.95, 2.51)	88	81	1.70 (0.91, 3.18)	0.2004
GATA4	rs3757949										
	GG	19	78	1.00	79	95	0.55 (0.30, 1.01)	57	62	0.73 (0.38, 1.40)	0.4582
	GC/CC	24	35	1.00	132	117	1.64 (0.85, 3.16)	69	72	1.50 (0.87, 2.59)	0.3257
UBE2V1	rs6125888										
	TT	34	100	1.00	44	53	0.41 (0.15, 1.12)	24	32	0.39 (0.13, 1.17)	0.5208
	TG/GG	10	13	1.00	167	162	1.36 (0.90, 2.07)	104	101	1.48 (0.94, 2.34)	0.1856
LINC00336	rs396746										
	AA	35	82	1.00	156	166	0.88 (0.58–1.34)	92	106	0.86 (0.54–1.37)	0.5480
	AC/CC	9	31	1.00	56	49	2.33 (1.00–5.41)	36	28	2.85 (1.14–7.12)	0.0340
DACT2	rs12204529										
	CC	36	72	1.00	149	152	0.77 (0.49–1.21)	87	100	0.76 (0.46–1.24)	0.3040
	CG/GG	8	40	1.00	62	63	2.42 (1.18–4.95)	41	34	2.95 (1.33–6.54)	0.0099
DACT2	rs3800537										
	AA	38	75	1.00	154	154	0.81 (0.52–1.26)	91	100	0.81 (0.50–1.31)	0.4289
	AG/GG	6	38	1.00	58	61	2.48 (1.18–5.21)	37	34	2.86 (1.25–6.56)	0.0164

[a] Adjusted for age (continuous), sex (male, female), education (< college, college, > college), family history of thyroid cancer (yes, no), alcohol consumption (yes, no), body mass index (BMI, < 25, 25–29.9, ≥30), and previous benign thyroid diseases (yes, no).

risks had been due to bias or chance, they should have been observed in the common SNP group as well. Overall, though we cannot completely rule out recall bias and exposure misclassification, they were likely to be non-differential and resulted in an underestimation of the true association.

This study was conducted between 2010 and 2011, when it was still possible to recruit enough cell phone non-users, which is a strength of this study. Most of these non-users were nearly 10 years older than users (mean age: 59.2 vs. 50.5). Today with the popularity of cell phones, it is difficult to recruit enough non-users as in this study. It is also noteworthy that at that time, only a small proportion of people had smart phones. Therefore, if cell phone use increased the risk of thyroid cancer, it was possibly due to use of earlier generation of cell phones. The thyroid gland is exposed to more RFR emitted from smart phones compared to earlier generations of cell phone and thus smart phones may pose a greater risk. As a result, findings from this study warrant a further evaluation in future studies.

Given these findings in conjunction with the IARC classification and recent additional studies, we suggest a precautionary approach to cell phone use. Approaches for reducing cell phone radiation include the usage of hands-free devices, limited cell phone use among teenagers, and recommendation for low power cell phone mode. However, the associations observed in this study do not necessarily imply a complete restriction of cell phone use, especially given the important roles of cell phones in today's life. Further evaluation is needed.

In conclusion, this study found that cell phone use increased the risk of thyroid cancer when genetic variants were present within some genes. Our study suggests that pathways related to DNA repair may be involved in the cell phone-thyroid carcinogenesis. This study identifies potential susceptible subgroups. More studies are urgently needed to confirm our findings and explain the mechanisms behind the interactions between genetic variants and cell phone use.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgement

This research was supported by the American Cancer Society (ACS) grants RSGM-10-038-01-CCE and 127509-MRSG-15-147-01-CNE, the National Institutes of Health (NIH) grant R01ES020361 and CA204120, and the Ministry of Science and Technology of the People's Republic of China grant 2016YFC1302500.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2019.109013.

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