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Chernobyl Papillary Thyroid Carcinoma Reveals a Complex Interplay between Environmental Exposures and Lead Genetic Variants Predisposing to Thyroid Cancer

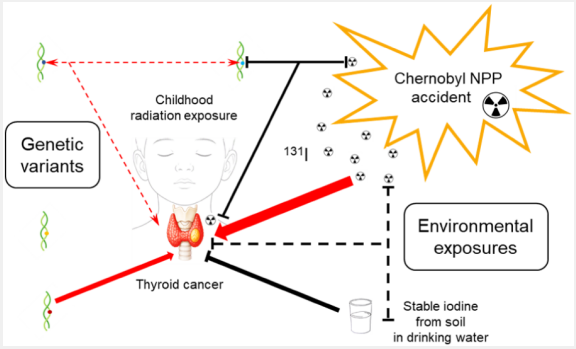
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ABSTRACT: Environmental exposures to radioactive and stable iodine and predisposing germline genetic variants contribute to the development of papillary thyroid carcinoma (PTC) after the Chernobyl accident, but their joint effects and interaction effects remain unknown. A retrospective observational case-control study enrolled 945 PTC patients and 1040 healthy control individuals from Belarus aged 0−18 years old at the time of exposure. Clinicopathological data, individual radiation doses to the thyroid, extent of stable iodine consumption, and genotypes for six predisposing genetic variants were used in the multiplicative and additive statistical models to address the individual environmental (E) and genetic factor (G) effects, and those of E×E, G×G, and G×E interactions. The radiation dose and soil iodine level were statistically significantly associated with PTC and displayed a negative interaction. Out of six, four genetic variants displayed significant association signals with a positive interaction between two of them. Importantly, one of these variants negatively interacts with the radiation dose. The soil iodine level did not interact with genetic components. The impact of radiation exposure was stronger than that of genetic variants. The findings show that environmental and genetic factors demonstrate complex nonindependent effects on the development of thyroid cancer after childhood radiation exposure and point at the absence of radiation risk augmentation by the major cancer-associated genetic variants. These observations can be used for radiation risk communication with the public.



INTRODUCTION

This year marks the 40th anniversary of the Chernobyl (Chornobyl) accident, the worst technogenic catastrophe of the 20th century involving radiation. An estimated total of 1.3×10^{19} Bq of radioactivity had been released to the environment, with ^{131}I accounting for 1.76×10^{18} Bq.[1] Through fallout, radioisotopes have affected territories in Ukraine, Belarus, and Russia with more than 5 million population, including ∼1.2 million children and adolescents.[2] Through the radioiodine incorporation into food chains, residents of the contaminated territories were internally exposed, with the highest thyroid doses observed in children and adolescents, reaching up to several tens of Gray (Gy) in some individuals. After a four- to five-year period of latency, an increase in childhood thyroid cancer incidence was initially reported in Belarus and then in Ukraine.[3,4] Radiation epidemiology studies provided evidence for a causative role of ^{131}I in this increase and analyzed the dose−response,[5−10] principally for the papillary thyroid carcinoma (PTC) that represented ∼95% of all histological types of thyroid cancer.[11]

Risk factors for thyroid cancer include a number of modifiable and nonmodifiable traits of different natures. Radiation, either external or internal, is the best-established environmental risk factor, whose effect is particularly pronounced if exposure takes place at a young age. The effects of thyroid exposure from ingested or inhaled radioiodine can be modulated by stable iodine intake in the Chernobyl-affected areas.[5,10] Higher stable iodine intake, in general, decreases chances for developing cancer through stoichiometric competition with radioactive iodine since their uptake by the thyroid is biochemically

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equivalent. In the absence of an iodine-rich diet, of pharmacological iodine supplementation, or of fortified foods (conditions common for Belarus at the time of the Chernobyl accident), drinking water is the major source of iodine. In turn, soil at a given inland location is the primary reservoir of environmental iodine, and soil-water exchange determines the amount of iodine in groundwater. Measurements of urinary iodine excretion in Belarus in the early and late 1990s showed mild to severe iodine deficiency in children.[12,13]

Evidence also connects thyroid cancer to predisposed germline genetic variants. With the development of high-throughput genomic technologies and an increasing sample size, the number of cancer-associated variants continues to grow. A recent Global Biobank Meta-analysis Initiative (GBMI) study reported 153 single-nucleotide variants (SNVs) associated with thyroid cancer on the genome-wide scale in populations of European ancestry.[14] Since the first genome-wide association study (GWAS) of thyroid cancer in 2009,[15] the highest statistical significance of association signals from four chromosomal loci (chr:2q35, 8p12, 9q22.33, 14q13.3) has been replicated in and backed by a wealth of research.[14,16−21] The only GWAS of radiation-related thyroid cancer published to date has also reported one variant on chr:9q22.33 common with that discovered in the GWAS in nonexposed individuals.[22] While SNV identifiers may vary across studies depending on genotyping platform and research methodology, cancer risk-conferring signals will undoubtedly be expected from other variants that are in linkage disequilibrium with and are mapped to the same chromosomal loci as those reported. Thus, we selected six common SNVs from the four chromosomal loci that displayed a strong association with thyroid cancer in published studies[15,23−31] or our preliminary genotyping results.[22,32−35]

Nonheritable thyroid cancer, similar to other complex diseases, is thought to be driven by an intricate interplay between various environmental, behavioral, and genetic factors. Internal irradiation is a causal environmental factor of the Chernobyl thyroid cancer (95% were PTCs[31]), whose effect can be modified by stable iodine. On the other hand, genetic association studies have identified the variants predisposing to thyroid cancer, principally in nonexposed populations (in which about 90% of tumors are also PTCs).[36] The genetic variants explored in this work are not radiation-related, and therefore, they are likely to contribute to thyroid cancer through distinct pathways, which ultimately converge with radiation response on a common phenotype. At present, little if anything is known about whether the association between the environmental exposures and thyroid cancer may differ according to predisposition to thyroid cancer genotype. Addressing this gap could help identify subpopulations particularly vulnerable to environmental insults. This study was designed to determine the individual effects of environmental exposures and of predisposing genetic variants, their joint effect, and interactions in a group of patients with PTC and healthy individuals from Belarus exposed to radiation after the Chernobyl accident.

MATERIALS AND METHODS

Patients and a Control Group

A total of 945 patients (683 females and 262 males; here and hereafter, sex assigned at birth is referred to as sex) diagnosed with PTC in 1988−2010 were recruited. Inclusion criteria for cases were: (i) age at the time of the Chernobyl accident of 0−18 years old, including *in utero*, in April−June 1986, (ii) residence in radiocontaminated regions, and (iii) histologically verified diagnosis of PTC. Demographic and diagnostic information was retrieved from the Minsk City Clinical Oncological Center (MCCOC, Minsk, Belarus) database. Morphological diagnosis of PTC was established by MCCOC pathologists and then verified for the purposes of this study according to the fifth edition of WHO Classification of Tumors.[37]

As a population control, 1040 healthy individuals (773 females and 267 males) were enrolled. Inclusion criteria for control subjects were: (i) age at the time of the accident between 0 and 18 years old, including *in utero*, in April−June 1986, (ii) residence in radiocontaminated regions, (iii) no thyroid abnormalities on neck ultrasound, and euthyroid state, including thyroid-stimulating hormone (TSH, 0.4−4.5 μU/ml), free thyroxine (FT4, 0.8−1.8 ng/dL), and antithyroid peroxidase antibody (TPOAb, 0−34 IU/mL) levels within the reference ranges at the time of sampling. Demographic and residential information was obtained by personal inquiry.

Blood samples from patient and control subjects were collected from February 2006 to March 2021. Patients who agreed to participate in the study were sampled during health checkups. Blood samples from the control subjects who met demographic and sonographic criteria and agreed to participate were collected during the periodic thyroid ultrasound screening programs in the Brest and Gomel regions and in Minsk city. Median age at sampling for cases was 27.2 years (range 13.1−53.3), and 28.5 years (range 18.7−41.4) for controls. Informed consent was obtained from all participants with the ability to opt out. The study complied with the Declaration of Helsinki, and the protocol of the study was approved by the ethics committees of participating institutions.

Environmental Exposures

For each study participant, individual thyroid doses due to ^{131}I intake were reconstructed using a validated ecological−biokinetic dosimetry system.[38] The methodology combined information on ^{131}I ground deposition density from environmental radiation monitoring databases, direct ^{131}I thyroid radioactivity measurements (when available), residential history during the exposure period, dietary information, and age-dependent thyroid biokinetics.[39−42] Environmental transfer and age-specific biokinetic models were used to reconstruct ^{131}I transport through the food chain to estimate the time-dependent ^{131}I thyroid activity, explicitly incorporating radioactive decay and temporal changes in the environmental contamination into the calculations.

Soil iodine content (in mg/kg of soil) at the place of residence of study participants in April−June 1986 was derived from the archive work[43] and formalized into five categories from 1 (the lowest) to 5 (the highest iodine content) as described before.[44]

DNA Extraction and Genotyping

DNA was extracted from peripheral blood mononuclear cells with a Puregene kit (Qiagen, Germantown, MD).[22] DNA concentration was measured with a Nanodrop 1000 spectrophotometer (Thermo Scientific, Waltham, MA), and samples were stored at −80 °C until use.

Six genetic variants, rs965513 and rs1867277 (chr:9q22.33), rs944289 (chr:14q13.3), rs2439302 (chr:8p12), and rs966423 and rs11693806 (chr:2q35), were selected for this study based on evidence of their association with thyroid cancer from our and other group reports (Supplementary Figure S1).[15,22−35] Genome scans of 401 PTC and 172 control specimens were performed with an Illumina Human610-Quad BeadChip on a BeadStation 500G Genotyping System, expanding our previous dataset.[22] The remaining samples were genotyped with five predesigned custom ABI TaqMan SNP assays and one custom TaqMan SNP assay (Supplementary Tables S1 and S2) in a LightCycler 480 (Roche, Indianapolis, IN) using TaqMan Genotyping Master mix (all reagents from Applied Biosystems by Thermo Fisher Scientific, Vilnius, Lithuania) and 10 ng genomic DNA per 10 μL reaction.

Statistical Analysis

The Fisher exact or Fisher−Freeman−Halton test for categorical variables and the Wilcoxon−Mann−Whitney test for continuous variables were applied. Individual radiation doses to the thyroid were log10-transformed and mean-centered prior to the regression analysis. Logistic (multiplicative scale) and linear (additive scale) regression

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models were adjusted for age at radiation exposure and sex unless otherwise specified. Minimization of the Akaike information criterion (AIC) was used for optimization of the multivariable model specification. The additive interaction was evaluated using the relative excess risk due to interaction (RERI) metrics derived from adjusted coefficient estimates from multivariable logistic regression models and/or from the regression coefficients (b) from the linear models. Internal validation of the regression models and RERI was performed using 1000 bootstrap replications, and the stability of estimates was determined by using the distribution-free approach. Statistical power, Hardy–Weinberg equilibrium, and pairwise correlations between the genetic variants were computed with the *genpwr*, *HardyWeinberg*, and *LDlinkR* packages in R 4.6.1, respectively. Other calculations were performed by using SAS 9.4. p-values of <0.05 were considered indicative of statistical significance. Statistical modeling and results reporting were in line with the STROBE (strengthening the reporting of observational studies in epidemiology) guidelines.

RESULTS

Baseline Characteristics of the Participants

The distributions of PTC patients and control subjects by sex (F/M ratio, 2.6:1 and 2.9:1, respectively) and by age at exposure (median 4.4 and 5.5 years old, respectively) did not differ significantly (p = 0.310 and p = 0.850, respectively, Table 1).

Table 1. Descriptive Characteristics of PTC Patients and Control Subjects

Parameters	Cases, n = 945	Controls, n = 1040	p-value
	n (%) or median (range; P25–P75)		
Sex[a] F/M (%M)	683/262 (27.7%)	773/267 (25.7%)	0.310
F:M ratio	2.6:1	2.9:1	
Age at exposure, years	4.4 (*in utero* – 18.2; 1.6–10.0)	5.5 (*in utero* – 18.3; 1.0–11.3)	0.850
Age at diagnosis, years	17.7 (4.2–41.3; 13.2–26.3)	NA[b]	NA
Period of latency, years	13.4 (1.8–24.5; 9.5–18.4)	NA	NA
Region of residence at exposure			3.71×10^{-152}
Brest	298 (31.5%)	911 (87.6%)	
Gomel	550 (58.2%)	108 (10.4%)	
Grodno	15 (1.6%)	0	
Minsk	42 (4.4%)	8 (0.8%)	
Mogilev	32 (3.4%)	12 (1.2%)	
Vitebsk	5 (0.5%)	0	
other	3 (0.3%)	1 (0.1%)	
Evacuated	36 (3.8%)	0	1.74×10^{-12}
Radiation dose to the thyroid, mGy	149 (1–8976; 46–325)	46 (0.002–1291; 18–132)	4.86×10^{-44}
Radiation dose quartiles			1.77×10^{-39}
(1) 0.002–25	137 (14.5%)	357 (34.3%)	
(2) 25–81	192 (20.3%)	305 (29.3%)	
(3) 81–225	294 (31.1%)	202 (19.4%)	
(4) 225–9000	322 (34.1%)	176 (16.9%)	
Soil iodine content, mg/kg	n = 942	n = 1039	4.13×10^{-74}
(1) 0.56–0.64	270 (28.7%)	271 (26.1%)	
(2) 0.87–0.94	148 (15.7%)	218 (21.0%)	
(3) 1.30–1.39	249 (26.4%)	11 (1.1%)	
(4) 1.60–4.20	104 (11.0%)	328 (31.6%)	
(5) 5.00–18.20	171 (18.2%)	211 (20.3%)	

[a]Here and hereafter, sex is assigned at birth. [b]NA: not available.

Consistently, neither sex adjusted for age at exposure (OR or b (95% CI), OR = 0.919 (0.752–1.123), b = −0.021 (−0.071–0.029)) nor age at exposure adjusted for sex (OR = 0.987 (0.971–1.003), b = −0.003 (−0.007–0.001)) were associated with PTC. However, a chance of developing PTC in individuals exposed at the age below 10 was statistically significantly elevated (OR = 1.350 (1.107–1.647), b = 0.075 (0.026–0.123)), underscoring the notion that younger age at exposure to radiation is associated with higher cancer risk. Diagnosis of PTC was established at a relatively young patient age (median 17.7, range 4.2–41.3 years old) after a median period of latency of 13.4 years (range 1.8–24.5 years).

The distributions of patients and control subjects by place of residence at the time of the Chernobyl accident were not symmetric: more than half of patients (58.2%) were from the Gomel region, the most radiocontaminated area of the country, whereas the majority of controls (87.6%) were residents of the less contaminated Brest region (Table 1). In line with this observation, thyroid radiation doses were significantly higher in patients (median 149 mGy, range 1–9000 mGy) than in controls (median 46 mGy, range 0.002–1290 mGy) (Supplementary Figure S2A). Soil iodine level distribution at the places of residence was also statistically significantly different between patients and controls (Supplementary Figure S2B).

Association of Environmental Exposures and Their Interaction with PTC

Radiation dose to the thyroid was strongly associated with thyroid cancer (Table 2) when tested on a log10 scale (OR = 2.868 (2.450–3.357) in the multiplicative and b = 0.221 (0.194–0.247) in the additive models or by quartiles. Expectedly, each increment in dose quartile resulted in a monotonic increase of the effect size when the lowest quartile was used as a reference. Among these approaches to dose effect estimation, the log10 scale model demonstrated the best performance in terms of the AIC value, the amount of information gained, or the coefficient of determination.

Soil iodine content was negatively associated with PTC (Table 2) when tested by separate iodine level categories (OR = 0.896 (0.845–0.951), b = −0.027 (−0.042–−0.013)) or by comparing the effect of the combined categories with the higher iodine content (i.e., 4–5) to that with the lower (i.e., 1–3) (OR = 0.380 (0.315–0.459), b = −0.235 (−0.278–−0.192)). The latter models performed better and were used in further analysis.

Models of joint environmental factor effect on PTC demonstrated statistical significance of both radiation dose (OR = 2.610 (2.264–3.062), b = 0.202 (0.170–0.233)) and soil iodine content categories (OR = 0.464 (0.381–0.564), b = −0.174 (−0.217–−0.130)).

To test the possibility of radiation effect modification by soil iodine level, we introduced an interaction term (E×E) between these variables to the previous model and found that the interaction was negative (OR = 0.707 (0.518–0.965)), $p_{heterogeneity}$ = 0.029 (Table 2, Figure 1A)) on a multiplicative scale. The model of joint environmental factor effect with an interaction term resulted in an ∼17.5% information gain and showed that while radiation exposure significantly increased the odds of developing thyroid cancer, this effect was attenuated by a factor of ∼0.71 if participants lived in the areas with the higher (≥1.60 mg/kg) soil iodine content as compared to those from the areas with the lower (≤1.39 mg/kg) iodine content. The relative excess risk due to interaction (RERI) and its 95% distribution-free confidence interval (−1.54 (−1.57–−1.52))

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Table 2. Association of Environmental Exposures with Radiation-Related PTC

Parameters	OR or *b* (95% CI)[a]	*p*-value	MRRsq or Rsq[b]	AIC[c]
Radiation dose				
Multiplicative models				
Radiation dose[d]	2.868 (2.450−3.357)	2.75×10^{-39}	0.1345	2544.32
Radiation dose, quartiles	1.774 (1.624−1.938)	5.06×10^{-37}	0.1149	2576.48
Radiation dose by quartiles			0.1192	2573.51
1	ref			
2	1.664 (1.273−2.176)	1.97×10^{-04}		
3	3.887 (2.970−5.086)	4.34×10^{-23}		
4	5.033 (3.805−6.656)	9.53×10^{-30}		
Additive models				
Radiation dose	0.221 (0.194−0.247)	1.63×10^{-57}	0.0971	2549.92
Radiation dose, quartiles	0.134 (0.115−0.152)	1.37×10^{-43}	0.0875	2578.14
Radiation dose by quartiles			0.0912	2574.41
1	ref			
2	0.110 (0.051−0.167)	2.23×10^{-04}		
3	0.319 (0.260−0.378)	1.36×10^{-25}		
4	0.378 (0.319−0.436)	6.51×10^{-35}		
Soil iodine content				
Multiplicative models				
Soil iodine categories	0.896 (0.845−0.951)	2.81×10^{-04}	0.0111	2732.97
Soil iodine categories 4−5 vs 1−3	0.380 (0.315−0.459)	2.53×10^{-24}	0.0725	2638.86
Additive models				
Soil iodine categories	−0.027 (−0.042−−0.013)	2.50×10^{-04}	0.0083	2732.90
Soil iodine categories 4−5 vs 1−3	−0.235 (−0.278−−0.192)	6.60×10^{-26}	0.0550	2638.73
Radiation dose + soil iodine categories				
Multiplicative model			0.1719	2478.26
Radiation dose	2.610 (2.264−3.062)	6.33×10^{-32}		
Soil iodine categories 4−5 vs 1−3	0.464 (0.381−0.564)	1.56×10^{-14}		
Additive model			0.1271	2481.21
Radiation dose	0.202 (0.170−0.233)	1.08×10^{-34}		
Soil iodine categories 4−5 vs 1−3	−0.174 (−0.217−−0.130)	7.62×10^{-15}		
Joint effect of environmental exposures with environment-environment interaction				
Multiplicative model			0.1747	2475.46
Radiation dose	3.092 (2.467−3.874)	1.06×10^{-22}		
Soil iodine categories 4−5 vs 1−3	0.469 (0.386−0.570)	3.29×10^{-14}		
Radiation dose × Soil iodine categories 4−5 vs 1−3	0.707 (0.518−0.965)	0.029		
Additive model			0.1300	2475.76
Radiation dose	0.237 (0.199−0.275)	1.63×10^{-36}		
Soil iodine categories 4−5 vs 1−3	−0.186 (−0.230−−0.143)	9.50×10^{-17}		
Radiation dose × Soil iodine categories 4−5 vs 1−3	−0.078 (−0.138−−0.019)	0.009		

[a]Odds ratio (OR) for the multiplicative models and the regression coefficient *b* for the additive models were adjusted for sex and age at exposure (95% confidence interval). [b]Max-rescaled R-square for the multiplicative models and the coefficient of determination for the additive models. [c]Akaike Information Criterion. [d]Here and hereafter in this table, radiation dose to the thyroid is given in mGy, log-transformed, and mean-centered.

attested to a smaller combined effect than expected from the sum of the individual effects of radiation exposure and soil iodine levels.

Concordant results were obtained in the additive model with the same predictors showing statistically significant main effects and a negative interaction (b = −0.078 (−0.138−−0.019), $p_{heterogeneity}$ = 0.009) between the two environmental exposures (Table 2, Figure 1B). The additive model explained 13% of the variance of the outcome and indicated the reduction of absolute risk of thyroid cancer associated with radiation exposure by 7.8 percentage points for study participants from the areas with the higher soil iodine content.

Both the multiplicative and additive models had stable regression coefficients (Supplementary Table S3).

Association of Genetic Variants and of Pairwise Gene−Gene Interactions with PTC

Statistical power to detect the association of the six selected genetic variants on a multiplicative scale was greater than 0.8 (Supplementary Table S4 and Figure S3). Descriptive characteristics of variants are presented in Supplementary Table S5. No deviations from Hardy−Weinberg equilibrium were detected. Except for the variants located on the same chromosomes (i.e., rs965513 and rs1867277 on chr:9q22.33, and rs966423 and rs11693806 on chr:2q35), all interchromosomal variant correlations were negligible. No heterogeneity in the distribution of genetic variants by regions of residence at the time of the accident was observed.

Four variants, rs965513 and rs1867277 (chr:9q22.33), rs944289 (chr:14q13.3), and rs2439302 (chr:8p12) displayed

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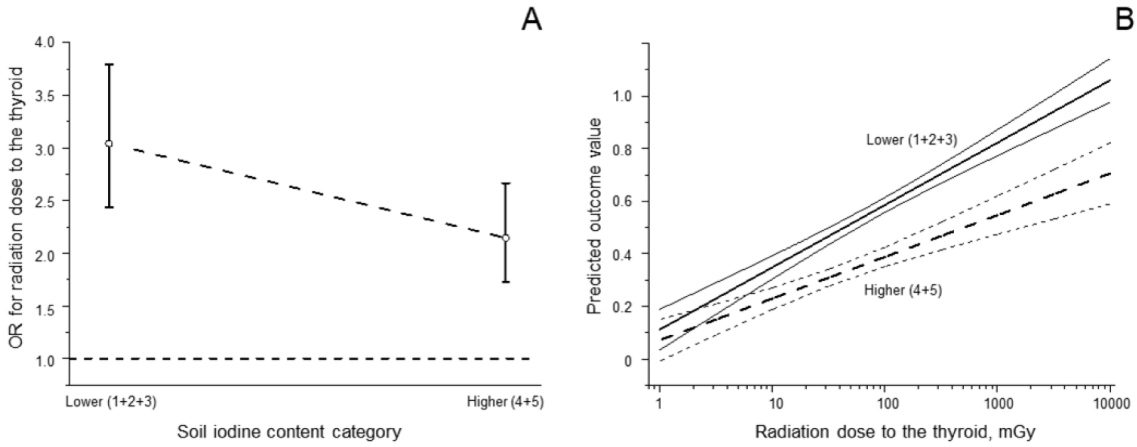


Figure 1. Negative interaction between radiation dose to the thyroid and the higher versus lower soil iodine content category. (A) Odds ratio for radiation dose to the thyroid at the lower and higher soil iodine categories in the multiplicative model. (B) Estimated in the additive model average value of the outcome (0 corresponds to "Control", 1 corresponds to "Case") for the higher (dashed line with 95% confidence interval) and lower (solid line with 95% confidence interval) soil iodine content categories at different radiation doses to the thyroid. In (B), note a steeper slope of the "lower" iodine content category line as compared to that for the "higher" category indicative of a significant interaction.

Table 3. Association of Genetic Variants with PTC

Variants	OR or *b* (95% CI)[a]	*p*-value	MRRSq or Rsq[b]	AIC[c]
Single-variant models				
Multiplicative models				
rs965513	1.601 (1.404–1.825)	2.07×10^{-12}	0.0361	2690.17
rs1867277	1.449 (1.276–1.645)	1.04×10^{-08}	0.0246	2705.09
rs944289	1.168 (1.029–1.327)	0.017	0.0062	2746.02
rs2439302	1.283 (1.130–1.458)	1.25×10^{-04}	0.0132	2690.77
rs966423	1.014 (0.893–1.150)	0.834	0.0026	2744.76
rs11693806	1.060 (0.914–1.229)	0.444	0.0038	2694.08
Additive models				
rs965513	0.115 (0.084–0.146)	6.37×10^{-13}	0.0271	2690.52
rs1867277	0.091 (0.060–0.122)	6.56×10^{-09}	0.0185	2705.28
rs944289	0.039 (0.007–0.071)	0.016	0.0046	2745.94
rs2439302	0.062 (0.030–0.093)	1.10×10^{-04}	0.0099	2690.77
rs966423	0.003 (−0.028–0.035)	0.829	0.0019	2744.74
rs11693806	0.015 (−0.022–0.051)	0.440	0.0029	2694.06
Multi-variant models				
Multiplicative model			0.0523	2626.53
rs965513	1.620 (1.418–1.850)	1.28×10^{-12}		
rs944289	1.182 (1.037–1.348)	0.013		
rs2439302	1.286 (1.129–1.464)	1.47×10^{-04}		
rs11693806	1.058 (0.910–1.231)	0.461		
Additive model			0.0393	2622.82
rs965513	0.115 (0.084–0.147)	5.58×10^{-13}		
rs944289	0.039 (0.007–0.070)	0.016		
rs2439302	0.059 (0.028–0.090)	1.82×10^{-04}		
rs11693806	0.013 (−0.024–0.050)	0.490		
Multi-variant models with gene–gene interaction				
Multiplicative model			0.0544	2625.33
rs965513	1.613 (1.412–1.844)	2.03×10^{-12}		
rs944289	1.005 (0.806–1.253)	0.966		
rs2439302	1.051 (0.815–1.357)	0.700		
rs11693806	1.055 (0.907–1.227)	0.489		
rs944289 × rs2439302	1.184 (0.984–1.425)	0.074		
Additive model			0.0409	2625.77
rs965513	0.115 (0.084–0.146)	5.60×10^{-13}		
rs944289	−0.002 (−0.055–0.051)	0.952		
rs2439302	0.008 (−0.054–0.069)	0.795		
rs11693806	0.013 (−0.024–0.049)	0.483		
rs944289 × rs2439302	0.043 (−0.001–0.087)	0.056		

[a]Odds ratio (OR) for the multiplicative models and the regression coefficient *b* for the additive models were adjusted for sex and age at exposure (95% confidence interval). [b]Max-rescaled R-square for the multiplicative models and the coefficient of determination for the additive models. [c]Akaike Information Criterion.

statistically significant association signals in the multiplicative and additive models, whereas rs966423 and rs11693806 (chr:2q35) did not (Table 3). The optimal multiplicative model of joint effects of genetic variants resulted in a ∼5.2% information gain, and the additive model explained 3.9% of the variance of the outcome. Even though the rs11693806

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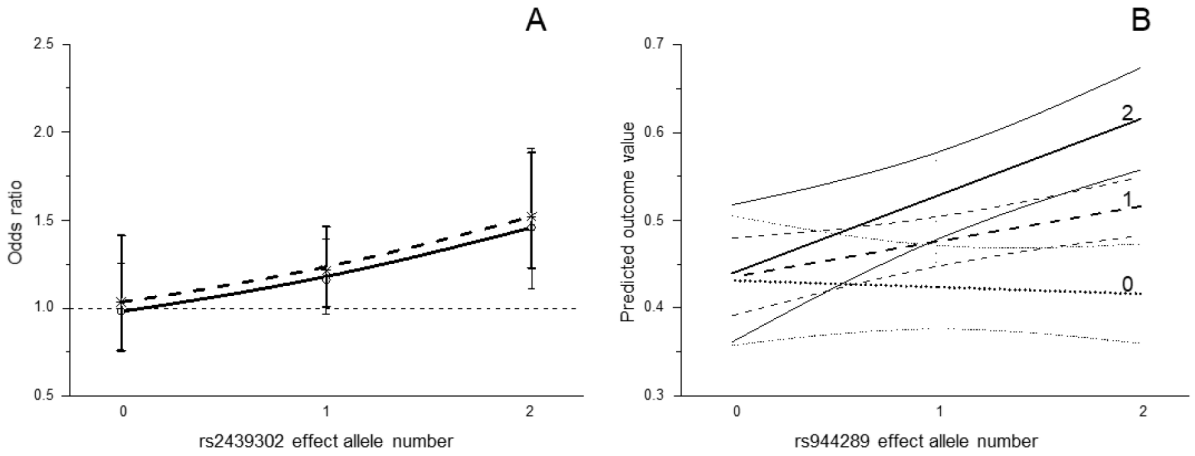


Figure 2. Positive pairwise interaction between rs944289 and rs2439302. (A) Odds ratio for rs944289 (circles) and rs2439302 (asterisks) at different numbers of the effect alleles of the interacting variant in the multiplicative model. Error bars represent the 95% confidence interval. Note the increasing effect of both variants with growing effect allele number of another variant. (B) Estimated in the additive model average value of the outcome (the higher, the greater chance of the "Case" prediction, the *Y*-axis) for different numbers of rs2439302 effect alleles (lines labeled "0" (dotted), "1" (dashed), and "2" (solid) with 95% confidence limits) at different numbers of rs944289 effect alleles (the *X*-axis). Note the increasing predicted value of the "Case" outcome for rs2439302 effect allele carriers (lines "1" and "2"), and a steeper slope of line "2" with increasing number of rs944289 effect alleles in contrast to rs2439302 effect allele noncarriers (line "0").

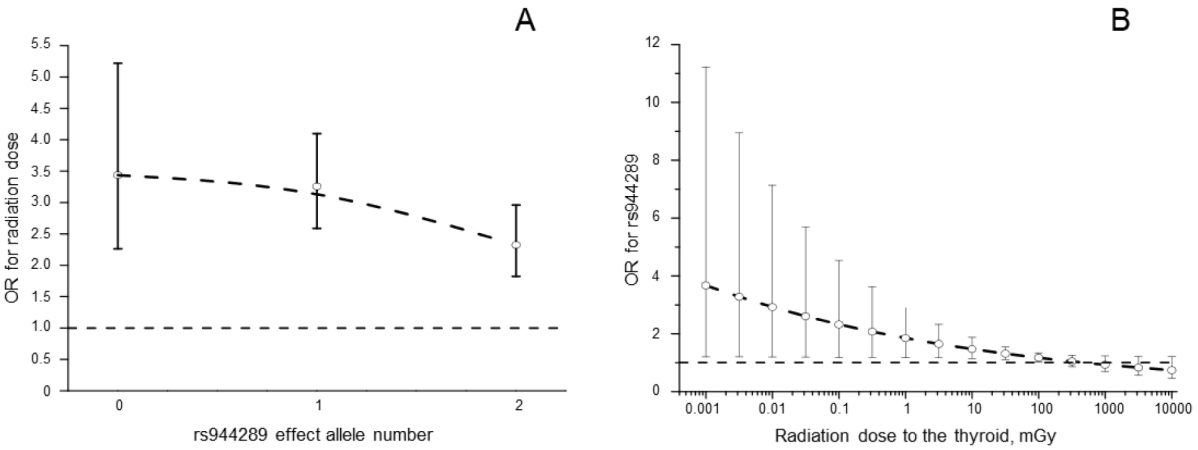


Figure 3. Negative gene−environment interaction between radiation dose to the thyroid and rs944289 in the multiplicative model. (A) Odds ratio for radiation dose at different numbers of rs944289 effect alleles, and (B) for rs944289 genotype at different radiation doses to the thyroid.

(chr:2q35) effect was not significant either in single-variant or multivariant models, its inclusion improved the multivariable model fit.

Tests for pairwise gene−gene (G×G) interaction revealed a positive epistatic effect for rs944289 (chr:14q13.3) and rs2439302 (chr:8p12) (OR = 1.218 (1.015−1.462), $p_{heterogeneity}$ = 0.034, Supplementary Table S6, Figure 2A) in the multiplicative model, and b = 0.048 (0.004−0.092), $p_{heterogeneity}$ = 0.034 in the additive model (Supplementary Table S6, Figure 2B). When this interaction was accounted for in the multivariable models, both types of models slightly improved, providing ∼5.4% of information gained and explaining ∼4.1% of the variance of the outcome, respectively, although the interaction terms did not reach formal statistical significance. The regression coefficients in the multivariable models were stable (Supplementary Table S7).

The multiplicative model suggested that each additional copy of the effect allele of rs944289 increased the per-effect allele odds ratio associated with rs2439302 by a factor of ∼1.2 and *vice versa*. The RERI value of 0.21 (0.21−0.22) confirmed that the combined effect of the two variants was higher than expected from the sum of their individual effects. The additive model suggested that each additional copy of the effect allele of rs944289 increased the per-allele effect of rs2439302 on absolute risk for thyroid cancer by 4.3 percentage points and *vice versa*.

Gene−Environment Interactions

One variant, rs944289 (chr:14q13.3), negatively interacted with radiation dose to the thyroid (OR = 0.795 (0.709−0.893), $p_{heterogeneity}$ = 0.047 (G×E interaction, Supplementary Table S8) in the multiplicative model. In the additive model, the interaction term also had a negative direction (b = −0.030 (−0.073−0.013), $p_{heterogeneity}$ = 0.169) but was not statistically significant. The regression coefficients were stable (Supplementary Table S9).

The multiplicative model resulted in 14.1% of information gained and demonstrated that for each additional copy of the rs944289 risk allele, the radiation exposure effect on the odds of developing thyroid cancer was reduced by a factor of ∼0.8. Since

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gene−environment interaction can also be interpreted as an effect of radiation exposure on rs944289 genotype-associated odds of thyroid cancer, it is plausible to expect a decrease of the rs944289 genotype effect by a factor of ∼0.8 per one-unit increase in radiation dose parameter (due to log-transformation, one dose unit corresponds to a 10-fold dose change). The RERI value of −0.36 (−0.38−−0.32) indicated that the combined effect of radiation exposure and rs944289 was lower than expected from the sum of their individual effects. Interestingly, plotting of the interaction showed that while the declining radiation dose effect remained statistically significant at any number of rs944289 risk alleles (Figure 3A), the effect of the genetic variant became statistically nonsignificant at radiation doses exceeding ∼120 mGy (Figure 3B).

None of the variants interacted with exposures to the higher versus lower categories of soil iodine content in either type of model (Supplementary Table S10).

Joint Effect of Environmental Exposures and Genetic Variants with Environment−Environment, Gene−Gene, and Gene−Environment Interactions

We created multivariable regression models combining the environmental and genetic factors and their interaction terms (Table 4). The optimal multiplicative and additive models were in good agreement and included radiation dose, soil iodine content categories, rs965513, rs944289, rs2439302, rs11693806, and interaction terms between radiation dose and soil iodine (E×E interaction), rs944289 and rs2439302 (G×G interaction), and rs944289 and radiation dose (G×E interaction). In the descending order, radiation exposure had the strongest effect (OR or *b*), followed by those of soil iodine and of rs965513 (chr:9q22.33).

The interaction between radiation exposure and soil iodine was concordantly negative in both models, not reaching statistical significance on the multiplicative (p = 0.083) but displaying such on the additive (p = 0.029) scale. The multiplicative model suggested a reduction of radiation exposure-associated cancer odds by a factor of ∼0.75, while the additive model demonstrated a 6.2% decrease of the absolute risk for thyroid cancer associated with radiation exposure for the participants from areas with the higher soil iodine levels as compared to those from areas with the lower iodine levels.

Gene−gene interaction between rs944289 (chr:14q13.3) and rs2439302 (chr:8p12) had a positive direction but did not reach statistical significance (p = 0.073 and p = 0.276) in the multiplicative and additive models, respectively. The multiplicative model suggested an increase in the odds of thyroid cancer by a factor of 1.2 for each additional copy of the effect allele for both variants.

Gene−environment interaction between rs944289 and radiation dose was reproducibly negative, displaying statistical significance in the multiplicative model (p = 0.028) and not reaching statistical significance in the additive model (p = 0.071). The multiplicative model showed a decrease in odds for developing thyroid cancer due to radiation exposure for each additional effect allele of rs944289 by a factor of ∼0.8 and/or the mentioned reduction of risk from this variant genotype for each 10-fold increase in radiation dose. The additive model suggested a 3.4% decrease of the absolute risk for thyroid cancer associated with radiation exposure for each additional effect allele of rs944289 and/or an equal reduction of risk associated with the rs944289 genotype for each 10-fold increase in radiation dose.

Table 4. Multivariable Model of Joint Effects of Genetic and Environmental Factors with Interactions

Parameters	OR or *b* (95% CI)[a]	*p*-value	MRRsq or Rsq[b]	AIC[c]
Multiplicative model			0.2275	2346.17
Radiation dose[d]	4.305 (2.939−6.307)	6.64×10^{-14}		
Soil iodine[e]	0.443 (0.362−0.542)	2.60×10^{-15}		
Radiation dose × Soil iodine	0.754 (0.547−1.038)	0.083		
rs965513	1.686 (1.459−1.949)	1.49×10^{-12}		
rs944289	1.021 (0.804−1.297)	0.864		
rs2439302	1.066 (0.805−1.413)	0.656		
rs11693806	1.103 (0.937−1.298)	0.240		
rs944289 × rs2439302	1.203 (0.983−1.473)	0.073		
rs944289 × Radiation dose	0.766 (0.604−0.971)	0.028		
Additive model			0.1685	2355.75
Radiation dose	0.259 (0.205−0.314)	1.93×10^{-20}		
Soil iodine	−0.189 (−0.232−−0.146)	8.58×10^{-18}		
Radiation dose × Soil iodine	−0.062 (−0.117−−0.006)	0.029		
rs965513	0.097 (0.068−0.126)	8.42×10^{-11}		
rs944289	0.013 (−0.037−0.063)	0.606		
rs2439302	0.036 (−0.016−0.088)	0.177		
rs11693806	0.025 (−0.010−0.060)	0.159		
rs944289 × rs2439302	0.021 (−0.017−0.059)	0.276		
rs944289 × Radiation dose	−0.034 (−0.070−0.003)	0.071		

[a]Adjusted for sex and age at exposure. OR for the multiplicative model and *b* (the regression coefficient) for the additive model. [b]Max-rescaled R-square (MRRSq) for the multiplicative model and the coefficient of determination (Rsq) for the additive model. [c]Akaike information criterion. [d]Radiation dose to the thyroid in mGy, log transformed, and mean-centered. [e]Soil iodine content categories 4−5 *vs* 1−3.

The models had robust regression coefficients (Supplementary Table S11) and resulted in an ∼22.8% information gain in the multiplicative model and in 16.9% of the variance of the outcome explained by the additive model. Graphical presentations of the single-factor and final multivariable models are shown in Figure 4.

Derived from and adjusted for the effects of other relevant interactions in the multiplicative model, the estimate of the RERI for the radiation exposure and soil iodine interaction at one additional effect allele of rs944289 was −1.65 (−1.68−−1.63). For radiation exposure and the rs944289 interaction, the RERI was −0.40 (−0.42−−0.38) per each additional effect allele of rs944289 and of rs2439302, a 10-fold increase in the thyroid dose, and high versus low soil iodine content contrasts. The negative RERI values in the multivariable model further support the negative environment−environment and gene−

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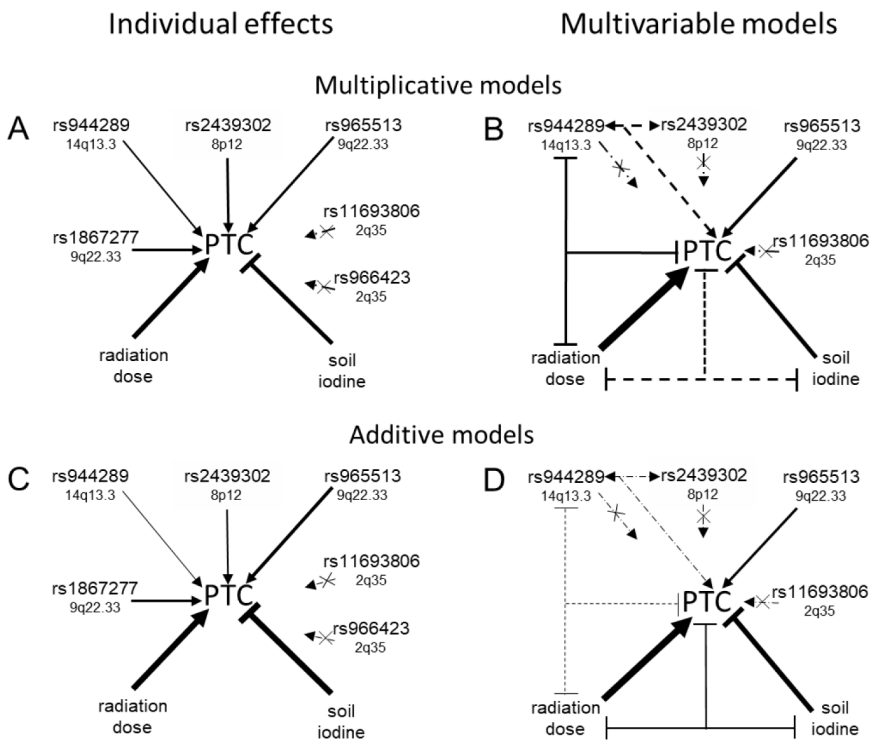


Figure 4. Individual (A, C) and joint effects of environmental factors and genetic variants with interactions (the multivariable models B, D) on PTC development in the multiplicative and additive models. Solid lines indicate statistically significant effect ($p < 0.05$), dashed lines indicate $p < 0.1$; dash-dotted crossed-out lines indicate nonsignificant effect ($p > 0.1$). Line widths are proportional to corresponding OR (for OR > 1.0) or 1/OR (for OR < 1.0) for the multiplicative models or to b-coefficient values in the additive models. Arrowheads indicate OR > 1.0 or $b > 0$; blunted line ends indicate OR < 1.0 or $b < 0$.

environment interactions demonstrating that the combined effect of these factors was less than the sum of their individual effects. The positive RERI of 0.28 (0.27−0.29) for the rs944289 interaction with rs2439302 per each additional risk allele pointed at the greater effect of the two genetic variants than expected from the sum of their individual effects, accounting for the interaction between rs944289 and radiation exposure.

All variables in the multivariable models retained their effect directions observed in the models of individual environmental and genetic factors described above. Of importance, the gene−environment interaction (between rs944289 and radiation dose) was negative and statistically significant, at least in the multiplicative model (and with a suggestive significance in the additive model), implying that genetic and environmental factors do not potentiate but rather attenuate their impacts on radiation-related PTC risk with an increasing level of the interacting counterpart in the complex models.

DISCUSSION

Our study in a large group of PTC patients and control subjects internally irradiated following the Chernobyl accident was aimed at the analysis of individual effects and of an interplay between environmental exposures and genetic variants predisposed to thyroid cancer. Quantitative environmental exposures were individual radiation doses to the thyroid due to radioactive iodine ingestion and the level of natural stable iodine consumption; genetic factors included six variants that had displayed the strongest association with thyroid cancer in previous works.

Thyroid cancer risk is known to be proportional to the internal radiation dose to the thyroid, and its magnitude was estimated in case-control and cohort radiation epidemiology studies.[5−10] We did not analyze dose−response here since this would require a different study design and methodology. Furthermore, such an analysis could be confounded by the imbalanced distribution of PTC patients and control subjects by regions of residence at the time of the accident. In our dataset, we nevertheless observed a statistically significant radiation dose association with cancer in all univariable and multivariable models, clearly confirming the risk relationship.

Stable iodine is a competitor with radioactive iodine isotopes in the Chernobyl scenario. We used soil iodine content as a proxy of iodine sufficiency/deficiency, as drinking water was the major natural source of stable iodine, and no systematic iodine supplementation was performed in the country at the time of the accident, in contrast to the present time. The soil iodine content was inversely associated with PTC in the individual and joint models. In agreement with earlier studies,[5,10] we independently found that the stable iodine-modified radiation effect and the interaction were negative. A plausible interpretation of this interaction is that the effect size of radiation exposure was declining when soil iodine content was in the highest categories, implying a reduction of possible harm. The results reinforce the validity of recently updated WHO guidelines on iodine thyroid blocking for people who are at risk of exposure to radioiodine during a nuclear emergency.[45]

Among the four chromosomal loci with six single-nucleotide variants previously associated with thyroid cancer, three conferred statistically significant signals (chr:9q22.33, chr:14q13.3, and chr:8p12 with four variants in total); the chr:2q35 locus (with two variants) showed no association. Note that this work was not aimed at the discovery of genetic variants

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underlying cancer predispositions. We specifically focused on the risk-conferring variants that have been replicated in independent studies and demonstrated the highest statistically significant associations. The sample size was sufficient to achieve the desired statistical power for all variants given published effect sizes (ORs for the multiplicative models).

Our previous genome-wide association study of radiation-related thyroid cancer detected one variant, rs965513 (chr 9q22.33), whereas signals of rs944289 (chr 14q13.3), rs2439302 (chr 8p12), and rs966423 and rs11693806 (chr 2q35) were not seen.[22] The likeliest reason was insufficient statistical power at any step of the multistage approach and the consequent meta-analysis. In the current work, associations of the variants on chr:14q13.3 and chr:8p12 with radiation-related PTC were confirmed and could not be reproduced for only the variants on chr:2q35. The latter may be explained by the differences between the participant characteristics and particularities of thyroid cancer in our study and other studies. First, our study enrolled relatively young participants, while the participants of the other studies were usually of middle and older age, at which thyroid cancer is more prevalent. Second, all cases in our study had a histologically verified diagnosis of PTC according to the latest WHO classification in contrast to broader phenotype definitions (e.g., malignant neoplasm of thyroid gland or nonmedullary thyroid cancer) in other studies. Lastly, all participants in our group had a history of radiation exposure, while the vast majority of subjects in other studies were nonexposed. Relationships of the genetic variants on chr:2q35 with age, histological type of thyroid cancer or benign condition, and cancer etiology remain to be established in future studies.

The multivariable model of genetic variant effects included four variants, rs965513 (chr:9q22.33), rs944289 (chr:14q13.3), rs2439302 (chr:8p12), and rs11693806 (chr:2q35). The second variant on chr:9q22.33, rs1867277, in spite of a considerable individual association signal, is known to lose significance when conditioned on rs965513 in multivariable models in a population of European ancestry.[35] Somewhat unexpectedly, inclusion of rs11693806, which did not show statistically significant individual association with radiation-related PTC, improved the model performance (both on the multiplicative and additive scales), indicating that the effect of this variant should not be disregarded.

We found a positive epistatic interaction between rs944289 (chromosome 14q13.3) and rs2439302 (chromosome 8p12). Since these variants are located on different chromosomes, their interaction is likely to reflect a functional relationship between the corresponding gene products in thyroid tumorigenesis. rs944289 regulates the expression of *PTCSC3* (papillary thyroid carcinoma susceptibility candidate 3), a thyroid-specific lincRNA with a tumor suppressor role.[46] rs2439302 is an intronic variant involved in the transcriptional regulation of the *NRG1* (neuregulin 1) gene implicated in thyroid cancer.[47] *PTCSC3* and *NRG1* expression levels are positively correlated in the normal thyroid and PTC tissues,[34] and furthermore, ectopic overexpression of *PTCSC3* affects neuregulin signaling in thyroid cancer cells,[46] suggesting that the pathways dependent on *PTCSC3* and *NRG1* are interrelated. Thus, functional interaction seems to be a more plausible explanation rather than statistical epistasis. Interaction between rs944289 and rs2439302 was not seen in the Japanese study of malignant and benign thyroid tumors.[34] Whether this interaction is ethnicity specific or could be detected exclusively in relatively young patients with radiation-related thyroid cancer remains an open question. In addition, since rs944289 was associated not only with PTC but also with follicular adenoma of the thyroid,[34] note that a dose-dependent risk for follicular adenoma was also reported,[48] although it was somewhat lower than that for thyroid cancer.

The availability of information on environmental exposures and of genetic data made the analysis of their joint effects and interactions possible. It was particularly important to establish whether the two types of risk factors for thyroid cancer act independently or modulate each other's effect. The worst-case scenario would be if the risk factors of different nature synergized because this would imply that a subpopulation of predisposing genetic variant carriers was at a particularly elevated risk for thyroid cancer after irradiation. According to our results, there was no evidence that this scenario occurred. On the contrary, our findings demonstrate the opposite since the only interaction between the environmental and genetic factors was negative. The effect of radiation dose was declining with increasing numbers of the risk alleles of rs944289 (chr:14q13.3) but remained significant even in subjects homozygous for the risk allele. In turn, the effect of the genetic variant declined with the dose increase and became statistically nonsignificant at the dose above ~120 mGy in the multiplicative model. This suggests that at doses higher than specified, the rs944289 contribution to thyroid cancer risk is no longer seen, which is consistent with an overall greater effect size and the amount of information gained or variance of the outcome explained in the models that included radiation dose as compared to those with genetic factors only. Of note, the negative interaction term was statistically significant in the final multiplicative model and had a suggestive significance in the additive model.

Reports on gene−environment interaction in radiation-related thyroid cancer are exceptionally rare and largely focus on DNA damage response genes. Interaction of *BRIP1* (BRCA1 interacting protein C-terminal helicase 1, also known as *FANCJ* (Fanconi anemia group J protein)) and *XRCC1* (X-ray repair cross-complementing protein 1) with radiation dose was reported in a study of patients with thyroid nodules (~3% with thyroid cancer) who had experienced exposure from nuclear tests in Kazakhstan.[49] A synonymous SNV in *ATM* (Ataxia-telangiectasia mutated) was found to interact with radiation dose in Belarusian children affected by the Chernobyl fallout.[27] Two works evaluated polymorphisms in DNA repair genes using stratified analyses of exposed versus nonexposed groups and showed statistically significant gene−environment interactions.[50,51] Cumulatively, these data suggest possible modification of radiation effect by DNA damage response genotypes, but a shortcoming of these works is the lack of replication studies reproducing the observations made.

Of interest, a target gene study of common variant association with thyroid cancer in the French Polynesian population reported an interaction between rs944289 (chr:14q13.3) and radiation exposure from nuclear tests. A statistically significant association of the rs944289 T/T genotype with thyroid cancer was found in a stratified analysis (in the recessive model of inheritance) in subjects with thyroid dose >2 mGy, subject to a departure from the linkage equilibrium caveat and an exceedingly small sample size.[30] The interaction was not significant in the model that considered all of the genotypes. The fact that in our work an interaction between rs944289 and radiation dose was also found deserves further research.

Overall, given a paucity of literature, our work adds a noticeable piece of information to a fragmentary understanding

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of gene−environment interactions in radiation-related thyroid cancer.

This study had several strengths and limitations. PTC patients and control subjects were well-balanced for baseline characteristics such as age at exposure and sex. All tumors were histologically verified as PTCs, and controls had no signs of thyroid diseases or structural abnormalities. The sample size was the largest among the case-control studies of radiation-related thyroid cancer. Individual radiation doses to the thyroid were available for all of the participants. Genetic variants did not deviate from Hardy−Weinberg equilibrium in PTC patients and control subjects and did not display heterogeneity in the distribution by regions of living, attesting to the adequacy of the gene−environment interaction analysis.

The limitations include an imbalance between cases and controls in the distribution of places of residence at the time of the accident that might have affected the extent of exposure to not only ionizing radiation but also to other environmental factors. We therefore do not present the individual or joint effects of different factors as analytical estimates of the risk magnitude but rather recognize effect directions, relative effect sizes, and the amounts of information gained or proportions of variance of the outcome explained as more revealing. Information on family history and on habitual and lifestyle factors, which can potentially modify radiation effects, was not available. The set of genetic variants analyzed was limited only to those from the top-tier chromosomal loci with the strongest associations with thyroid cancer, unlikely to fully capture the gene−environment interplay. The possibility of the existence of other variants that may cooperate with radiation or modulate radiation risk cannot be ruled out and needs to be addressed in further studies. However, no candidates among common single-nucleotide variants were noted in our previous genome-wide study.[22] Perhaps other types of genetic variants, such as rare SNVs, structural variants, or copy number variations, need to be considered either, but their detection would require other genomic technologies.

In conclusion, our study provides evidence of the environmental and genetic factor contribution to the development of thyroid cancer in individuals internally exposed to radioiodine at a young age after the Chernobyl accident. Radiation had a higher impact than predisposing single-nucleotide variants. Both environmental and genetic factors displayed complex relationships, seen as effect modifications within and across the two risk factor types. The most important finding was the lack of potentiation of each other's effect on the development of cancer. These results may be useful for radiation risk communication to the public, helping to prevent unfounded radiophobia.

■ ASSOCIATED CONTENT

Data Availability Statement

The human genotype data generated in this study are not publicly available due to participant privacy requirements. Access to individual data may require special approvals from ethical boards of participating institutions and needs to be communicated with the corresponding author. Other data are presented within the article and its supplementary data files in a form suitable for meta-analyses.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/EHP.6c00281.

TaqMan SNP genotyping assays and genotyping methods (Table S1); PCR conditions for endpoint genotyping assays (Table S2); validation of the regression coefficients stability for the environmental factor effects (Table S3); information for statistical power calculations and plotting (Table S4); descriptive characteristics of genetic variants (Table S5); pairwise gene−gene interactions (Table S6); validation of the regression coefficients stability for the genetic variant effects (Table S7); gene−environment interactions between genetic variants and radiation dose to the thyroid (Table S8); validation of the regression coefficients stability for gene−environment interaction (Table S9); gene−environment interaction between genetic variants and soil iodine content (Table S10); validation of the regression coefficients stability in the optimal multivariable models (Table S11); statistical significance of the association signals of genetic variants in GWAS reports (Figure S1); distribution of study participants by environmental exposures (Figure S2); statistical power to detect association signals of genetic variants (Figure S3); supplementary figure captions (PDF)

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Author Contributions

T.I.R., F.M., S.Y., and V.A.S. conceived the study and designed the experiments. T.I.R., T.A.L., M.V.F., M.T., V.D., E.O., I.V.V., V.F.M., N.M.A., and M.L.L. developed methodology and curated data. V.A.K., E.O., L.I.D., N.T., F.M., S.Y., N.M., and V.A.S. supervised the project. T.I.R. and V.A.S. analyzed the data and drafted the manuscript. All authors contributed to the results, discussion, and manuscript writing and editing.

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Notes

No hazardous materials or operations were involved in the preparation to and analysis performed in this study. All experiments were performed in accordance with standard institutional biosafety and chemical hygiene regulations. The contributions of the NIH authors were made as part of their official duties as NIH federal employees, are in compliance with agency policy requirements, and are considered Works of the United States Government. However, the findings and conclusions presented in this presentation are those of the authors and do not necessarily reflect the views of the NIH or the U.S. Department of Health and Human Services. Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/World Health Organization.
The authors declare no competing financial interest.

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