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Role of DNA Repair Variants and Diagnostic Radiology Exams in Differentiated Thyroid Cancer Risk: A Pooled Analysis of Two Case–Control Studies

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1 Role of DNA repair variants and diagnostic radiology exams in differentiated thyroid
2 cancer risk: a pooled analysis of two case-control studies

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60 **Abstract**

61 **Background:** Given the increased use and diversity of diagnostic procedures, it is
62 important to understand genetic susceptibility to radiation-induced thyroid cancer.

63 **Methods:** Based on self-declared diagnostic radiology examination records in addition to
64 existing literature, we estimated the radiation dose delivered to the thyroid gland from
65 diagnostic procedures during childhood and adulthood in two case-control studies
66 conducted in France. A total of 1071 differentiated thyroid cancer (DTC) cases and 1188
67 controls from the combined studies were genotyped using a custom-made Illumina
68 OncoArray DNA chip. We focused our analysis on variants in genes involved in DNA
69 damage response and repair pathways, representing a total of 5817 single-nucleotide
70 polymorphisms in 571 genes. We estimated the odds ratio per milli-Gray (OR/mGy) of the
71 radiation dose delivered to the thyroid gland using conditional logistic regression. We
72 then used an unconditional logistic regression model to assess the association between
73 DNA repair gene variants and DTC risk. We performed a meta-analysis of the two
74 studies. **Results:** The OR/mGy was 1.02 (95% CI: 1.00, 1.03). We found significant
75 associations between DTC and rs7164173 in CHD2 ($p = 5.79 \times 10^{-5}$), rs6067822 in
76 NFATc2 ($p = 9.26 \times 10^{-5}$), rs1059394 and rs699517 both in ENOSF1/THYS, rs12702628 in
77 RPA3, and an interaction between rs7068306 in MGMT and thyroid radiation doses ($p =$
78 3.40×10^{-4}). **Conclusions:** Our results suggest a role for variants in CDH2, NFATc2,
79 ENOSF1/THYS, RPA3 and MGMT in DTC risk.

80 **Impact:** CDH2, NFATc2, ENOSF1/THYS and RPA3 have not previously been shown to
81 be associated with DTC risk.

82 .

83 1. Introduction

84 Differentiated thyroid cancer (DTC) is the most common cancer of the endocrine system
85 (1). The registered incidence of DTC has recently been increasing, especially in
86 developed countries mostly due to increased screening (2). Exposure to thyroid ionizing
87 radiation (IR) during childhood was the first risk factor linked with DTC, an association
88 that has been well characterized over several decades (3–8).

89 In a pooled study performed on doses higher than ≥ 1 Gy (9,10), the excess of DTC
90 relative risk per Gray (ERR/Gy) delivered to the thyroid gland during childhood ranged
91 between 5 and 10. When restricting the pooled analysis to doses lower than 0.2 Gy,
92 however, the ERR/Gy was slightly higher (11). A higher magnitude of excess risk for low
93 dose exposure during childhood was also observed in a cohort study of Japanese atomic
94 bomb survivors (12). Nevertheless, some uncertainties remain about how the recent
95 increase in the use of diagnostic procedures involving irradiation, such as CT
96 (computerized tomography), might affect DTC incidence (13,14).

97 Despite being more subject to recall bias than cohort studies, case-control studies may
98 be more helpful for improving understanding of thyroid low-dose radiation risk since case-
99 control studies utilize a high number of cases and permit a more detailed investigation of
100 a high number of potential risk cofactors, which are costlier to investigate in cohort
101 studies. Since DTC risk after low radiation dose exposure is also likely modulated by
102 individual susceptibility, investigating the association between DNA variants and DTC risk
103 after low radiation dose could also facilitate an improved understanding of this risk. IR
104 exposure causes DNA damage as well as other physical and chemical biomolecule
105 alterations. DNA double-strand breaks (DSBs) are a characteristic cellular response to IR
106 exposure (15). Exposure to low-dose IR (from levels 50mGy and lower) from X-ray

107 examinations has been demonstrated to increase the risk of chromosomal translocation
108 (16), suggesting the possibility of long-term adverse health effects.

109 DSBs trigger the DNA repair system, but the effect of these DSBs varies with cumulative
110 exposures and individual susceptibility. To our knowledge, only one published study has
111 investigated an interaction between genetic background and the radiation-related DTC
112 risk after diagnostic radiation exposure (17). This study identified 24 single-nucleotide
113 polymorphisms (SNPs) with a p-value of variant-RI doses interaction was < 0.05 for all
114 types of DTC cases (papillary and follicular). Currently, few genes including *FOXE1*,
115 *ATM*, and *LIG1* have been associated with DTC risk after IR exposure, but most
116 published studies of these genes were conducted in highly irradiated populations.
117 Moreover, these identified genes were associated with sporadic DTC (18).

118 Given the increasing use of diagnostic radiology exams and the proliferation of radiology
119 procedure types, it is important to explore the side effects of multiple low-radiation
120 exposures, such as potential effects on DTC development, especially for patients
121 exposed at a young age.

122 In the current study, we investigated the association between diagnostic low-dose IR
123 exposures and DTC risk. We quantified the doses delivered to the thyroid gland during
124 childhood and adulthood in two French case-control studies. We also investigated the
125 role of genetic variants located in 604 DNA damage signaling and repair genes in
126 modifying the effect of exposure to diagnostic procedure radiation on DTC risk.

127 2. Materials and methods

128 2.1. Case-control studies

129 Our study included cases and controls from two studies conducted in distinct regions
130 from metropolitan France.

131 The CATHY study (19) was a case-control study conducted in Marne, Ardennes, and
132 Calvados, three French administrative areas covered by a cancer registry. Eligible cases
133 were all DTC patients aged 25 years and older that were diagnosed between 2002 and
134 2007 and resided in these areas. Controls were recruited by selecting and contacting
135 telephone numbers at random, then frequency-matching the individuals to patients by sex
136 and five-year age groups; controls were randomly selected among healthy individuals
137 residing in the same study areas at the time of the matched cases diagnoses. From the
138 621 cases and 706 controls initially included in the CATHY study, saliva DNA samples
139 (Oragene® DNA testing kit) were available for 583 cases and 643 controls.

140 The Young-Thyr study (20) is a case-control study conducted in eastern regions of
141 France: Alsace, Champagne-Ardennes, Corse, Franche-Comté, Lorraine, Rhône-Alpes,
142 and Provence-Alpes-Côte d'Azur. Eligible cases were all DTC patients diagnosed with
143 DTC between January 1st, 2002, and December 31st, 2006 that were younger than 35
144 years of age with their main residence in a region of eastern France. Controls were
145 selected from the general population and individually matched to a single patient of the
146 same sex, year of birth (within one year), and region of residence during the year when
147 the patient was diagnosed with cancer. From the 805 cases and the 876 controls
148 included in the Young-Thyr study, DNA from saliva (Oragene®) was available for 715
149 cases and 692 controls.

150 Participants from both studies answered similar questionnaires that were collaboratively
151 developed. Information on a personal and familial history of thyroid disease, hormonal
152 and reproductive factors, weight, height, dietary habits, tobacco smoking, and medical
153 history was collected during in-person interviews. Participants from both studies gave
154 their informed written consent before being interviewed by trained interviewers. Both

155 studies were approved by the Ethics Committee and the French National Commission for
156 Data Protection (CNIL).

157 Clinical and epidemiological data from both studies were harmonized and aggregated in
158 one database. During this process, 30 subjects were excluded because they were
159 duplicates in the two studies.

160 [2.2. Radiologic procedure history](#)

161 In the questionnaire, participants were asked to report their history of diagnostic radiology
162 examinations by providing the year and the reason for each examination. The exams
163 considered were conventional radiography, CT scans, and nuclear medicine.
164 Examinations linked to investigating thyroid pathology were excluded and were not
165 considered in the dose estimation or any analysis. Examinations carried out during
166 childhood (before the age of 20 years) and adulthood (over 20 years) were analyzed
167 separately. All procedures reported by participants were classified by period (before
168 1980, 1980-1989, 1990, and after) to take into account the development of radiologic
169 procedure technology over this time.

170 [2.3. Thyroid radiation dose estimates](#)

171 To estimate the absorbed radiation doses administered to the thyroid gland for different
172 types of diagnostic radiology examinations, we reviewed papers published up to July
173 2018 that included absorbed dose estimates to the thyroid. From 1970 to 2002, only one
174 study provided estimates of absorbed doses to organs, including the thyroid gland (21),
175 and was used to calculate dose estimates from conventional radiography.

176 If sex-specific data were available, a mean dose was used. Since the available data
177 about childhood exams were very limited, specific doses were available only for children
178 under the age of two years old without consideration of the period of exposure. Children

179 older than two years were assumed to receive the same doses as adults. All doses per
180 exam that were equal to or less than 0.01 mGy were considered to be null because of the
181 magnitude of daily natural irradiation in France. Table 1 summarizes the different values
182 used per diagnostic procedure type (conventional radiography, CT scan, nuclear
183 medicine), per period (before 1980, 1980-1989, 1990 and after), and per age at
184 examination (≤ 2 years old, > 2 years).

185 2.4. Genotyping and quality control

186 DNA was extracted from saliva samples using a semi-automated salt precipitation
187 method. All subjects were genotyped using the Infinium OncoArray-500K BeadChip
188 (Illumina). This array has been previously described in detail (22) and contains 499,170
189 SNPs. We incorporated 13,759 additional custom markers based on prior evidence of
190 association in genes involved in relevant biological pathways, such as thyroid function.

191 The quality control process was applied to the data of each study separately. A threshold
192 of 5% was applied for a missing call rate per SNP and individual. The Hardy-Weinberg
193 equilibrium (HWE) was also assessed per SNP among controls, using an exact test with
194 a p-value threshold at 10^{-5} . Only SNPs with a minor allele frequency (MAF) above 5%
195 were included in the analyses.

196 The FastPop R package was used to infer intercontinental ancestry with a principal
197 component-derived method (23). Only individuals identified as European were kept in the
198 genetic analyses. A total of 443 cases and 532 controls from CATHY and 629 cases and
199 656 controls from Young-Thyr were included in the analysis of SNPs.

200 SNPs of DNA damage signaling and repair genes according to the Gene Ontology
201 database (24,25) were examined. We initially selected exonic and intronic variants in 604

202 genes. After the quality control steps, a total of 5817 SNPs in 571 genes were retained
203 for the analysis (all genes are listed in the Supplementary Table S1).

204 2.5. Statistical methods

205 We used a conditional logistic regression model to estimate the odds ratio of DTC per
206 mGy (OR/mGy) of radiation dose received by the thyroid gland. Because in our study,
207 thyroid doses were very low and cell killing not likely to play significance, and because
208 our goal was not to define the best model for thyroid cancer risk after low dose but rather
209 the best model to investigate the interaction between thyroid radiation and genetic
210 factors, we only investigate models with one parameter for the thyroid radiation dose. In
211 this way, we compared a linear model ($OR = Cst (1 + \alpha \text{ dose})$) to a “constant” model
212 without a radiation dose ($OR = Cst$) and other models with one parameter, such as
213 quadratic ($OR = 1 + \alpha \text{ dose}^2$) and exponential ($OR = 1 + e (\alpha \text{ dose})$), rather to traditional
214 dose-response models used in radiation epidemiology (26). These comparisons were
215 done using Akaike Information Criterion (AIC) (27). Similarly, we investigated the
216 potential role of a dose-response modifier by introducing a term for interaction in the
217 models. The analysis of the radiation dose was performed by using the PECAN module
218 of Epiwin® software. To assess the association between SNPs and DTC risk, odds ratios
219 (ORs) and 95% confidence intervals (95% CIs) were derived from unconditional logistic
220 regression models, assuming a log-additive model since the stratum was not considered
221 in this step. Analyses were first conducted in the Young-Thyr study to filter our SNPs and
222 limit the number of tests to be performed later; only the 100 SNPs with the lowest p-
223 values from this step were tested in the CATHY study. We also conducted a meta-
224 analysis combining results from both studies; overall z-statistics and p-value for these
225 100 top SNPs were then calculated from a weighted sum of the individual statistics.
226 Weights were proportional to the square root of the number of individuals examined in

227 each sample and selected such that the squared weights summed to 1.0, as
228 implemented in the METAL program (28). This step aims to improve signal detection in
229 the genetic analysis by avoiding a large number of tests, and to substantiate homologous
230 signals in both studies since our population is relatively limited.

231 To correct for multiple tests in the main effect analysis, the FDR procedure (29) was
232 calculated for each result of the meta-analysis. We investigated the interaction between
233 SNPs and radiation doses using the likelihood ratio test, comparing models with and
234 without the interaction term following the same steps described above.

235 All analyses were adjusted for age (five-year period), sex, thyroid cancer family history
236 (yes/no), goiter history (yes/no), radiotherapy history (yes/no), BMI (continuous), height
237 (continuous), educational level (primary school, secondary school, bachelors or higher),
238 smoking status (never/former smoker/smoker), number of pregnancies longer than seven
239 months in women (three classes), and study (CATHY/Young-Thyr) only in the pooled
240 analysis. Analyses of genetic variants were additionally adjusted for the first three
241 principal components to take into account the population stratification. Subgroup analysis
242 was also performed separately for papillary histological type cases and according to
243 tumor size (microcarcinoma and macrocarcinoma).

244 The log-linear model poses fewer convergence problems than the linear model, for that
245 reason the association and interaction tests between radiation doses and DNA variants
246 were performed using a log-linear model. Since we did not apply any cut-off p-values for
247 SNPs selected to be included in the meta-analysis step, in this study we chose to only
248 show our best five results from each analysis.

249 Association analyses and meta-analyses were performed using R 3.6 and METAL (28).
250 SNPs were annotated using the VEP tool (30), and gene regions were plotted with
251 LocusZoom software (31).

252 3. Results

253 Demographic characteristics of the pooled study population (Young-Thyr and CATHY)
254 are described in Table 2. More than 75% of our population were women and non-
255 smokers. Papillary thyroid cancer type was the most frequent type of thyroid cancer
256 observed, with a mean age at diagnosis younger than 40 years old. However, the mean
257 age at diagnosis was lower in the Young-Thyr study than in the CATHY study, as shown
258 in Supplementary Table S2 (27 years *versus* 51 years).

259 3.1. Diagnostic radiation and thyroid cancer risk

260 3.1.1. Thyroid doses determined by diagnostic radiology examination estimates

261 Estimated IR doses administered to the thyroid during childhood were lower than those
262 given after 20 years of age. Among children, the most frequent exam was panoramic
263 dental radiography, which was reported in 971 individuals. Nuclear medicine exams were
264 rarely reported among children; the most frequent exam scan was bone scans reported in
265 14 children (Table 3). During adulthood, the most frequent conventional radiography
266 exam was chest radiography, which was seen in 30.8% of adults. Skull CT scan was the
267 most common computed tomography exam during adulthood. Nuclear medicine exams
268 were also relatively rarely reported among adults (Table 3). The median thyroid doses
269 delivered during childhood were lower than doses administered during adulthood. The
270 maximum childhood estimated thyroid dose was 194.2 mGy among the whole population,
271 the mean among cases was 2.8 mGy and 2.0 mGy among controls. A total of 1672
272 subjects reported not having received any thyroid-irradiating diagnostic procedure during
273 childhood. The estimated maximum dose delivered to the thyroid during adulthood in a

274 diagnostic radiology procedure was 260.0 mGy, and the mean dose was 5.6 mGy and
275 5.5 mGy among cases and controls, respectively (Supplementary Tables S3 and S4). A
276 total of 1466 subjects did not report experiencing any thyroid-irradiating diagnostic
277 procedures during adulthood. Detailed information on diagnostic radiology exams and
278 thyroid doses in cases and controls in each study are shown in Supplementary Tables
279 S2, S3, and S4. Characteristics and thyroid doses among genotyped subgroups from
280 both studies are presented in Table 2. The DTC risk in relation to the radiation doses in
281 this population is detailed in Supplementary Table S5.

282 3.1.2. Differentiated thyroid cancer risk in relation to thyroid radiation doses

283 Only estimated radiation dose received by the thyroid gland during childhood was found
284 to be associated with an increased DTC risk, unlike doses received during adulthood. In
285 the linear model, the DTC OR per mGy administered to the thyroid was equal to 1.02
286 (95% CI: 1.00, 1.03). When restricting the analysis to papillary thyroid carcinoma, the OR
287 per mGy was very similar. The fit of the model was improved by the addition of a
288 quadratic term to take into account a possible higher effect of high doses, although not
289 significant ($p = 0.06$). No significant difference ($p > 0.05$) was found between the dose
290 responses for men and for women. No interaction was apparent between the thyroid
291 radiation dose and obese status, age at DTC occurrence, study, number of pregnancies,
292 female sex, smoking status, height, or the personal radiotherapy history. In a log-linear
293 model, the odds ratio for a dose of 1 mGy was 1.01 (95% CI: 1.01, 1.04) (Table 4).
294 Results from a sub-analysis by tumor size, shown in Table 4, yielded similar DTC risk in
295 relation to thyroid IR doses to these from the whole population analysis.

296 3.2. Differentiated thyroid cancer risk in relation to DNA damage repair and signaling 297 gene variants

298 Association analysis between DTC risk and the 5817 variants in DNA damage response
299 genes from the Young-Thyr study including all histological types yielded only two SNPs
300 with a p-value lower than 5×10^{-4} : rs4962347 (chromosome 10, *C10orf90*) and
301 rs16983787 (chromosome 10, *SMC6*). None of the top 100 variants with the lowest p-
302 values reached the threshold p-value of 5×10^{-4} in the CATHY study. In the meta-analysis,
303 results of the association test with DTC risk showed a significantly reduced risk for
304 carriers of the minor allele [T]; both SNPs, rs6067822 in *NFATc2* and rs7164173 in
305 *CHD2*, had a p-value of 5.79×10^{-5} and 9.26×10^{-5} respectively, under an additive model of
306 inheritance. Associations with both variants were in the same direction in CATHY and
307 Young-Thyr (Table 5A). Other variants in *NFATc2* present among the top 100 SNPs
308 associated with DTC in the Young-Thyr study are described in Supplementary Figure 1.
309 Rs7164173 was the only SNP in *CHD2* among the top 100 SNPs. Rs105939 and
310 rs699517 in *ENOSF1/THYS* were in our best results, but statistical significance was not
311 achieved ($OR_{\text{meta-analysis}} = 1.30$, $p\text{-value}_{\text{meta-analysis}} = 7.81 \times 10^{-4}$). Only one variant in *RPA3*
312 (rs12702628 in 7p21.3) was found to be significantly associated with DTC risk.

313 When the analysis was restricted to only papillary carcinoma histological types, only
314 rs7164173 was significant ($p\text{-value}_{\text{meta-analysis}} = 9.33 \times 10^{-5}$) (Table 5B). In the *NFATc2*
315 region, two SNPs, rs77971457 and rs6067822, had respective $OR_{\text{meta-analysis}}$ values of
316 1.45 and 0.77 but did not reach the significance threshold. Rs1290997 and rs1950764 in
317 *RAD51B* had $OR_{\text{meta-analysis}}$ values of 0.74 and 0.60, respectively (Table 5B). The
318 polymorphism rs1950764 had a $p\text{-value}_{\text{meta-analysis}} > 5 \times 10^{-4}$. Detailed results for SNPs in
319 *RAD51B* are shown in Supplementary Figure 2. Results from the best SNPs in the
320 macrocarcinoma analysis (Table 5C) yielded two SNPs in the *MLK7-AS1* gene

321 (rs72625242, rs16861406) in 2q31.1 in addition to two other SNPs in chromosome 2
322 (*PMSD1* and *SMC6*) and the *C10orf90* gene in chromosome 10. In the microcarcinoma
323 analysis, a significant result in 2q31.1 was found (rs75361806, *TLK1*) (Table 5D). The
324 best results from this later analysis also yielded three SNPs in the *MACROD2* gene
325 (20p12.1).

326 3.3. Differentiated thyroid cancer risk related to the interaction between thyroid doses 327 and variants of DNA damage repair and signaling genes

328 We investigated the interaction between variants in DNA damage response genes and
329 thyroid exposure to radiation in DTC risk. In the meta-analysis, the SNP-radiation
330 interaction term yielded a p-value_{meta-analysis} = 3.4×10^{-4} and an OR_{interaction} = 0.65 for
331 rs7068306 in *MGMT* (Table 6). A second *MGMT* SNP, rs7087131, was also among the
332 top 100 SNPs identified in the Young-Thyr study. Results on the modifying effect of
333 rs7068306 genotypes on DTC risk according to diagnostic radiation exposure study
334 separately in CATHY and Young-Thyr are presented in Supplementary Table S6.

335 4. Discussion

336 Our main objective was to investigate the potential genetic susceptibility to DTC after
337 exposure to low IR doses from diagnostic procedures performed during childhood. In our
338 study, the estimated OR/mGy for thyroid radiation doses received during childhood
339 (OR/mGy = 1.02 (95% CI: 1.00, 1.03)) was similar to the OR/mGy values of the pooled
340 DTC study by Veiga et al. (10) when considering analyses restricted to thyroid radiation
341 doses lower than 100 mGy (OR/mGy = 1.010, (95% CI: 1.004 - 1.018)) or to thyroid
342 radiation doses lower than 200 mGy (OR/mGy = 1.011, (95% CI: 1.007 - 1.02)) (11).
343 Compared to the latest publication on the US radiologic technologist cohort, including
344 90,305 radiologic technologists in the U.S. who were followed during 1983–1998, the
345 values of our coefficients for thyroid radiation doses received during childhood are slightly

346 higher than the coefficients estimated in the general analysis and the papillary carcinoma
347 sub-analysis (32). Our estimates are also slightly higher than estimates in both the most
348 recent analysis among Japanese atomic-bomb survivors(12) and the IARC study of the
349 highly contaminated area of Belarus following the Chernobyl nuclear accident (8).

350 The genetic analyses showed an association between DTC risk and SNPs: rs6067822 in
351 intron 1 of *NFATc2* (20q11.22), rs7164173 in intron 3 of *CHD2* (15q21.3), rs1059394 (3
352 prime UTR variant), and rs699517 (3 prime UTR variant) both in *ENOSF1/THYS*
353 (18p11.32), and rs12702628 intron variant in *RPA3* (7p21.3). To our knowledge, none of
354 these genes have previously been reported to be associated with DTC risk. The effect
355 direction of these SNPs was similar in the Young-Thyr and CATHY studies and reached
356 the significance threshold for the meta-analysis; furthermore, *NFATc2* and *CHD2* genes
357 have been implicated in the response to ionizing and ultraviolet radiation *in vitro* studies
358 (33,34). Moreover, cells with mutations in *CHD2* were found to be defective in their ability
359 to repair DNA damage, especially after ionizing and ultraviolet radiation exposure (34).
360 Genes of the *NFAT* family encode for transcription factors, which have a role in cancer
361 progression, and also are important for responding to ionizing and ultraviolet radiation
362 exposure (35–37); these genes were previously found to be associated with other types
363 of cancer risk, such as melanoma, breast, colorectal and oral cancers (38–41).
364 Rs6067822 in *NFATc2* and rs7164173 in *CHD2* showed a similar stabilizing effect in
365 general and papillary subgroup analyses. Our results from the papillary thyroid carcinoma
366 sub-analysis yielded a significant association of rs1290997 in *RAD51B* with DTC risk.
367 Another variant in this gene, rs1950764, was among our top five SNPs but did not reach
368 the significance threshold. These findings suggest a role for *RAD51B* in the etiology of
369 radiation-related DTC. Interestingly, the *RAD51B* gene was involved in DNA damage
370 repair after ultraviolet irradiation exposure (42,43) and associated with breast cancer risk

371 (44,45). We report this result with great caution because 525 SNPs in this gene were
372 tested in the first step of the analysis (Supplementary Table S1).

373 An association was found between two SNPs (rs1059394 and rs699517) falling within the
374 *ENOSF1/THYS* gene region. These SNPs are non-coding transcript exon variants, and
375 this region is known to be associated with ovarian and endometrial cancers (46,47).

376 The polymorphism rs12702628 in replication protein A3 gene (*RPA3*), which was
377 associated with DTC risk in our study, has previously been found to be involved in
378 tumorigenesis, especially in gastric cancer (48).

379 The macrocarcinoma and microcarcinoma analyses both yielded significant results in
380 2q31.1. However, since these are subgroups results, they should be taken with caution,
381 especially for the microcarcinoma analysis due to the low number of cases.

382 The minor allele of *MGMT* rs7068306 was found to interact with thyroid IR doses during
383 childhood in reducing the risk of DTC after exposure. The first study to report an
384 association between an *MGMT* variant and radiation-related DTC risk was performed in
385 Belarusian children exposed to radiation (49). The polymorphism rs2296675, associated
386 with DTC risk in the Belarusian population, is located 94 kb from rs7068306 in intron 4 of
387 the *MGMT* region. A correlation coefficient of $r^2 = 0.005$ was found between rs7068306
388 and rs2296675. In a study of a Caucasian population, Sandler et al. found an interaction
389 between other *MGMT* variants: rs1762444, rs4750763, and rs12219606, and exposure to
390 radiation from diagnostic procedures (17). These SNPs are located in intron 2 and are
391 244kb, 26kb, and 15kb from rs7068306, respectively. The r^2 values between these three
392 SNPs and rs7068306 are 0.009 and 0.044 (Supplementary Table S7). The r^2 values
393 between rs7068306 and the SNPs tested in studies by Lonjou and Sandler were
394 estimated in a European reference population of 1000 Genomes project (50). Results

395 from the present study were obtained after estimation and quantification of thyroid doses,
396 based on a combination of self-reported radiologic procedure history and literature doses
397 separately on childhood and adulthood observations. The Sandler et al. study used a
398 different procedure since no doses were taken into account; only categories of diagnostic
399 procedure exposure based on self-reported history were evaluated. Taken together,
400 results from these different studies highlight the role of *MGMT* in modulating the effect of
401 IR on cells of the thyroid.

402 The expression of *CLIP2*, a gene located on 7q11.22, has been found to be strongly
403 linked with previous radiation exposure in thyroid cancer (51). In our study, only 22 SNPs
404 located on chromosome 7 were tested (Supplementary Table S1), of which, only two
405 were near the *CLIP2* gene region. None of these were among the 100 best SNPs in our
406 study, since the low numbers of concerned SNPs prevented us from confirming any
407 results about locus 7q11.22.

408 **Limitations of the study**

409 Investigating the thyroid radiation dose-response from self-reported radiation
410 examinations carried out in case-control studies is sensitive to recall bias. This is
411 particularly true when addressing public health issues highly debated by the public, such
412 as the health effects of irradiation. As Hallquist and Jansson previously showed, in case-
413 control studies investigating the impact of self-reported diagnostic radiology procedures
414 on DTC risk, this bias produces under-reporting of examinations by both cases and
415 controls, but significantly more by controls; furthermore, this bias could cause an
416 overestimate of the IR effect (52). We cannot exclude such a bias in our study, which
417 could result in an overestimation of the radiation dose effect. However, in the Young-Thyr
418 study, we previously showed that despite DTC patients being more likely than controls to
419 believe that the consequences of the Chernobyl accident were responsible for DTC

420 occurrences, self-reported vegetable consumption during the two months after the
421 Chernobyl accident, known to be a major source of radioactive contamination, was
422 correlated with the status of participants, cases or controls, but not with their beliefs (53).
423 Thus, exposure could be over-reported in patients, particularly when they believe that this
424 exposure contributed to their disease. In this type of study, case and control self-
425 declarations are often impacted by recall bias, especially in terms of the number of radio
426 diagnostic exams and images in the present study. Despite these caveats, case-control
427 studies could help to improve understanding of the risks associated with low-dose IR
428 radiation by utilizing a large number of cases and permitting more detailed investigations
429 on several potential risk factors, which are costlier to investigate in cohort studies.

430 For some types of exams, there are no available thyroid dose estimates available in
431 current literature, especially during childhood. This disadvantage could decrease the
432 precision of our estimates; consequently, to harmonize our analyses we considered the
433 same doses for all children older than 2 years. The simplest way to account for age
434 variation of radiation dose exposure (0-2 years compared to older) in our analysis, has
435 probably a limited effect because the reference doses were the same for cases and
436 controls. Thyroid dose estimates were based on self-declarations of diagnostic exam
437 history. In this data, dates for each exam are not precise, causing the impossibility to
438 impose a lagging period and raising the problem of reverse causation. Despite the
439 absence of specific dates for each procedure, we only kept data from radiological
440 procedures that were not carried out for diagnosing thyroid cancer. There is some
441 heterogeneity in demographic and cancer characteristics between our two studies:
442 patients from the Young-Thyr study were younger at cancer diagnosis and inclusion in
443 the study compared to cases from CATHY. Furthermore, diagnostic radiology
444 technologies that were available in childhood differ substantially between the participants

445 of the CATHY and Young-Thyr studies; additionally, the availability and frequency of
446 these examinations differ (Supplementary Tables S2, S3, and S4). To better discern
447 signals from the genetic analysis and to increase the statistical power, we chose to
448 perform a meta-analysis to substantiate homologous signals in both studies by keeping a
449 limited number of SNPs in this step to avoid a high number of tests.

450 Despite the small size of our study populations, our results suggest a role for *NFATc2*,
451 *CHD2*, *RPA3*, and *ENOSF1/THYS* that has not previously been associated with DTC risk
452 and confirm the previously demonstrated role of *RAD51B* and *MGMT*. However,
453 functional and validation studies are needed to better understand and confirm the
454 biological role of these variants.

455 5. Conclusion

456 We present evidence that DTC risk is significantly increased in higher thyroid radiation
457 doses received during childhood from radio diagnostic examinations. In addition, we
458 demonstrated an interaction between this thyroid radiation dose and the minor allele of
459 rs706830 located in *MGMT*. Our results also suggest an association between
460 polymorphisms in *NFATc2*, *CHD2*, *ENOSF1/THYS*, *RPA3*, and *RAD51B*. Taken
461 together, despite the limited size of both populations studied, these results underline the
462 role of DNA repair pathways in DTC risk. More studies of larger populations are needed
463 to validate and characterize the interaction between DNA repair genes and exposure to
464 low IR doses.

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484

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- 674

Table 1 References used for thyroid radiation dose estimates per diagnostic procedure type

Exams types	Doses in mGy				References
	Childhood exposure age < 2	Childhood exposure age > 2 years and adulthood exams			
		Before 1980	1980-1989	1990 and after	
Conventional Radiography					
Skull	- §	3.6	3.6	0.42	Chang et al. 2017
Dental (panoramic)	- §	0.56	0.07	0.02	Chang et al. 2017
Paranasal sinuses	- §	0.02	0.04	0.04	Chang et al. 2017
Intravenous urography	0.38*	0.38	0.21	0.21	Inskip et al. 1995
Chest	0.13	0.16	0.31	0.19	Almén and Mattsson 1995 / Chang et al. 2017
Spine	2.8*	2.8	4.5	0.99	Chang et al. 2017
CT Scan					
Skull	3	0.43	0.49	0.64	Lee et al. 2007 / Chang et al. 2017
Chest	5.9	15	20.5	22	Mabille et al. 2008 / Chang et al. 2017
Spine	13.5	17	24	25.5	Mabille et al. 2008 / Chang et al. 2017
Abdomen	0.17	0.28	0.38	0.41	Mabille et al. 2008 / Chang et al. 2017
Nuclear medicine					
Bone scan	1.1*	1.1	0.96	1.1	Chang et al. 2017
Brain scan	- §	1.3	3.6	9	Chang et al. 2017
Lung scan (perfusion/ventilation)	- §	0.2	0.25	0.25	Chang et al. 2017
Heart scan	- §	11	17	12	Chang et al. 2017
Liver scan	- §	0.15	0.15	0.15	Chang et al. 2017
Renal scan	- §	0.17	0.31	0.17	Chang et al. 2017

§: No exposed subject at this age

*: No available data for children, adult data used

Table 2 Clinical and demographic description of the population included in DTC risk in relation to thyroid radiation doses analysis and genetic analysis

	Whole population		The population included in the genetic analysis	
	Cases (n = 1393)	Controls (n = 1580)	Cases (n = 1072)	Controls (n = 1188)
Gender (%)				
Men	300 (21.5)	398 (25.2)	228 (21.3)	302 (25.4)
Women	1093 (78.5)	1182 (74.8)	844 (78.7)	886 (74.6)
Age at diagnosis/reference year (years)				
Mean	37.58	37.21	37.4 (15.0)	37.6 (15.2)
Median [Min, Max]	32.0 [9.00, 83.0]	32.0 [9.00, 83.0]	32.0 [11.0, 83.0]	32.0 [9.00, 80.0]
Smoking status (%)				
Non-smoker	739 (53.1)	768 (48.6)	232 (52.4)	271 (50.9)
Former smoker	304 (21.8)	306 (19.4)	140 (31.6)	149 (28.0)
Smoker	350 (25.1)	506 (32.0)	71 (16.0)	112 (21.1)
Alcohol consumption (Number of alcohol glasses per week) (%)				
No consumption	778 (55.9)	763 (48.3)	582 (54.3)	559 (47.1)
Less than 10	504 (36.2)	673 (42.6)	403 (37.6)	521 (43.9)
More than 10	110 (7.9)	144 (9.1)	87 (8.1)	108 (9.1)
BMI (Kg/m²)				
Mean (SD)	24.6 (5.21)	24.1 (4.88)	24.7 (5.36)	24.2 (4.89)
Median [Min, Max]	23.5 [11.0, 51.8]	23.1 [13.4, 49.1]	23.6 [11.0, 51.8]	23.1 [13.4, 48.7]
Goitre history (%)				
No	899 (64.5)	1468 (92.9)	695 (64.8)	1102 (92.8)
Yes	494 (35.5)	112 (7.1)	377 (35.2)	86 (7.2)
Thyroid cancer family history (%)				
No	1542 (97.6)	1322 (94.9)	1023 (95.4)	1158 (97.5)
Yes	38 (2.4)	71 (5.1)	49 (4.6)	30 (2.5)
Radiotherapy history (%)				
No	1558 (98.6)	1354 (97.2)	1043 (97.3)	1168 (98.3)
Yes	29 (2.8)	22 (1.3)	19 (1.7)	20 (1.6)
Educational level (%)				
Bachelor's degree or higher	765 (54.9)	982 (62.2)	618 (57.6)	743 (62.5)
Secondary school	418 (30.0)	406 (25.7)	315 (29.4)	311 (26.2)
Primary school level	210 (15.1)	192 (12.2)	139 (13.0)	134 (11.3)
Childhood thyroid radiation doses in mGy (%)				
0	1021 (73.3)	1161 (73.5)	777 (72.5)	876 (73.7)
]0,1]	112 (8.0)	147 (9.3)	89 (8.3)	104 (8.8)
]1,5]	139 (10.0)	150 (9.5)	116 (10.8)	113 (9.5)
]5,10]	25 (1.8)	45 (2.8)	18 (1.7)	36 (3.0)
]10,20]	49 (3.5)	57 (3.6)	35 (3.3)	42 (3.5)
>20	46 (3.3)	20 (1.3)	37 (3.5)	17 (1.4)
Mean (sd)	2.79 (10.3)	1.98 (6.18)	2.89 (11.1)	2.11 (6.62)
Median [Min, Max]	0 [0, 194]	0 [0, 80.9]	0 [0, 194]	0 [0, 80.9]
Adulthood thyroid radiation doses in mGy (%)				
0	669 (48.1)	797 (50.4)	523 (48.8)	591 (49.7)
]0,1]	247 (17.7)	283 (17.9)	187 (17.4)	220 (18.5)
]1,5]	245 (17.6)	262 (16.6)	182 (17.0)	193 (16.2)
]5,10]	59 (4.2)	61 (3.9)	46 (4.3)	46 (3.9)
]10,20]	53 (3.8)	43 (2.7)	44 (4.1)	35 (2.9)
>20	119 (8.5)	134 (8.5)	90 (8.4)	103 (8.7)
Mean (sd)	5.63 (17.3)	5.50 (17.9)	5.28 (16.6)	5.54 (17.2)
Median [Min, Max]	0 [0, 245]	0.02 [0, 262]	0.02 [0, 245]	0.02 [0, 157]
Number of children (%)				
0 (and men)	666 (47.8)	829 (52.5)	514 (47.9)	622 (52.4)
1-3	648 (46.6)	529 (43.8)	542 (50.6)	542 (45.6)
4-6	67 (4.8)	44 (3.4)	10 (0.9)	20 (1.7)
>6	11 (0.4)	4 (0.3)	6 (0.6)	4 (0.3)
Study				
Young-Thyr (%)	805 (57.8)	876 (55.4)	629 (58.7)	656 (55.2)
Cathy (%)	587 (42.2)	704 (44.6)	443 (41.3)	532 (44.8)
Thyroid cancer histology (%)				
Follicular	140 (10.1)		109 (10.2)	
Papillary	1243 (89.2)		955 (89.1)	
Missing	10 (0.7)		8 (0.7)	
Thyroid cancer size in mm (%)				
< 10	431 (31.0)		341 (31.8)	
> 10	957 (68.8)		729 (68.0)	
Missing	4 (0.28)		2 (0.2)	

Table 3 Number of subjects by age and exam type

	Cases n (%) having at least 1 listed exam		Controls n (%) having at least 1 listed exam	
	<20 years	>=20 years	<20 years	>=20 years
Conventional radiography				
Skull	89 (6.4)	93 (6.7)	94 (5.9)	82 (5.2)
Sinus	67 (4.8)	124 (8.9)	77 (4.9)	133 (8.4)
Dental	416 (29.9)	260 (18.7)	555 (35.1)	309 (19.6)
Spine	180 (12.9)	277 (19.9)	199 (12.6)	296 (18.7)
Chest	159 (11.4)	451 (32.4)	198 (12.5)	465 (29.4)
Intravenous urography	27 (1.9)	94 (6.7)	31 (2.0)	74 (4.7)
CT scan				
Abdomen	7 (0.5)	47 (3.4)	2 (0.1)	33 (2.1)
Chest	8 (0.6)	46 (3.3)	0 (0)	33 (2.1)
Skull	53 (3.8)	137 (9.8)	47 (3.0)	117 (7.4)
Spine	31 (2.22)	122 (8.75)	29 (1.83)	160(10.12)
Nuclear medicine				
Cerebral	1 (0.1)	3 (0.2)	0 (0)	9 (0.6)
Heart	1 (0.1)	2 (0.1)	1 (0.1)	7 (0.4)
Lung	1 (0.1)	3 (0.2)	0 (0)	7 (0.4)
Bones	8 (0.6)	43 (3.1)	6 (0.4)	52 (3.3)
Hepatic	0 (0)	2 (0.1)	0 (0)	2 (0.1)
Renal	4 (0.3)	5 (0.4)	5 (0.3)	13 (0.8)

Table 4: Dose-response analysis for thyroid radiation dose: – Whole population and subgroups

	Whole population: Adjusted analysis				Only micro-carcinomas cases (431 cases and 1580 controls)				Excluding micro-carcinomas cases (962 cases and 1580 controls)			
	Coefficient (95%CI) for 1 mGy	OR ^a (95%CI) at 1 mGy	Deviance	P-value	Coefficient (95%CI) for 1 mGy	OR ^a (95%CI) at 1 mGy	Deviance	P-value	Coefficient (95%CI) for 1 mGy	OR ^a (95%CI) at 1 mGy	Deviance	P-value
No radiation dose-			3966.7				2370.9				3029.4	
The radiation dose received during childhood												
Linear	0.017 (0.00060, 0.035)	1.02 (1.00, 1.03)	3959.5	0.007	0.024 (-0.0024, 0.051)	1.02 (1.00, 1.05)	2363.6	0.008	0.015 (-0.0041, 0.035)	1.01 (0.99, 1.04)	3025.2	0.04
Quadratic	0.00053 (-0.00047-0.0011)	1 (1.00, 1.00)	3957.9	0.003	0.00078 (-0.00011, 0.0017)	1 (1.00, 1.00)	2361.8	0.003	0.00048 (-0.00015, 0.00079)	1 (1.00, 1.00)	3024	0.02
Exponential	0.022 (0.0081-0.036)	1.01 (1.01, 1.04)	3058.4	0.004	0.026 (0.010, 0.042)	1.03 (1.01, 1.04)	2362	0.003	0.021 (0.0049-0.037)	1.02 (0.99, 1.05)	3024.6	0.03
The radiation dose received during adulthood												
Linear	8.7 10 ⁻⁵ (-6.0.10 ⁻⁴ , 7.7.10 ⁻⁴)	1 (1.00, 1.00)	3966.7	>0.9	-8.6 10 ⁻⁴ (-5.8.10 ⁻³ , 4.0.10 ⁻³)	1 (0.99, 1.01)	2370.8	> 0.9	-2.7 10 ⁻⁵ (-5.4 10 ⁻³ , 5.3.10 ⁻³)	1 (1.0, 1.00)	3029.4	> 0.9
Quadratic	-9.1 10 ⁻⁶ (-2.610 ⁻⁵ , 7.4 10 ⁻⁶)	1 (1.00, 1.00)	3966.2	>0.5	-6.0 10 ⁻⁵ (-3.1 10 ⁻⁵ , 1.9 10 ⁻⁵)	1 (1.00, 1.00)	2370.7	> 0.9	-1.5 10 ⁻⁵ (-1.5 10 ⁻⁵ , 1.5 10 ⁻⁵)	1 (1.00, 1.00)	3028.5	0.4
Exponential	1.2 10 ⁻⁴ (-0.0089, 0.0091)	1 (0.99, 1.01)	3966.7	>0.9	-1.6 10 ⁻³ (-0.014, 0.011)	1 (0.99, 1.01)	2370.8	> 0.9	-3.4 10 ⁻³ (-0.011, 0.011)	0.99 (0.99, 1.01)	3029.4	> 0.9

^a Stratified on age, sex, and study, and adjusted on thyroid cancer family history, radiotherapy history, BMI, height, smoking habits, and number of pregnancies

Table 5 SNPs with the lowest p-values associated with DTC risk in the meta-analysis among all DTC types cases (A), among only papillary DTC cases (B), macrocarcinoma cases (C), and microcarcinoma cases (D)

A/ SNPs with lowest p-values associated with DTC risk in the meta-analysis including all histological types												
SNP	Locus	RA	EA	EAF	Gene	Young-Thyr		CATHY		Meta-analysis		
						OR ^a	P-value	OR ^a	P-value	OR ^a	P-value	FDR p-value
rs12702628	7p21.3	A	G	0.4	RPA3	1.25	1.03 10 ⁻²	1.22	4.37 10 ⁻²	1.24	1.12 10 ⁻⁰³	0.02
rs7164173	15q26.1	G	T	0.1	CHD2	0.7	1.05 10 ⁻³	0.69	1.06 10 ⁻²	0.68	9.26 10 ⁻⁰⁵	0.004
rs1059394	18p11.32	C	T	0.3	ENOSF1/THYS	1.34	2.91 10 ⁻³	1.19	8.97 10 ⁻²	1.3	7.81 10 ⁻⁰⁴	0.01
rs699517	18p11.32	C	T	0.3	ENOSF1/THYS	1.34	2.91 10 ⁻³	1.19	8.97 10 ⁻²	1.3	7.81 10 ⁻⁰⁴	0.01
rs6067822	20q13.2	G	T	0.3	NFATc2	0.64	1.6 10 ⁻³	0.7	1.13 10 ⁻³	0.64	5.79 10 ⁻⁰⁵	0.005
B/ SNPs with lowest p-values associated with papillary thyroid carcinoma risk in the meta-analysis (563 cases from Young-Thyr and 392 cases from CATHY)												
SNP	Locus	RA	EA	EAF	Gene	Young-Thyr		CATHY		Meta-analysis		
						OR ^a	P-value	OR ^a	P-value	OR ^a	P-value	FDR p-value
rs1950764	14q24.1	G	A	0.2	RAD51B	0.56	2.87 10 ⁻⁰³	0.66	7.27 10 ⁻⁰²	0.6	6.08 10 ⁻⁰⁴	0.01
rs1290997	14q24.1	G	T	0.2	RAD51B	0.77	2.01 10 ⁻⁰³	0.7	7.18 10 ⁻⁰²	0.74	4.36 10 ⁻⁰⁴	0.01
rs7164173	15q26.1	G	T	0.3	CHD2	0.69	3.24 10 ⁻⁰³	0.68	1.02 10 ⁻⁰²	0.68	9.33 10 ⁻⁰⁵	0.009
rs77971457	20q13.2	G	T	0.1	NFATc2	1.44	1.09 10 ⁻⁰³	1.47	1.76 10 ⁻⁰²	1.45	5.06 10 ⁻⁰⁴	0.01
rs6067822	20q13.2	G	T	0.3	NFATc2	0.81	3.47 10 ⁻⁰³	0.72	4.63 10 ⁻⁰²	0.77	5.59 10 ⁻⁰⁴	0.01
C/ SNPs with lowest p-values associated with large thyroid carcinoma (>10mm) risk in the meta-analysis (501 cases from Young-Thyr and 237 cases from CATHY)												
SNP	Locus	RA	EA	EAF	Gene	Young-Thyr		CATHY		Meta-analysis		
						OR ^a	P-value	OR ^a	P-value	OR ^a	P-value	FDR p-value
rs72625242	2q31.1	C	T	0.22	MLK7-AS1	1.927	6.27 10 ⁻³	0.9934	1	1.927	6.25 10 ⁻³	0.004
rs17619600	2q37.1	T	C	0.15	PMSD1	1.855	1.20 10 ⁻³	1.01	0.9999	1.855	1.20 10 ⁻³	0.004
rs7578070	2p24.2	A	G	0.41	SMC6	1.538	1.86 10 ⁻³	1.03	0.9998	1.538	1.86 10 ⁻³	0.004
rs16861406	2q31.1	A	G	0.21	MLK7-AS1	1.912	2.56 10 ⁻³	1.009	1	1.912	2.56 10 ⁻³	0.005
rs5023821	10q26.2	T	C	0.25	C10orf90	0.6249	1.14 10 ⁻³	1.026	0.9998	0.6249	1.14 10 ⁻³	0.004
D/ SNPs with lowest p-values associated with small thyroid carcinoma (<10mm) risk in the meta-analysis (128 cases from Young-Thyr and 206 cases from CATHY)												
SNP	Locus	RA	EA	EAF	Gene	Young-Thyr		CATHY		Meta-analysis		
						OR ^a	P-value	OR ^a	P-value	OR ^a	P-value	FDR p-value
rs75361806	2q31.1	A	G	0.05	TLK1	25.55	1.12 10 ⁻²	1.02	1	25.5494	1.12 10 ⁻²	0.03
rs73234091	20p12.1	T	C	0.05	MACROD2	30.89	6.99 10 ⁻³	1.007	1	30.8891	6.99 10 ⁻³	0.03
rs17757541	18q21.33	C	G	0.06	BCL2	7.188	1.22 10 ⁻²	1.005	1	7.1877	1.12 10 ⁻²	0.01
rs116851051	20p12.1	T	C	0.1	MACROD2	28.39	1.12 10 ⁻²	0.9935	1	28.3897	1.12 10 ⁻²	0.035
rs2327965	20p12.1	A	G	0.05	MACROD2	27.11	1.12 10 ⁻²	1.016	1	27.1096	1.12 10 ⁻²	0.03

RA=Reference allele

EA= Effect allele

EAF= Effect allele frequency

^a: Adjusted on age, sex, childhood IR thyroid doses, thyroid cancer family history, radiotherapy history, goiter history, BMI, height, educational level, smoking status, number of pregnancies, and three first genetic components

Table 6 Five SNPs with the lowest p-values in SNPs - diagnostic radiation thyroid doses interaction term from the meta-analysis

SNP	Locus	Reference allele	Effect allele	EAF	Gene	Young-Thyr		CATHY		Meta-analysis		
						OR ^a	P value	OR ^a	P value	OR	P value	FDR correction
rs10779613	1q41	T	C	0.4	<i>SMYD2</i>	0.60	1.19 10 ⁻⁰³	0.94	6.08 10 ⁻⁰¹	0.80	5.42 10 ⁻⁰³	0.1
rs17514740	7p11.2	G	C	0.4	<i>EGFR</i>	0.71	9.39 10 ⁻⁰³	1.19	1.84 10 ⁻⁰¹	1.30	4.64 10 ⁻⁰³	0.1
rs7068306	10q26.3	C	G	0.3	<i>MGMT</i>	0.63	1.91 10 ⁻⁰³	0.70	5.85 10 ⁻⁰²	0.65	3.40 10 ⁻⁰⁴	0.03
rs10402248	19p13.3	C	T	0.4	<i>MUM1</i>	0.65	4.79 10 ⁻⁰³	0.85	2.54 10 ⁻⁰¹	0.75	4.03 10 ⁻⁰³	0.1
rs6066138	20q13.12	G	A	0.2	<i>EYA2</i>	1.52	9.73 10 ⁻⁰³	1.22	9.01 10 ⁻⁰²	1.32	2.20 10 ⁻⁰³	0.1

EAF= Effect allele frequency

OR = Odds Ratio for the interaction between Effect Allele and radiation dose, considered as a continuous variable in an exponential dose-response model

^a: Adjusted on age, sex, thyroid cancer family history, radiotherapy history, goiter history, BMI, height, educational level, smoking status, number of pregnancies, and three first genetic components

Cancer Epidemiology, Biomarkers & Prevention

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