REVIEW

Genetic susceptibility to radiation-related differentiated thyroid cancers: a systematic review of literature

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Abstract

The first study establishing exposure to ionizing radiations (IRs) as a risk factor for differentiated thyroid cancer (DTC) was published 70 years ago. Given that radiation exposure causes direct DNA damage, genetic alterations in the different DNA repair mechanisms are assumed to play an important role in long-term IR-induced DNA damage prevention. Individual variations in DNA repair capacity may cause different reactions to damage made by IR exposure. The aim of this review is to recapitulate current knowledge about constitutional genetic polymorphisms found to be significantly associated with DTC occurring after IR exposure. Studies were screened online using electronic databases – only fully available articles, and studies performed among irradiated population or taking radiation exposure as adjustment factors and showing significant results are included. Nine articles were identified. Ten variants in/near to genes in six biological pathways, namely thyroid activity regulations, generic transcription, RET signaling, ATM signaling and DNA repair pathways were found to be associated with radiation-related DTC in these studies. Only seven variants were found to be in interaction with IR exposure in DTC risk. Most of these variants are also associated to sporadic DTC and are not specific to IR-related DTC. In the published studies, no data on children treated with radiotherapy is described. In conclusion, more studies carried out on larger cohorts or on case-control studies with well-documented individual radiation dose estimations are needed to get a comprehensive picture of genetic susceptibility factors involved in radiation-related DTC.

Key Words:

- thyroid
- molecular genetics
- carcinoma

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Introduction

Differentiated thyroid cancer (DTC) is the most frequent malignancy of the endocrine system (Siegel *et al.* 2017), of which the main risk factor is ionizing radiation (IR) exposure, particularly if occurring during childhood. Papillary thyroid carcinoma (PTC) is the most frequent histology type of DTC, representing almost 80% of DTC cases. PTC is also the most frequent type among familial DTC, which represents between 3 and 9% of new DTC cases diagnosed each year (Vriens *et al.* 2009).

The first study establishing IR exposure as a risk factor for DTC was published 70 years ago and was conducted on children exposed to thymus irradiation soon after birth (Duffy & Fitzgerald 1950). More recently, this major risk factor was confirmed among Japanese atomic bomb survivors and Chernobyl-irradiated populations (Socolow *et al.* 1963, Tronko *et al.* 2017).

Radiation exposure causes direct DNA damage, and most frequently double-strand breaks (Michalik 1993). Therefore, efficient DNA repair mechanisms play an important role in long-term IR DNA damage effect prevention. This implies, *inter alia*, that individual variation in DNA repair capacity may cause different reaction to DNA damage induced by IR exposure. Thus, the question of an individual genetic susceptibility to radiation-related DTC may be raised. However, while at the somatic level (i.e. in the tumor tissue), molecular signature of radiation-related thyroid tumors was the subject of several studies (Detours *et al.* 2007, Ory *et al.* 2011), few data on the contribution of genetic risk factors to radiation-related DTC have been reported so far.

The aim of this systematic review is to recapitulate current knowledge on constitutional genetic variants associated with DTC occurring after irradiation, as well as knowledge about the potential interaction between genetic factors and IR exposure in DTC risk.

Literature search strategy and inclusion criteria

We performed a literature search to identify relevant published studies up to July 2019 using PubMed and Web of Science as sources in accordance with 'Preferred Reporting Items for Systematic review and Meta-Analysis Protocols' (PRISMA-P) (Supplementary Table 1, see section on [supplementary data](#) given at the end of this article) (Moher *et al.* 2009, 2016). The following sets of keywords were used to identify relevant studies:

'radiation related thyroid cancer genetic risk', 'radiation thyroid cancer DNA polymorphism', 'radiation thyroid cancer DNA variant' with the Boolean operator 'OR' between the three sets.

To be included in this review, the study should fulfill the following criteria: (i) the article was fully available in English language, (ii) genetic polymorphisms should have been investigated on germline DNA (usually blood or saliva DNA) and a significant result is reported, and (iii) cases having developed DTC had received IRs to the thyroid, and radiation doses were used as an adjustment factor in the association analysis or the interaction between radiation exposure and genetic factors was considered. Articles dealing with sporadic DTC susceptibility only were not considered for this review.

Results

Using the defined sets of key words, a first number of records were identified. Titles and abstracts of these articles were scanned to identify studied populations, irradiation type and type of analyses. At the end of this step, 14 articles were selected for full text assessment. When screening the 'Materials and methods' section, five articles were excluded for three reasons: analysis had been performed on tumor DNA (Rogounovitch *et al.* 2006, Vodusek *et al.* 2016), no positive association with DTC was evidenced (Boaventura *et al.* 2016), and/or the full text was not available (Shkarupa *et al.* 2014, 2015) (Fig. 1). Finally, nine articles fulfilled our criteria and reported significant association or interaction between genetic factors and radiation-related DTC. These articles are presented in Table 1. SNPs and a length polymorphism showing significant association with radiation-related DTC in at least one study are presented in Table 2, and SNPs showing significant interaction with radiation exposure in at least one study are presented in Table 3. We recapitulated only significant findings from selected studies by biological pathways. The genes harboring these polymorphisms or being located nearby are involved in thyroid activity regulations, generic transcription, *RET* signaling, *ATM* signaling or DNA repair pathways.

Thyroid activity regulation pathway

Thyroid activity is regulated by a complex system of hormones and receptors. Notably, this system involves the following genes: thyroid-stimulating hormone receptor (*TSHR*), Forkhead box E1 (*FOXE1*) also known

Figure 1

Flow diagram for selection of the studies included in this review.

as thyroid transcription factor 2 (*TTF-2*), which regulates the transcription of thyroglobulin (*TG*) and thyroperoxydase (*TPO*), and NK2 homeobox 1 (*NKX2-1*; also known as thyroid transcription factor 1 (*TTF-1*)) genes, which regulate the transcription of genes specific for the thyroid, lung, and diencephalon (Guazzi *et al.* 1990). The contribution of common variants in *FOXE1*, *NKX2* and *TSHR* has been investigated in the context of radiation-related DTC. Findings from these studies are summarized hereafter.

FOXE1

FOXE1 (*TTF-2*) at 9q22.33 is predominantly expressed in the thyroid gland and in the anterior pituitary gland. The FOX family of transcription factors participates in the induction of the WNT5A (wingless-type MMTV integration site family member 5A) expression (Katoh & Katoh 2009). *FOXE1* plays an essential role in thyrocyte precursor migration, thyroid organogenesis and differentiation (Trueba *et al.* 2005). This transcription factor recognizes a binding site on the promoters of *TG* and *TPO*, which are genes exclusively expressed in the thyroid.

Among irradiated populations (Tables 2 and 3), the first publications aimed to assess the contribution of SNPs at the *FOXE1* locus in radiation-related DTC. A case-control study conducted in the Belarusian population suggested a role of the *FOXE1* intronic variant rs965513 (Takahashi *et al.* 2010). The role of *FOXE1* was then confirmed by an independent study involving Belarusian children exposed to radiation (Damiola *et al.* 2014). A suggestive association was found for carriers of the minor allele of

rs965513 ($OR_{\text{per allele}} = 1.4$, 95% CI 0.9–2.1) and of the minor allele of rs1867277 located in the 5'UTR of *FOXE1* ($OR_{\text{per allele}} = 1.6$, 95% CI 1.0–2.3). In French Polynesia, rs965513 was also associated with DTC ($OR = 1.5$, 95% CI 1.1–2.0) under allelic model of inheritance), but no significant association with rs1867277 was found (Maillard *et al.* 2015). In the same study, subjects being homozygotes for the minor allele of the poly-alanine stretch polymorphism rs71369530 located in exon 62 of *FOXE1* were also at increased DTC risk ($OR = 4.1$, 95% CI 1.0–15.9) (Maillard *et al.* 2015) (Tables 2 and 3).

Lastly, a case-control study carried out in a Japanese non-irradiated population as well as in a Belarus population sample that had been exposed to IR revealed association of DTC with rs965513 and rs1867277 in both groups, but no association with rs71369530 (Nikitski *et al.* 2017).

In sporadic DTC cases, rs965513 at 9q22.33 was the leading SNP nearby *FOXE1* associated with genetic DTC in the first genome-wide association study (GWAS) conducted on this cancer ($OR = 1.7$, 95% CI 1.5–1.9) (Gudmundsson *et al.* 2009). Several SNPs in linkage disequilibrium (LD) with this SNP were associated with DTC susceptibility at this locus (Gudmundsson *et al.* 2009). The minor allele of rs966513 and the minor allele of rs1867277 were subsequently found to be associated with both sporadic and familial DTC in the Portuguese population ($OR_{\text{rs966513}} = 2.5$, 95% CI 1.8–3.6 $OR_{\text{rs1867277}} = 1.7$, 95% CI 1.2–2.4) (Tomaz *et al.* 2012). Fine-mapping studies showed that the associations of DTC with rs965513 and rs1867277 were not independent as the two SNPs lie in the same LD block (Jones *et al.* 2012, Tcheandjieu *et al.* 2016).

Table 1 Characteristics of the reviewed studies.

Study and year of publication	Design and sample size	Population ancestry	Type of exposure	Reported outcome	Studied genes/loci	Results	Comments
Lönn <i>et al.</i> 2007	Case-control study nested within a cohort of US radiologic technologist: 167 PTC cases 491 controls	White American for 98% of cases and 97% of controls	Occupation exposure among US radiologic technologist cohort	PTC risk	EPAC GFRA1 GFRA3 RET TSHR	Increasing risk found for RET p. Gly691Ser carriers (rs1799939), especially among women under 38 years.	All persons included in the cohort were certified by the American registry of radiologic technologist for more than 2 years between 1926 and 1982.
Sigurdson <i>et al.</i> 2009	Case-control study: 907 subjects with thyroid nodules of whom 25 had PTC 914 controls	Kazakh and Russians who lived near Semipalatinsk nuclear test site and who were younger than 20-year-old at the time of the tests	Fallouts from nuclear tests in Kazakhstan	Thyroid nodule risk; Thyroid cancer risk	APEX BRCA1 BRCA2 BRIP1 CHEK2 EPAC GFRA1 GFRA3 RAD18 RET TGFB1 TSHR XRCC1 ZNF350	Polymorphisms in rs1800862 (RET) and in DNA repair and proliferation genes may be related to risk of thyroid nodules. Borderline gene-radiation interaction was found for a variant in rs1799782 (XRCC1).	The reconstruction of individual radiation doses to the thyroid gland was based on fallout patterns of 11 nuclear tests, residential history and childhood diet and especially locally produced milk consumption.
Akulevich <i>et al.</i> 2009	Case-control study: 123 IR-exposed PTC cases 132 sporadic PTC cases 198 IR-exposed controls 398 unexposed controls	All Caucasians and were younger than 18 y. o. at the time of the Chernobyl accident.	Fallouts from Chernobyl nuclear accident in Russia and Belarus	PTC risk and SNPs interactions with IR exposure	ATM MTF1 TP53 XRCC1 XRCC3	SNPs in DNA damage response genes may be potential risk modifiers of IR-induced or sporadic PTC. An interaction was found between IR and a rs1042522 (TP53)	IR thyroid doses varied from 43 to 2640 mGy among exposed Belarussian cases and controls. IR exposure in cases and controls from Belarus were evaluated in dosimetric investigations and ranged 21–1500 mGy.
Takahashi <i>et al.</i> 2010	Case-control study: 187 PTC cases 172 controls	All Caucasians and younger than 15 y.o. when exposed.	Fallouts from Chernobyl nuclear accident.	Genetic individual susceptibility to radiation-related PTC	Genome-wide association study	FOXE1 locus (rs965513) associated with radiation-related PTC	All cases and 620 controls are considered to have received IR doses to the thyroid ranging 21–1500 mGy.

Damiola <i>et al.</i> 2014	Case-control study: 83 radiation-related PTC cases 324 controls	Belarusian children living in the area contaminated by fallout from the Chernobyl accident.	Fallouts from Chernobyl nuclear accident, Belarus.	Genetic individual susceptibility to radiation-related PTC	1p12-13 <i>ATM</i> <i>FOXE1</i> <i>NKX2</i> <i>Pre-miR-146a</i> <i>TSHR</i> <i>WDR3</i>	Some SNPs rs3092993, rs1801516 (<i>ATM</i>) and rs1867277 (<i>FOXE1</i>) associated with radiation-related PTC; an interaction between rs1800889 (<i>ATM</i>) and exposure to IR	The reconstruction of individual radiation doses to the thyroid gland were based on residential history, dietary habits, and environmental contamination.
Maillard <i>et al.</i> 2015	Case-control study: 165 PTC cases 258 controls	Polynesians younger than 15 y.o at the time of the first nuclear test in French Polynesia.	Fallouts from nuclear tests in French Polynesia	Genetic individual susceptibility to radiation-related DTC	<i>ATM</i> <i>FOXE1</i> <i>NKX2</i>	Some SNPs rs1867277 (<i>ATM</i>) and rs71369530 (<i>FOXE1</i>) SNPs associated with DTC; an interaction between rs944289 (<i>NKX2-1</i>) and exposure to IR	Doses reconstructed from available data and evaluated in dosimetric investigations
Shkarupa <i>et al.</i> 2016	Case-control study: 38 radiation-related TC female? cases 64 sporadic cases 45 controls	Ukrainian	Fallouts from Chernobyl	Relationship between polymorphism XPD p. Lys751Gln and radiation-related TC and assessment of chromosome aberration	1 SNP in <i>XPD</i>	Homozygous carriers of the minor allele <i>XPD</i> Gln751Gln have an increased risk of TC	Multiple level of exposure: Chernobyl recovery workers, evacuees, and the residents of contaminated areas.
Lonjou <i>et al.</i> 2017	Case-control study: 75 PTC cases 254 controls	Belarusian children living in the area contaminated by fallout from the Chernobyl accident.	Fallouts from Chernobyl nuclear accident, Belarus.	Genetic individual susceptibility to radiation-related PTC	Assessment of a panel of 141 DNA repair- related SNPs located in 43 genes: <i>APEX1</i> <i>BARD1</i> <i>BLM</i> <i>BRCA1</i> <i>BRCA2</i> <i>BRIP1</i> <i>ERCC1</i> <i>ERCC2</i> <i>ERCC3</i> <i>ERCC4</i> <i>ERCC5</i> <i>ERCC6</i> <i>EXO1</i> <i>FANCA</i> <i>LIG1</i> <i>LIG3</i> <i>LIG4</i> <i>NBN</i> <i>OGG1</i>	Association of rs2296675 (MGMT) with DTC	Individual radiation dose to the thyroid was reconstructed based on the residential history and dietary habits, and information on environmental contamination for each settlement.

(Continued)

Table 1 Continued.

Study and year of publication	Design and sample size	Population ancestry	Type of exposure	Reported outcome	Studied genes/loci	Results	Comments
Sandler <i>et al.</i> 2018	Case-control study: 462 PTC cases 254 controls	Connecticut residents	Diagnostic radiation exposure	Relationship between DNA repair genes and both sporadic and radiation-related TC	PARP1 PCNA PMS1 PMS2 POLB POLD1 RAD23B RAD51 RAD52 RAD54L WRN XPA XPC XRCC1 XRCC3 XRCC4 XRCC5 ALKBH3 ERCC5 HUS1 LIG1 MGMT PARP4 RPA3 TOPBP1 UBE2A XRCC2	Some SNPs: rs10768994 and rs2163619 (ALKBH3), rs10421339 (LIG1) and rs10234749 (XRCC2) interact with IR exposure in DTC risk.	For the gene- radiation interaction study, exposure was defined as exposure to any of the listed procedures. Non-exposure was defined as lack of exposure to any of these 12 procedures

Moreover other SNPs in LD with rs965513 and rs1867277 may alter transcription factors or regulatory binding sites of EWSR1-FLI1, E2F1 and AP-2 α (Tcheandjieu *et al.* 2016). These latter proteins are indeed overexpressed in sporadic PTC cases and may play a role in PTC pathogenesis (Di Vito *et al.* 2011).

NKX2-1

NKX2-1 at 14q13.3 encodes another thyroid-specific transcription factor which binds to the thyroglobulin promoter and regulates the expression of thyroid-specific genes. It was shown to regulate the expression of genes involved in morphogenesis such as in forebrain, thyroid and developing lung. *NKX2-1* also plays an important role in differentiated thyroid tissue architecture maintenance (Kusakabe *et al.* 2006).

In the population from French Polynesia where nuclear weapons tests occurred (Tables 2 and 3), we reported a significant interaction between rs944289 located 337kb telomeric of *NKX2-1* and irradiation exposure. Subjects with the T/T genotype and who received 2mGy or less to the thyroid gland were at increased risk of DTC as compared to subjects with C/C and C/T genotypes (OR=6.1, 95% CI 1.2–31.3) (Maillard *et al.* 2015). This result stands for subjects with the T/T genotype who received a radiation dose at greater than 2mGy (OR=6.94, 95% CI 1.31–37.0). However, no association between rs944289 and DTC risk was evidenced when interaction with IR was not considered in the analysis (Maillard *et al.* 2015).

The first GWAS conducted on sporadic DTC in the Icelandic and European populations identified SNPs at the 14q13.3 locus containing *NKX2-1*. OR associated with the leading SNP rs944289 at this locus was OR_{per allele}=1.44, 95% CI 1.26–1.63 (Gudmundsson *et al.* 2009). Similar risk estimates were found for rs944289 in the Japanese population (OR=1.4, 95% CI 1.2–1.5) (Matsuse *et al.* 2011) and in an independent European population sample composed of 508 cases and 626 controls (OR_{per allele}=0.7, 95% CI 0.6–0.9) (Tcheandjieu *et al.* 2016). The protective OR in the last study is due to the different risk allele (C instead of T allele in the two other studies).

Taken together, *NKX1-2* seems to play a role in both sporadic and radiation-related DTC.

TSHR

TSHR at 14q31.1 encodes the thyrotropin and thyrostimulin membrane receptor which is a major controller of thyroid cell metabolism. SNPs in *TSHR*

were associated with benign and autoimmune thyroid pathologies (Roberts *et al.* 2017).

In the context of radio-related DTC, the missense variant rs1991517 (p.Asp727Glu) and two additional SNPs (the intronic variant rs2284716 and the synonymous variant rs2075179 (p.Asn187) were investigated among US radiologic technologists study (Lönn *et al.* 2007) and no statistically significant association was found. However, an increased PTC risk was found for carriers of the minor allele of rs1991517 in the population from Kazakhstan exposed to nuclear tests at Semipalantisk sites, and the reported risk estimates was quite high (OR_{per allele}=8.3, 95% CI 2.5–28.0) (Sigurdson *et al.* 2009) (Tables 2 and 3).

Of note, the contribution of rs1991517 to sporadic DTC risk was investigated in two populations from Canada and from the British Isles (304 sporadic cases and 400 controls in total) and failed to show an association (Matakidou *et al.* 2004).

Generic transcription pathway

ZNF350

ZNF350 located at 19q14 encodes a zinc finger protein which binds to *BRCA1* (Zheng *et al.* 2000) and *RNF11* (Li & Seth 2004). To our knowledge, *ZNF350* role in TC risk was only investigated among the irradiated population living near the Semipalatinsk nuclear test site in Kazakhstan in the candidate gene study. In this Belarusian population, carriers of the minor allele of the missense variant rs22778420 (p.Leu66Pro) had a reduced risk of developing PTC (OR_{per allele}=0.3, 95% CI 0.1–0.9) as compared to non-carriers (Sigurdson *et al.* 2009).

RET signaling pathway

RET

The rearranged during transfection (*RET*) proto-oncogene at 10q11.21 encodes a transmembrane receptor which is a member of the tyrosine protein kinase family of proteins. The first study involving *RET* in the etiology of PTC was published in 1990 (Grieco *et al.* 1990). It was then showed that *RET* undergoes oncogenic activation through cytogenetic rearrangements and that 77 point mutations constitutively activate the RET kinase (Mulligan 2014).

With regard to its role on DTC susceptibility in radiation-exposed populations, one study conducted among US radiologic technologists (Lönn *et al.* 2007) found a borderline significant increased DTC risk for carriers of the minor allele of rs1799939 (p.Gly691Ser). This risk was especially pronounced among young women aged

Table 2 SNPs associated with radiation related differentiated thyroid cancer risk.

Genes	SNPs	Reference allele	Variant	Studies	OR	95% CI
FOXE1	rs965513	A	G	Takahashi <i>et al.</i> 2010 Maillard <i>et al.</i> 2015 Maillard <i>et al.</i> 2015	1.65 ^a 1.5 4.11 ^b	1.43–1.91 1.06–2.02 1.07–15.9
FOXE1	rs71369530 (Length polymorphism)	Short (coding for 12–14 alanines)	Long (coding for alleles coding for 16–19 alanines)			
FOXE1	rs1867277	G	A	Damiola <i>et al.</i> 2014	1.55 ^a	1.03–2.34
ATM	rs3092993	A	C	Damiola <i>et al.</i> 2014	0.34 ^a	0.13–0.89
ATM	rs1801516	G	A	Damiola <i>et al.</i> 2014 Maillard <i>et al.</i> 2015	0.34 ^a 3.13 ^a	0.16–0.73 1.17–8.31
MGMT	rs2296675	A	G	Lonjou <i>et al.</i> 2017	2.54 ^a	1.50–4.30
ZNF350	rs2278420	T	C	Sigurdson <i>et al.</i> 2009	0.3 ^a	0.1–0.9
TSHR	rs1991517	A	G	Sigurdson <i>et al.</i> 2009	3.1 ^a	1.3–7.4
RET	rs1799939	G	A	Lönn <i>et al.</i> 2007	1.4 ^a 2.1 ^{a, c}	0.9–2.0 1–11.8 ^{a, c}
ERCC2 (XPD)	rs1052559	C	A	Shkarupa <i>et al.</i> 2016	3.66 ^a	1.04–12.84

^aOR under allelic model of inheritance. ^bOR among homozygous minor allele carriers versus other genotypes. ^cOR among young women under 38 years old at diagnosis.

younger than 38 years at diagnosis (Table 2). In line with these results, another study conducted in the population from Kazakhstan (Sigurdson *et al.* 2009) found an increased risk of radiation-related thyroid nodules and a suggestive association with increased risk of PTC for carriers of the minor allele of rs1800862 (p.Ser836Ser) (Table 2).

In sporadic PTC susceptibility, a role for the SNP rs1800861 (p.Leu769Leu, G/T) was suggested in a sample composed of 247 sporadic PTC cases and 219 controls from four different populations where individuals with the GG genotype of rs1800861 were over-represented in the PTC cases (Lesueur *et al.* 2002). Heterozygous individuals for the same SNP (genotype TG) were also found at increased risk of DTC after multivariate adjustment ($OR_{\text{genotype}} = 2.0$, 95% CI 1.2–3.4) in an independent study (Ho *et al.* 2005). However, in an Indian population, carriers of the G allele were underrepresented in both follicular thyroid carcinoma (FTC) and PTC cases as compared to healthy controls (Khan *et al.* 2015).

Finally, the minor allele C of rs1800862 (p.Ser836Ser) was also found to be over-represented in PTC cases as compared to controls ($OR_{\text{per allele}} = 1.6$, 95% CI 1.1–2.4) in a Portuguese population sample (Santos *et al.* 2014).

ATM signaling pathway

Ataxia-telangiectasia mutated serine/threonine kinase (ATM) downstream signaling pathways include a canonical pathway which is activated by double-strand DNA breaks and activates the DNA damage checkpoint. The non-canonical pathways are activated by other forms of cellular stress. Activation of the IR-related ATM canonical pathway results in the phosphorylation of a vast network of substrates, including the key checkpoint kinase and the tumor suppressor p53 (TP53). ATM is recruited and activated by DNA double-strand breaks. It is the master regulator of DNA damage response since the first step in this response to double-strand breaks induced by ionizing irradiation is sensing of the DNA damage by ATM (Karlseder *et al.* 1999).

ATM

The ATM gene at 11q22-23 was first associated to DTC in 2009, in a study involving IR-exposed and non-exposed populations from the Chernobyl areas (Akulevich *et al.* 2009). Among the irradiated population, Akulevich *et al.* reported that thyroid doses ranged between 4 and

Table 3 SNPs showing interaction with ionizing radiation exposure.

Genes	SNPs	Major allele	Minor allele	Studies	OR _{interaction} (95% CI)
ALKBH3	rs10768994	T	C	Sandler <i>et al.</i> 2018	2.88 (1.13–7.29)
LIG1	rs2163619	G	A		2.40 (1.3–4.42)
LIG1	rs10421339	G	C		2.50 (1.34–4.69)
XRCC2 ^a	rs10234749 ^a	C	A		7.82 (2.20–27.78) ^a
NKX2-1	rs944289	C	T	Maillard <i>et al.</i> 2015	6.94 (1.31–37.0) ^b
ATM	rs1800889	T	C	Damiola <i>et al.</i> 2014	0.01 (0–0.91)
TP53	rs1042522	G	C	Akulevich <i>et al.</i> 2009	1.8 (1.06–2.36)

^aOnly in the thyroid microcarcinoma sub-analysis. ^bAmong homozygous carriers of the minor allele who received a thyroid radiation dose >2 mGy.

1640mGy, the biggest doses having been seen among youngest participants. In this first study, IR exposure was taken as binomial adjustment variable (yes/no) in all analyses. The minor allele of the missense SNP rs1801516 (p.Asp1853Asn) was found to be associated with a reduced PTC risk, regardless of radiation exposure ($OR_{\text{per allele}}=0.7$, 95% CI 0.5–0.9). In the same study, it was shown that the intronic SNP rs664677 interacts with radiation exposure. Analysis of combined *ATM/XRCC1* genotypes (rs18011516 and rs25487) demonstrated that PTC risk was inversely proportional to the number of minor alleles of the tested SNPs. Some *ATM/TP53* genotypic combinations (rs18015516/rs664677/rs609429/rs1042522) were associated with both radiation-related and sporadic DTC. In particular, the combined GG/TC/CG/GC genotype was strongly associated with the radiation-related PTC ($OR_{\text{genotype}}=2.10$, 95% CI 1.17–3.78) (Akulevich *et al.* 2009).

Another result among populations exposed to radiation was a significant decreased PTC risk observed in Belarusian children from the Chernobyl areas for carriers of the rs1801516 minor allele (A), ($OR_{\text{per allele}}=0.34$, 95% CI 0.16–0.73) and of the intronic SNP rs3092993 minor allele (C) ($OR_{\text{per allele}}=0.13$, 95% CI 0.13–0.83). Moreover, among 14 tested *ATM* SNPs, a suggestive interaction was found between the silent substitution p.Pro1526Pro (rs1800889) and IR exposure (Damiola *et al.* 2014). However, in the French Polynesian population exposed to IR during French nuclear tests, the minor allele (A) of rs1801516 was associated with an increased risk of PTC ($OR_{\text{per allele}}=3.13$, 95% CI 1.2–8.3) (Maillard *et al.* 2015).

Among six *ATM* SNPs tested in a case–control study including 592 sporadic DTC cases and 885 healthy controls, the minor alleles (G) of both rs189037 and rs1800057 were found to be associated to respectively ($OR_{\text{rs189037}}=0.8$, 95% CI 0.6–1.0 and $OR_{\text{rs1800057}}=1.9$, 95% CI 1.1–3.1 under dominant model of inheritance and after adjustment on age, sex, race/ethnicity, and study center) (Xu *et al.* 2012). In the same study, carriers of a combination of six to seven and eight to ten risk alleles were associated with a 30% ($OR_{6-7 \text{ SNPs}}=1.3$, 95% CI 1.0–1.7) and 50% ($OR_{8-10 \text{ SNPs}}=1.5$, 95% CI 1.1–2.1) increased risk of DTC, respectively (Xu *et al.* 2012).

TP53

TP53 at 17p13.1 encodes a tumor suppressor protein which is a central stress protein in the DNA damage response. The degree of DNA damage and the extent of modifications of p53 (e.g. phosphorylation, acetylation,

methylation), depending on its varying spectrum responsive genes, determines which of the two alternative pathways are activated by p53: cell survival or cell death (Pflaum *et al.* 2014).

In the irradiated population from the Chernobyl area, Akulevich *et al.* found an interaction between the *TP53* missense variant rs1042522 (p.Arg72Pro) and IR exposure, with $OR_{\text{per allele}}=1.7$, 95% CI 1.1–2.4 (Akulevich *et al.* 2009). As mentioned earlier, an association was found with IR-related DTC cases and some *ATM/TP53* genotypes combinations (rs1801516/rs664677/rs609429/rs1042522).

In relation to sporadic DTC, rs1042522 had been investigated in several studies. In a Brazilian sample of 295 cases and controls, Granja *et al.* found a five times increased PTC risk and almost ten times increased risk of FTC both for homozygotes of the rare allele (Granja *et al.* 2004). Rs1042522 and the duplication located in intron 3 of *TP53* (rs17878362) were investigated in 84 Iranian-Azeri DTC cases (Dehghan *et al.* 2015), and a decreased risk of DTC was evidenced in this Azeri population for carriers of (-16ins -Pro) haplotype ($OR=0.5$, 95% CI 0.3–0.9).

DNA repair pathways

Several genes acting in different DNA repair pathways have also been associated with DTC risk in irradiated populations.

Homologous recombination pathway

Homologous recombination (HR) is a mechanism that repairs a variety of DNA lesions, including double-strand DNA breaks (DSBs), single-strand DNA gaps and inter-strand crosslinks (Prakash *et al.* 2015).

XRCC2 *XRCC2* is located at 7q36.1. Several studies, included a meta-analysis by He *et al.*, investigated few *XRCC2* SNPs in DTC risk in the general population and none of them concluded to an association (He *et al.* 2014). However, an interaction between the SNP rs10234749 in the promoter of the gene and diagnostic radiation exposure was found in an American white population composed of 168 DTC microcarcinoma cases and 465 healthy controls (Sandler *et al.* 2018) (Table 3).

Direct reversal repair pathway

Damage caused by different factors such as methylating and alkylating agents may be repaired by the direct reversal repair pathway (DRR) which involves, *inter alia*,

O-6-methylguanine-DNA methyltransferase (*MGMT*) and the gene encoding for *Escherichia coli* AlkB protein (*ALKBH3*).

MGMT *MGMT*, located at 10q26, encodes a methyltransferase involved in cellular defense against mutagenesis and toxicity of some agents, including alkylating agents (Walter *et al.* 2015). Its role in radiation-related PTC susceptibility was first described in a study involving Belarusian children exposed to Chernobyl fallout (Lonjou *et al.* 2017). Among the 141 SNPs located in 43 DNA repair genes that had been investigated, only the intronic SNP rs2296675 was associated with an increased PTC risk (Table 2). Furthermore, in a gene-based analysis conducted on 43 DNA repair genes, *MGMT*, *ERCC5* and *PCNA* were associated with radiation-related PTC ($P_{\text{gene}} \leq 0.05$) although only the association with *MGMT* stood after Bonferroni correction (Lonjou *et al.* 2017).

In their analysis of genetic interaction with diagnostic radiations conducted in the Connecticut population, Sandler *et al.* tested two other SNPs, the intronic variant rs4750763 and the intergenic variant rs1762444, near to *MGMT*. For these two, ORs were respectively 3.8 (95% CI 1.4–10.0, $P_{\text{interaction}} = 0.02$) and 3.4 (95% CI 1.4–8.3, $P_{\text{interaction}} = 0.02$). In the same study, a significant association between the intronic variant rs12769288 and PTC risk was found in the Caucasian population, with an $\text{OR}_{\text{per allele}} = 0.6$, 95% CI 0.4–0.9, when IR exposure was not taken into account in the analysis. Finally, authors found that subjects with the T/C or T/T genotypes for the intronic variant rs10764901 had a reduced risk of PTC association between PTC risk as compared with subjects with the CC genotype (OR=0.43, 95% CI 0.26–0.72) (Sandler *et al.* 2018). However, this result should be taken with caution as no significant association was observed under the additive model.

ALKBH3 *ALKBH3* at 11p11.2 encodes the ‘*Escherichia coli* AlkB protein’ implicated in DNA lesions generated in single-stranded DNA. Despite its role in protection against the cytotoxicity of methylating agents, a possible role in DTC susceptibility was investigated in only one study performed in two population samples: the US radiologic technologists cohort, exposed to low-radiation doses, and cases from the general population diagnosed and treated for PTC at University of Texas Cancer Institute (Neta *et al.* 2011). In the US radiologic technologists cohort, individuals with the T/C genotype of rs10838192 (located upstream of *ALKBH3*) were found to be at increased PTC

risk in the pooled population ($\text{OR}_{\text{genotype}} = 2.33$, 95% CI 1.05–5.17). Of note, given the low-exposure doses received by US radiologic technologists and the late age of exposure, the authors did not consider PTC cases among radiologic technologists as radiation-related cases. More recently, an interaction between the *ALKBH3* intronic SNP rs10768994 and diagnosis radiation was found among individuals with the T/T genotype in American Caucasian population (OR=2.88, 95% CI 1.13–7.29, $P_{\text{interaction}} = 0.008$) (Sandler *et al.* 2018).

Nucleotide excision repair pathway

Nucleotide excision repair (NER) is a DNA repair mechanism by excision that removes DNA damage induced by ultraviolet light. Two genes involved in this pathway, *LIG1* and *ERCC2*, have been investigated in radiation-related DTC.

LIG1 *LIG1* at 19q13.33 encodes a protein from the DNA ligase protein family. The gene product is involved in DNA replication, recombination, and base excision repair, and *LIG1* mutations into mice models led to increased tumorigenesis (Ellenberger & Tomkinson 2008). *LIG1* SNPs have been associated with non-small-cell lung cancer (Tian *et al.* 2015). An interaction between diagnostic IR exposure and two intronic variants, namely rs2163619 and rs10421339, was reported. The OR for these two SNPs were 2.40 (95% CI 1.30–4.42) and 2.50 (95% CI 1.34–4.69), respectively (Sandler *et al.* 2018).

ERCC2 (XPD) *ERCC2* or *XPD* at 19q13.32 encodes a protein involved in transcription-coupled NER, which recognizes and repairs many types of structurally unrelated lesions, such as bulky adducts and thymidine dimers (Fleijter *et al.* 1992). Different disorders are caused by defects in this gene, including the cancer-prone syndrome xeroderma pigmentosum complementation group D, the photosensitive trichothiodystrophy, and the Cockayne syndrome.

In a study conducted among Chernobyl recovery workers, evacuees and residents of contaminated area, Shkarupa *et al.* investigated the relationship between the XPD missense variant p.Lys751Gln and frequency and spectrum of chromosome aberrations in peripheral blood lymphocytes of TC patients (no precise histology) exposed to IR due to the Chernobyl accident. An increased TC risk was observed for subjects homozygous carriers of the minor allele of rs1052559 (p.Gln751/p.Gln751) exposed to IRs under the dominant model of inheritance

(OR=3.66, 95% CI 1.04–12.84). Moreover, among cases that had been exposed to IR during Chernobyl disaster, homozygous carriers of the minor allele variants of *XPB* gene were characterized by a high level of spontaneous chromosome aberrations (Shkarupa *et al.* 2016).

When combined genotypes were analyzed by Silva *et al.*, two *ERCC2* missense variants, rs1052559 (p.Lys751Gln) and rs1799793 (p.Asp312Asn), were found to be associated with an increased risk of sporadic PTC among Caucasian Portuguese population. The OR for homozygotes individuals for the minor allele of both SNPs: (C/C and A/A combined genotype) was 2.99 (95% CI 1.23–7.27). However, no association was found when the two SNPs were analyzed separately (Silva *et al.* 2005).

Discussion

Despite the importance of IR exposure as a risk factor for DTC, few studies provide reliable information on genetic factors contributing to the susceptibility to radiation-related DTC.

The oldest study in our selection is Lönn *et al.* (Lönn *et al.* 2007) performed among the US radiologic technologists cohort, in addition to the low number of cases, they were all exposed during adulthood, which does not help to establish the link between DTC development and radiation exposure. Findings from this study should be taken cautiously. It is the same case for the findings from Sigurdson *et al.* (Sigurdson *et al.* 2009) study since they have only 25 cases of DTC in their study population even irradiated younger than cases in Lönn's study. The other gene candidate studies performed in irradiated populations (Akulevich *et al.* 2009, Damiola *et al.* 2014, Maillard *et al.* 2015, Shkarupa *et al.* 2016, Lonjou *et al.* 2017) reported significant findings but no replication study or meta-analyses with other data were performed to validate their results. The reported findings still need to be validated in other studies. Sandler *et al.* reported significant interaction between diagnostic irradiation exposure and four SNPs; however, they did not quantify the absorbed doses at the thyroid, but they used directly data from questionnaires. Besides, these interactions are not found in other studies and here also no validation study was done. Takahashi *et al.* study is the only GWAS performed on this subject, it is also the only study with replicated findings. Results from the study by Takahashi *et al.* are the most reliable, but since the environmental background of patients, including individual thyroid radiation dose and detailed clinical information are available, these results lack precision and certainty.

According to the data presented in this review, it is not clear whether some genetic factors are specifically associated with radiation-related DTC, since most of the known associated SNPs had already been associated to sporadic DTC. Moreover, most of reviewed studies had limited power to detect association due to the relatively small size of the investigated population samples.

Most of the SNPs found to be associated to radiation-related DTC are located in or in the vicinity of genes involved in DNA repair pathways, including double-strand break repair. Among these SNPs, two were in or near *MGMT*, one was in *XRCC2*, two were in *LIG1*, one was in *ALKBH3* and one was in *ERCC2*. Other SNPs associated to radiation-related DTC are in or near genes involved in thyroid hormone metabolism such as *FOXE1*, *TSHR* and *NKX2-1*. The latter are associated with both sporadic and radiation-related DTC risk. With regard to radiation-related DTC, the reported associations should be considered with caution, given the small sample size and the absence of replication in independent populations, with the exception of SNP rs965513 which were replicated in the study by Takahashi *et al.* (Takahashi *et al.* 2010).

Moreover, some results from different studies are partially controversial and puzzling, notably the results on the minor allele (G) of the *ATM* SNP rs1801516, which is associated with a reduced DTC risk in the French Polynesian population and with an increased DTC risk in the Chernobyl population (Damiola *et al.* 2014, Maillard *et al.* 2015).

It should also be noted that most of the reviewed studies were gene candidate studies, performed on a limited number of SNPs due to statistical power issues. However, this study design does not provide information on the entire genetic variability at a given locus.

So far, most of the reported risk alleles associated with radiation-related DTC show modest-to-moderate increased risk, with large 95% confidence interval, pointing out the lack of power of these studies (Tables 2 and 3).

Taken together, studies published so far are quite heterogeneous, in particular in terms of population groups of various geographical/ethnic origin (e.g. populations exposed to fallout of the Chernobyl accident in Belarus and Ukraine, populations from French Polynesia and Kazakhstan near areas where nuclear weapon tests have been performed or US radiologic technologists). Characteristics of exposure including the way and the age at IR exposure and the characteristics of thyroid cancer itself (histology, size) are other sources of heterogeneity. Moreover, individual estimates of radiation doses to the thyroid are generally quite imprecise (Table 1) and variable from one study to another, questioning the effect

of IR on these DTC cases. The exposure may have occurred in different ways (internal/external) and at variable ages (adulthood for the US radiologic technologists, childhood for studies investigating DTC in areas exposed to Chernobyl fallout). Concerning cancer characteristics, most of the cases of some studies (i.e. Sandler *et al.* 2018) are microcarcinomas, which makes the interpretation of the results more uncertain.

Current results suggest that genetic susceptibility to radiation-related DTC could involve a large number of common variants associated with low-to-medium effect size. Rarer variants than those assessed in GWAS may also contribute to the disease. Resequencing projects on much larger datasets may provide more information on the relevance of IR-related DTC question.

Conclusion

A limited number of studies identified associations between radiation-related DTC and few SNPs or genes, and most of these genetic factors were also found to be associated with sporadic DTC. While browsing the available literature on radiation-related DTC, we noticed that there is no attempt to quantify the genetic risk associated with sensitivity to IR exposure, for example using polygenic risk score. More studies on larger cohorts with well-documented individual radiation dose estimations, particularly studies involving cases for whom DTC occurred after radiotherapy are needed to get a comprehensive picture of genetic susceptibility factors involved in radiation-related DTC.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/ERC-19-0321>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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