Are we really at the dawn of understanding sporadic pediatric thyroid carcinoma?

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Abstract

Data from the National Cancer Institute and from the literature have disclosed an increasing incidence of thyroid cancer in children, adolescents and adults. Although children and adolescents with thyroid cancer tend to present with more advanced disease than adults, their overall survival rate is excellent; however, there is no clear explanation for the differences observed in the clinicopathological outcomes in these age groups. There has been an ongoing debate regarding whether the clinicopathological differences may be due to the existence of distinct genetic alterations. Efforts have been made to identify these acquired genetic abnormalities that will determine the tumor's biological behavior and ultimately allow molecular prognostication. However, most of the studies have been performed in radiation-exposed pediatric thyroid carcinoma. Therefore, our understanding of the role of these driver mutations in sporadic pediatric differentiated thyroid cancer development is far from complete, and additionally, there is a strong need for studies in both children and adolescents. The aim of this review is to present an extensive literature review with emphasis on the molecular differences between pediatric sporadic and radiation-exposed differentiated thyroid carcinomas and adult population.

Key Words
- sporadic pediatric papillary thyroid carcinomas
- radiation-exposed papillary thyroid carcinomas
- RET/PTC
- BRAF
- RAS
- ETV6-NTRK3

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Introduction

The incidence of thyroid cancer has increased worldwide over the last decades. Essentially, one of the largest annual increases from 2006 to 2010 was for thyroid cancer (Davies & Welch 2006, Lise *et al*. 2012, Siegel *et al*. 2014*a*). Differentiated thyroid cancer (DTC) is most frequently diagnosed among adults aged 45–54, with a mean age at diagnosis of 50 (SEER Stat Fact Sheets: thyroid cancer, available at http://seer.cancer.gov/statfacts/html/thyro.html accessed July 2015) and with a female predominance. Currently, it is the fifth most common cancer in women in the United States (Siegel *et al*. 2014*a*), and in Italy, it is the second most frequent cancer in women below age of 45 (Pellegriti *et al*. 2013). In São Paulo, Brazil, not only the thyroid cancer incidence rates were consistently higher than in the United States but also the female predominance was higher than that reported in SEER (Veiga *et al*. 2013).

Although rare in the young population, DTC rates are also increasing significantly in children and adolescents. Among DTC, papillary thyroid cancer (PTC) accounts for

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nearly 90% and follicular thyroid carcinoma (FTC) accounts for about 5–10% of all thyroid cancer that occurs in the pediatric population (Demidchik *et al*. 2007, Hogan *et al*. 2009). It has been suggested that FTC is very rare and occurs in a slightly older age group (Jarzab *et al*. 2005). Medullary thyroid carcinoma, poorly differentiated thyroid carcinoma and undifferentiated thyroid carcinoma are rare in young patients (Hogan *et al*. 2009) and are not the focus of this review.

Regardless the ethnicity, an increased trend in incidence rates of pediatric thyroid carcinomas was found in most regions of the United States in both genders (Vergamini *et al*. 2014). When stratified by age, the annual incidence rate of cancer in children and adolescents is 0.43 (5–9 years), 3.50 (10–14 years) and 15.16 per million (15–19 years) (Vergamini *et al*. 2014). Others have also demonstrated that the incidence rates increased with age (Hogan *et al*. 2009, Siegel *et al*. 2014*b*). In fact, among 15- to 19-year-old adolescents, thyroid is the eighth most common cancer diagnosed and the second most common cancer among girls (Wu *et al*. 2003, Ward *et al*. 2014). Similar to that observed in adults, there is a female predominance (Landau *et al*. 2000, Hogan *et al*. 2009, Lazar *et al*. 2009).

The reasons for increasing incidences rates of pediatric thyroid cancer are currently unknown. Previous studies suggested that the increasing incidence of thyroid cancer among adults was predominantly due to better access to medical care and increased diagnostic scrutiny (Davies & Welch 2006). It is possible that advances in ultrasound imaging technologies have improved diagnosis and, consequently, over time, may have contributed to detect small and asymptomatic pediatric thyroid cancers.

Although increased diagnostic scrutiny may account for some of the rise, the increased incidence across all tumor sizes in young patients argue in favor of a true increase (Vergamini *et al*. 2014). Besides, it has been suggested that some of this increase may be due to environmental factors and lifestyle changes (Boas *et al*. 2006). Finally, the increase in the incidence of PTC with no similar increase in the incidence of other histological types of thyroid cancer is an argument in favor that environmental factors may contribute to the increase (Mazzaferri 1993).

There are significant molecular, pathological and clinical differences in DTC among children, compared to the adult population. To indorse best practice standards for the diagnosis and management of thyroid cancer in the pediatric population, a task force appointed by the American Thyroid Association (ATA) recently provided the first recommendations specifically addressing the management of thyroid nodules and DTC in children and adolescents (Francis *et al*. 2015). The authors suggested applying these recommendations to patients up to 18 years old, when the majority of pediatric patients have completed growth and development.

The aim of this review is to present an extensive literature review with emphasis on the molecular differences between the pediatric and adult population. Although several studies of pediatric DTC included individuals up to 21 years of age, we mainly focused on studies that involved individual $\leq$18 years of age.

Clinical presentation

The thyroid cancer in children usually presents as a solitary nodule (Welch Dinauer *et al*. 1998, Grigsby *et al*. 2002). The occurrence of palpable cervical adenopathy at diagnosis is also a common finding in pediatric DTC (Grigsby *et al*. 2002). Previous studies reported significant differences in the clinical presentation and outcomes of DTC in pediatric patients compared to adults (Jarzab & Handkiewicz-Junak 2007).

Although thyroid nodules are uncommon in the pediatric population, there is a greater risk of malignancy in nodules diagnosed in children and adolescents than in adults (26% vs 5%) (Niedziela 2006, Gharib & Papini 2007, Romei & Elisei 2012). Moreover, pediatric cases are more likely to present a more advanced stage of the disease at diagnosis, often a more aggressive local disease and higher rates of distant metastases (Zimmerman *et al*. 1988, Chow *et al*. 2004, Kumagai *et al*. 2004, Jarzab *et al*. 2005, Alzahrani *et al*. 2015). Neck lymph node metastasis at diagnosis was reported in nearly 90% of pediatric cases, while they were detected in 35% of adults (Zimmerman *et al*. 1988). Other series reported lymph node involvement at diagnosis in 40–90% of pediatric cases (Newman *et al*. 1998, Landau *et al*. 2000, Dinauer *et al*. 2008, Lazar *et al*. 2009, O'Gorman *et al*. 2010), compared to 20–50% of adults (Zaydfudim *et al*. 2008, Ahn *et al*. 2015) (Table 1).

Distant metastasis was found in virtually 7–30% of pediatric patients compared to 2–9% of adults (Zimmerman *et al*. 1988, Newman *et al*. 1998, La Quaglia *et al*. 2000, Chow *et al*. 2004, Handkiewicz-Junak *et al*. 2007, Dinauer *et al*. 2008, Hogan *et al*. 2009, O'Gorman *et al*. 2010). Mostly pediatric patients present distant metastasis in the lungs, but few cases have been also reported in the brain, soft tissue or bone (Newman *et al*. 1998, Jarzab & Handkiewicz-Junak 2007) (Table 1).

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Table 1 Clinical features of pediatric thyroid carcinomas

Author	Cases (*n*)	RI exposure (%)	Mean age/ (range years)	Gender (female) (%)	Multi-focality (%)	Bilateral (%)	ET (%)	Cervical meta (%)	Distant meta (%)	Recur-rence (%)	Survival (%)
Zimmerman *et al.* (1988)	58	No	<17	69	NA	NA	24	90	7	30	76
Newman *et al.* (1998)	329	13	15.2 (0.4–20.8)	76	NA	NA	32	74	25	32	99
Welch Dinauer *et al.* (1998)	137	5	19 (3–21)	76	30.7	NA	NA	39	6	20	99
Fenton *et al.* (2000)	33	No	18 (6–21)	71	48	NA	NA	NA	NA	15	100
Alessandri *et al.* (2000)	38	21	12.6 (4.5–16.8)	74	ND	NA	42	60	5	45	100
Landau *et al.* (2000)	30	No	<16	77	23	NA	NA	57	10	40	70
Grigsby *et al.* (2002)	56	No	15.8 (4–20)	77	57	30	36	73	13	34	98
Kumagai *et al.* (2004)	29	No	11.3 (<15)	77	NA	NA	23	68	23	ND	NA
Lazar *et al.* (2009)	27	7	12.8 (6.1–17)	78	88.9	NA	52	67	41	18	100
Hogan *et al.* (2009)	1753	NA	15.9 (1–19)	81	NA	NA	NA	46	8	NA	NA
O'Gorman *et al.* (2010)	54	9	13 (F); 13.4 (M)	67	75.9	28	NA	46	15	NA	NA
Ito *et al.* (2012)	110	No	17 (7–19)	89	NA	NA	8	41	7	24	98
Sassolas *et al.* (2012)	28	NA	8–19	NA	NA	NA	32	50	7	NA	NA
Givens *et al.* (2014)	19	No	13.6 (2.8–18)	NA	NA	NA	42	68	26	11	NA
Henke *et al.* (2014)	27	No	18.6 (5.8–21.2)	79	NA	22	37	63	4	37	100
Alzahrani *et al.* (2015)	97	No	17 (8–20)	81	43	NA	53	78	16	34	100

NA, not available.

Nevertheless, a marked heterogeneity within the pediatric group has been reported. Pediatric cases tend to be more symptomatic in the prepubertal group (Jarzab *et al.* 2005). Children present with more aggressive local disease and are more likely to have lymph node metastases at diagnosis. In fact, it was demonstrated that prepubertal children had a greater degree of extrathyroid extension and lymph node involvement than adolescents (Alessandri *et al.* 2000, Lazar *et al.* 2009). Additionally, they are more prone to develop subsequent distant metastases (Jarzab *et al.* 2005, Dinauer *et al.* 2008, Lazar *et al.* 2009, O'Gorman *et al.* 2010, Rivkees *et al.* 2011), and they also experience recurrence more frequently and earlier than adolescents (Alessandri *et al.* 2000). The biological hypothesis for greater differentiation and responsiveness to treatment is discussed below.

The mean tumor size tends to be larger in pediatric patients. Comparison between 58 pediatric (<17 years old) and 981 adult consecutive PTC patients treated at the Mayo Clinic revealed that the mean tumor size was greater in pediatric cases (3.1 cm; ±1.7) than in adults (2.1 cm; ±1.7). The authors also showed that tumors larger than 4 cm were more prevalent in pediatric cases (36%) than in adults (15%) (Zimmerman *et al.* 1988). Furthermore, papillary microcarcinomas (≤1 cm) are rarely reported in pediatric cases (3% of cases), whereas microcarcinomas comprise about 30% of all thyroid carcinomas diagnosed in adults (Chow *et al.* 2004). It is likely that in populations undergoing extensive screening, small pediatric PTC will be detected. Excluding the screening programs conducted in the Belarus area after the Chernobyl accident in 1986 (Ashizawa *et al.* 1997) and the screening of children from different Japanese prefectures after the Fukushima Daiichi Nuclear Power Plant accident in 2011 (Ashizawa *et al.* 1997, Yasumura *et al.* 2012, Hayashida *et al.* 2013), studies reporting the prevalence of small thyroid nodules in the pediatric population are scarce. Ultrasound examination in children from Fukushima, Aomori, Yamanashi and Nagasaki prefectures revealed that between 35 and 51% of children who underwent thyroid ultrasound examination showed thyroid cysts and nearly 1% showed thyroid nodules ≤0.5 cm (Hayashida *et al.* 2013, Yamashita & Suzuki 2013).

Another difference between pediatric and adult DTC is the higher rates of bilateral and multifocal disease in childhood. Pediatric patients present bilateral disease in about 30% of cases (Grigsby *et al.* 2002, Lazar *et al.* 2009) and multifocal disease in 30–80% of cases (Welch Dinauer *et al.* 1998, Grigsby *et al.* 2002, Gorman *et al.* 2010). This higher rate of bilateral and multifocal disease is one of the arguments used to recommend for a more comprehensive thyroid surgery in pediatric patients (Francis *et al.* 2015).

PTC variants, such as follicular variant of PTC (FVPTC) and diffuse sclerosing PTC (DSPTC), are more frequently found in pediatric patients than in adults (Neiva *et al.* 2012). Although there is no consensus on the prognosis of a different histological type, it was recently demonstrated that DSPTC is frequently associated with bilateral disease,

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extrathyroidal extension, lymph node involvement, lung metastasis and lower rates of recurrence-free survival than that of non-DSPTC (Koo *et al*. 2009).

Treatment and prognosis

Because pediatric DTC is an uncommon malignancy, randomized trials have not been applied to test best-care options in this group of patients (Rivkees *et al*. 2011). Therefore, the optimal initial and long-term treatment and follow-up remain controversial.

Despite a more advanced disease at presentation and a higher risk of recurrence, the prognosis of childhood DTC is generally fairly good. The reported mortality rate is low or even zero in some series (Newman *et al*. 1998, Alessandri *et al*. 2000, Henke *et al*. 2014). For this reason, the ATA guideline for children with thyroid nodules and DTC developed recommendations based on the available scientific evidence and expert opinion (Francis *et al*. 2015). The authors suggested reconsidering the former recommendation that all children with DTC should be similarly treated with a more extensive surgery and routine RAI therapy (Rivkees *et al*. 2011). A more comprehensive surgical approach raises the risk of important clinical complications, mainly transient or permanent hypoparathyroidism and recurrent laryngeal nerve damage. The RAI therapy is associated with an increase in the risk of second primary malignancy, especially salivary cancer (Marti *et al*. 2015).

The ideal surgical approach for the majority of patients is total thyroidectomy (TT) (Francis *et al*. 2015). However, in patients with a small unilateral tumor and without extrathyroidal extension, a near-TT can be considered to lower the risk of injury to either the recurrent laryngeal nerve or parathyroid glands (Rivkees *et al*. 2011, Francis *et al*. 2015). Previous studies that assessed the outcomes of a less comprehensive surgical approach in pediatric patients have shown a higher risk of relapse rates with lobectomy vs TT (Hay *et al*. 2010, Handkiewicz-Junak *et al*. 2007). Despite the high rate of cervical metastasis in pediatric DTC, routine central lymph node dissection is no longer recommended. The central neck dissection should be performed when there is evidence of central and/or lateral neck metastasis or gross extrathyroidal invasion (Francis *et al*. 2015)

Regarding RAI indications, the current recommendation in pediatric DTC is for treatment of nodal or other locoregional disease that is not amenable to surgery as well as distant metastases that are iodine-avid. Moreover, the RAI therapy can also be consider in children with T3 tumors or extensive regional nodal involvement (Francis *et al*. 2015). Similar to adults, there is no evidence of benefit of RAI remnant ablation in pediatric patients with intra-thyroidal disease and no lymph node disease (Lamartina *et al*. 2015).

Risk factors

The link between ionizing radiation during childhood and thyroid cancer has been known since 1950. The first sharp rise in the incidence of thyroid cancer was reported in epidemiological studies after external radiation to treat common childhood conditions such as acne, *tinea capitis* and enlarged tonsils or thymus gland. A pool analysis of seven studies demonstrated a high risk of thyroid cancer in subjects irradiated at a young age, even for radiation doses as low as 0.10 Gy. Although the risk of developing thyroid cancer is still present more than 40 years after exposure, it is higher between 15 and 30 years. The risk decreased significantly with increasing age at exposure, with very little risk after age 20 (Ron *et al*. 1995).

The second peak of thyroid cancer was observed in 1996, 10 years after the Chernobyl nuclear power station accident, when over 10^{18} Bq of radioactivity was released into the atmosphere, mainly ^{131}I and ^{137}Cs. The highest levels of contamination occurred in Belarus, Ukraine and western Russia. Children and adults have been exposed to a relatively high dose of ^{131}I. Predominantly, through ingestion of contaminated food and drink, their thyroid has accumulated a high dose of ^{131}I. As childhood thyroid is very radiosensitive, one would expect a high prevalence of thyroid disease in those subjects exposed to radiation at a young age. In fact, the incidence rate of childhood thyroid carcinoma in the heavily contaminated region of Belarus reached 40 per million, while an annual incidence of 1 per million was reported in this area before the accident. The highest risk group was those patients aged 0–4 years at the time of exposure. After 1996, the incidence declined progressively, and after 2001, only sporadic cases (not exposed to radiation) were reported in pediatric patients (<15 years old) (Demidchik *et al*. 2007, Williams 2008, Tuttle *et al*. 2011).

The radiation-associated risk of thyroid cancer to the exposed children and residents after the Fukushima Daiichi Nuclear Power Plant accident on March 2011 is still unclear. The RAI measured after the accident was one-tenth or less that measured after the Chernobyl accident, and the radiation exposure dose measured in children from neighboring regions after the accident was at a near negligible level. The Fukushima prefecture started the

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Fukushima Health Management Survey Project aimed at long-term health care administration and early medical diagnosis/treatment for prefectural residents. As the first round of screening, a thyroid ultrasound examination was conducted from October 2011 to March 2014 in nearly 300 000 individuals aged <18 years. From a total of 108 (0.8%) children with suspicious nodules, 84 had thyroid carcinoma, most (96%) were PTC (Yamashita & Takamura 2015). Although a not significant increase in the prevalence of thyroid cancer has been reported after the Fukushima Daiichi Nuclear Power Plant accident (Iwaku *et al*. 2014), a sharp increase in the incidence of thyroid cancer was observed 4–5 years after the Chernobyl accident, and, therefore, it was preceded by a latency phase. Only a long-term follow-up will clarify whether a third peak of thyroid cancer might occur after the Fukushima Daiichi Nuclear Power Plant accident.

These findings recognized the extreme sensitivity of children's thyroid to radiation, compared to adults. Many epidemiologic studies have explored whether the exposure to radiation during medical diagnostic and therapeutic procedures represent a risk factor for pediatric thyroid cancer. It has been demonstrated that the thyroid exposure to X-rays due to dental radiographic procedures (Memon *et al*. 2010) or primary beam during computed tomography scan of the neck during childhood is associated with a low but not negligible risk of cancer (Mazonakis *et al*. 2007, Pellegriti *et al*. 2013). Regarding therapeutic procedures, it is well known that survivors of pediatric cancer may suffer from late sequelae of treatment, including secondary malignant neoplasia in the irradiated region. Secondary thyroid carcinoma after radiotherapy to the neck has been reported in many publications. Interestingly, the risk of a subsequent thyroid cancer after a first tumor in childhood rose with an increasing radiation dose (greatest risk 20–29 Gy) but doses higher than 30 Gy is consistent with a cell-killing effect (Sigurdson *et al*. 2005). As an example, the cumulative incidence for patients with up to 30 years of follow-up after the diagnosis of Hodgkin's lymphoma (HL) was 4.4% for thyroid carcinoma and the mean interval after HL diagnosis was 13.2 years (range 4.0–29.2 years). The most frequent thyroid carcinoma identified in these patients is PTC (Dorffel *et al*. 2000, Levy *et al*. 2012, Marti *et al*. 2012).

This pediatric thyroid cancer peak incidence and a 'latency phase' reinforce that a long-term follow-up of patients should be undertaken for survivors of both the Fukushima Daiichi Nuclear Power Plant accident and any cancer during childhood involving radiotherapy to the thorax or head and neck region.

Hints from cancer biology

Recently, the Cancer Genome Atlas (TCGA) Research Network, using next-generation DNA and RNA-sequencing, copy-number variation, miRNA, methylomic, transcriptomic and proteomic profiles, combined with clinic-pathological data, characterizes the landscape of nearly 500 PTCs of adults. The study confirmed that PTC is associated with mutations in genes that code for proteins involved in the MAPK pathway such as *RET, BRAF* and *RAS*. The TCGA also identified new cancer-causing gene mutations that occur in PTC (*EIF1AX, CHEK2, PM1D*), as well as new fusion transcripts and somatic copy number alteration (recurrent 22q deletion and 1p amplification) that reduced the so-called 'dark matter' of the PTC. The large collection of genetic alterations, combined with a comprehensive transcriptomic and proteomic analysis, revealed fundamental biological differences between PTCs. This increased knowledge helped stratify PTC into subgroups, which ultimately will refine pre-operative diagnosis of thyroid nodules and prognosis and treatment of adult PTC (The Cancer Genome Atlas Research Network 2014).

Several studies have suggested that the spectrum of mutations may differ between tumors of pediatric patients and tumors of adults (Bongarzone *et al*. 1996). Moreover, few studies have indicated that radiation-exposed and sporadic pediatric thyroid carcinomas are different biological types of cancer with the same histology (Nikiforov *et al*. 1997).

To obtain a whole picture of the genomic landscape of the radiation-exposed pediatric thyroid carcinomas, a research team performed RNA-sequencing in five patients with thyroid carcinoma from the regions of Ukraine and who were younger than 10 years at the time of the Chernobyl nuclear accident. They selected patients who were negative for known BRAF mutations and known fusion transcripts (*RET/PTC, TPR-NTRK1, PAX8-PPARG* and *AKA9-BRAF*). Moreover, the research group performed low-pass whole-genome sequencing of five radiation-exposed and five patients with sporadic pediatric thyroid carcinoma who were from the same geographical regions (Ricarte-Filho *et al*. 2013). The authors identified new kinase fusion oncogenes in radiation-exposed thyroid carcinomas. First, this study ratifies that the MAPK pathway plays a critical role in pediatric PTC development (Ricarte-Filho *et al*. 2013). Second, the prevalence of fusion

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oncogenes in radiation-induced tumors (84%) was much higher than the prevalence in sporadic cases (33%). This finding supports the concept that ionizing radiation induces chromosomal rearrangement but contests the notion that the prevalence of fusion oncogenes is similar in both sporadic and radiation-induced pediatric PTC. Last, it reinforces the idea that spectrum of mutations in pediatric tumors differ from adults.

The hints from molecular biology suggest that the clinical and pathological differences observed between pediatric and adults might be fundamentally due to their biological differences. Therefore, the therapy that may be recommended for an adult may not be appropriate for a child, which validates the development of unique pediatric guidelines (Francis *et al*. 2015).

The major known somatic events associated with radiation-exposed and sporadic pediatric thyroid carcinomas reported in the literature are summarized below (Fig. 1, Supplementary Tables 1 and 2, see section on supplementary data given at the end of this article.).

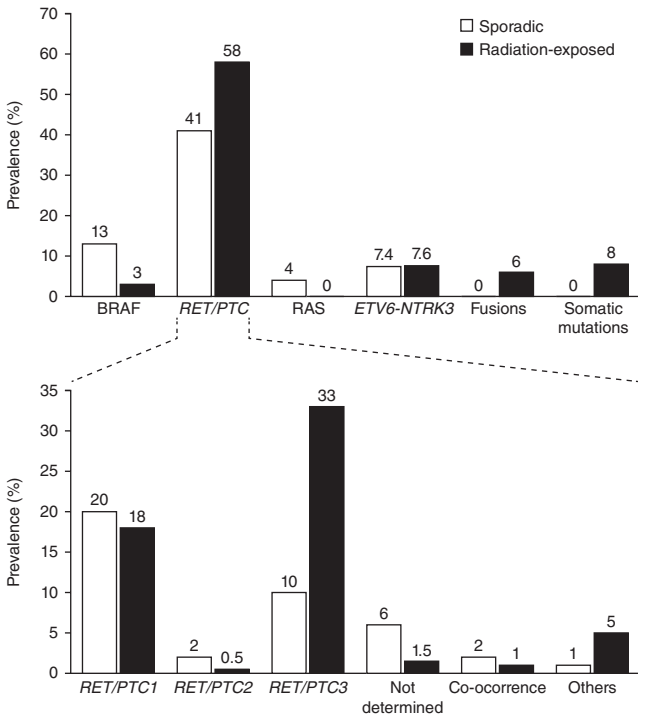

Figure 1
Overall prevalence of point mutations and rearrangements identified in sporadic pediatric and radiation-exposed pediatric papillary thyroid carcinomas. Other fusion groups include *PAX8-PPARG, AKAP9-BRAF, AGK-BRAF, NTRK1, CREB3L2-PPARG*. The other somatic mutation groups include BRAF V600_K601E and TSHR S425I. The prevalence of *RET/PTC* isoforms is show in detail in the bottom panel. The prevalence and categories of mutations are detailed in Supplementary Tables 1 and 2.

RET/PTC fusions transcripts

The *RET* (rearranged during transfection) gene, located in the chromosome 10q11.2, encodes for a cell membrane receptor tyrosine kinase (TK). *RET* rearrangement was initially described in an irradiated PTC (Fusco *et al*. 1987). Through chromosome rearrangement, *RET* was fused to the NH_2 terminus of a heterologous gene denominated *CCD6* (formerly named H4). *RET* gene is not expressed in normal follicular thyroid cells. However, the fusion product expresses intrinsic and constitutive TK activity. This not only was the first example of oncogene activation in solid tumors but also was the first *RET* rearrangement described in PTC and, hence, named *RET/PTC1* (Fusco & Santoro 2007).

In the subsequent years, other RET/PTC isoforms were identified in sporadic and radiation-exposed PTC. Currently, nearly 20 types of *RET/PTC* rearrangements were identified (Fusco & Santoro 2007, Romei *et al*. 2008, Ricarte-Filho *et al*. 2013, The Cancer Genome Atlas Research Network 2014). In all isoforms the TK domain of RET is conserved and fused to other genes. Although *RET/PTC* rearrangement was described in benign lesions, in most series it was specifically found in PTC. An elegant work that was performed by the Nikiforova group shows that this thyroid specificity is likely due to nuclear architecture of thyroid cells, i.e., spatial proximity between partners and *RET* may influence their participation in the *RET/PTC* rearrangements in the human thyroid cell (Nikiforova *et al*. 2000).

While in most series *RET/PTC* fusion is the second most common genetic event in PTC of adults (Romei & Elisei 2012), it is the main genetic event found in both sporadic and radiation-induced pediatric PTC (Figs 1 and 2).

In this systematic review of literature, we estimate the overall prevalence of *RET/PTC* in pediatric sporadic and radiation-exposed PTC. The overall prevalence of *RET/PTC* differs between sporadic and radiation-exposed pediatric PTC carcinomas (41% vs 58% respectively) (Fig. 1) (Student's *t*-test; $P=0.034$). The reported prevalence of *RET/PTC* in sporadic PTC varies from 22% (France/Italy) to 65% (USA), while its prevalence in radiation-exposed varies from 33% (Belarus) to 76% (Belarus) (Fig. 2, Supplementary Tables 1 and 2). The highest incidence was found in post-Chernobyl pediatric PTC patients. As radiation exposure induces DNA double-strand breaks and *RET* gene and their partners are juxtaposed in

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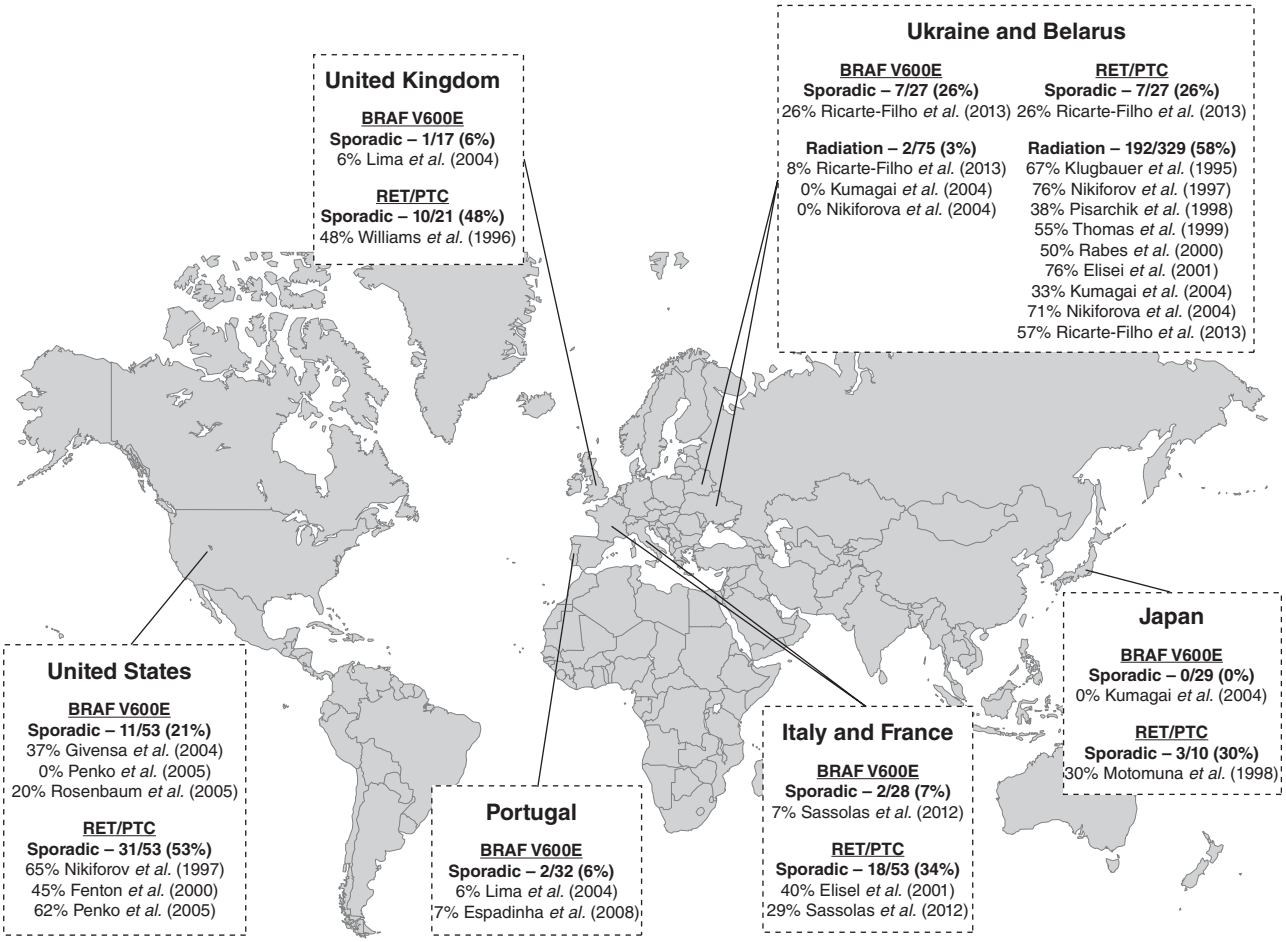

Figure 2
The worldwide prevalence of RET/PTC and BRAF V600E in sporadic and radiation-exposed pediatric PTC is shown. Studies from the same country were groups and the prevalence calculated.

the nuclei of thyroid cells, it facilitates chromosome recombination. Few studies reported PTC with concomitant *RET/PTC* in sporadic (Fenton *et al*. 2000, Penko *et al*. 2005) and radiation-induced PTC (Elisei *et al*. 2001). The reported prevalence of concomitant *RET/PTC* rearrangements in sporadic cases was 2% and radiation-exposed was 1% (Fig. 1).

Even if part of these differences can be attributed to geographic variability, the major differences in the prevalence of *RET/PTC* have been reported in radiation-exposed cases from the Belarus area (Klugbauer *et al*. 1995, Nikiforov *et al*. 1997, Thomas *et al*. 1999, Pisarchik *et al*. 1998, Rabes *et al*. 2000, Elisei *et al*. 2001, Kumagai *et al*. 2004, Nikiforova *et al*. 2004, Ricarte-Filho *et al*. 2013) (Fig. 2). It has been suggested that other factors, probably influenced by ethnic or genetic background, may act independently from or in cooperation with radiations to trigger *RET* rearrangement (Elisei *et al*. 2001). It has also been suggested that tumor heterogeneity and the use of different detection methods may contribute to the variability in the reported prevalence of RET/PTC (Zhu *et al*. 2006, Nikiforov & Nikiforova 2011).

Others have reinforced that tumor latency changes the prevalence and the type of *RET/PTC* rearrangement. Higher prevalence of *RET/PTC*3 rearrangements was found in faster developing tumors and in the most heavily contaminated areas (Rabes *et al*. 2000). Others have also found that *RET/PTC3* is preferentially found in radiation-associated pediatric PTC with a short latency period, whereas *RET/PTC1* is mainly found in later occurring PTC (Smida *et al*. 1999).

Regarding the prevalence of different *RET/PTC* isoforms, *RET/PTC1* and *RET/PTC3* are by far the most prevalent isoforms identified in tumors from two groups (Fig. 1, Supplementary Tables 1 and 2). *RET/PTC1* was found at comparable prevalence in sporadic (20%)

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and radiation-induced pediatric PTC (18%), while the prevalence of *RET/PTC3* was higher in radiation-exposed (33%) than in sporadic (10%) pediatric PTC (Fisher exact test; $P=0.01$). Although very few studies have examined the prevalence of *RET/PTC2*, this isoform was more prevalent in the sporadic group (Nikiforov *et al*. 1997, Fenton *et al*. 2000).

In the radiation-induced group, *RET/PTC3* fusion oncogene was associated with more aggressive variants such as solid variant and DSPTC, whereas *RET/PTC1* was mainly found in classical and FVPTC (Rabes *et al*. 2000, Elisei *et al*. 2001).

Even though it was described in a radiation-exposed PTC 28 years ago, it is still not clear whether *RET/PTC* rearrangement correlated with age or a more aggressive phenotype and histological subtype in sporadic pediatric PTC.

BRAF V600E mutation

The BRAF V600E, the T1799A nucleotide transversion that leads to a substitution of valine to glutamic acid, is the most common and specific genetic alteration found in PTC of adults (Kimura *et al*. 2003, Xing 2005, Frasca *et al*. 2008, Oler & Cerutti 2009, The Cancer Genome Atlas Research Network 2014).

This review of the literature and appraisal of the overall prevalence of BRAF V600E in the pediatric population shows that the prevalence of BRAF V600E is lower in radiation-exposed tumors (3%) than in sporadic cases (13%), although the observed differences did not reach statistical significance. In the sporadic group, the prevalence ranges from 0% to 37%, while in the radiation-exposed group, the prevalence ranges from 0% to 8% (Fig. 2).

Though patient age was not specified in all series, none of the patients with BRAF mutation were younger than 10 years (Lima *et al*. 2004, Sassolas *et al*. 2012, Ricarte-Filho *et al*. 2013, Givens *et al*. 2014). The lack of the BRAF V600E mutation in children and a lower prevalence of mutation in adolescents suggest that the prevalence of BRAF V600E increases with age and that BRAF V600E may not play a major role in pediatric tumors.

Recently, a group reported a high prevalence (63%) of BRAF V600E mutation in pediatric PTC (Henke *et al*. 2014). The median age of patients enrolled in this study was 18.6 years and the number of patients younger than 10 years old and their *BRAF* mutation status were not mentioned. As the methodology used to detected BRAF V600E was PCR-RFLP, instead of PCR-sequencing, this study was not included in overall analysis.

All together, the prevalence of BRAF V600E is significantly lower than *RET/PTC* in both sporadic and radiation-exposed pediatric groups (Fisher exact test; $P=0.0055$).

RAS point mutations

Activating mutation in codons 12, 13 or 61 of *RAS* genes (*NRAS*, *KRAS* and *HRAS*) has also been described in PTC. According to the catalogue of somatic mutations in cancer (http://sanger.ac.uk/cosmic), *NRAS* is the most frequently mutated *RAS* isoform in PTC. The highest rates of mutation were found in exon 2 of *NRAS* (13%). The Q61K mutation results in substitution from a glutamine (Q) to a lysine (K), at position 61. Recently, *NRAS* was also reported as the second most common mutation found in PTC by the TCGA study (The Cancer Genome Atlas Research Network 2014).

A strong association has been found between the presence of *RAS* mutations and histology in PTC of adults, with *RAS* mutations characterizing FVPTC (Zhu *et al*. 2003, Adeniran *et al*. 2006, Rivera *et al*. 2010, Park *et al*. 2013, The Cancer Genome Atlas Research Network 2014). High prevalence of mutations in the *RAS* gene has been described in FTC (18–57%) and follicular thyroid adenoma (FTA) (24–53%) (Fukahori *et al*. 2012). This mutation is also found in poorly differentiated and anaplastic carcinomas (18–31%) (Pita *et al*. 2014).

Relatively few studies have evaluated the occurrence of *RAS* point mutation in pediatric DTC and the incidence rates range from 0% to 7% in sporadic tumors (Kumagai *et al*. 2004, Sassolas *et al*. 2012, Ricarte-Filho *et al*. 2013) and 0% in radiation-exposed tumors (Suchy *et al*. 1998, Kumagai *et al*. 2004, Ricarte-Filho *et al*. 2013). In these studies only mutations at codon Q61 of NRAS were described. Although Suchy *et al*. (1998) found mutations at codons 14 and 15 of HRAS, these were silent mutations or did not interfere with GTPase activity or protein binding capacity, respectively. Thus, different from adults, *RAS* mutations exert a minor role in the pathogenesis of pediatric PTC.

ETV6-NTRK3 fusions transcripts

The *ETV6-NTRK3* is a new fusion oncogene recently described in 7% of pediatric radiation-exposed PTC (Ricarte-Filho *et al*. 2013). The *ETV6-NTRK3* fusion results from an interchromosomal translocation, which

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juxtaposes exons 1–4 of *ETV6* to exons 12–18 of *NTRK3*. The chimeric transcript is able to activate MAPK and PI3K signaling pathways and promotes cell growth of NIH-3T3 cells as well as colony formation in soft agar (Ricarte-Filho *et al*. 2013). Further validation analysis showed that 7% of sporadic pediatric PTC from the Ukraine area had *ETV6-NTRK3* fusion (Ricarte-Filho *et al*. 2013). The authors found that pathological characteristic of both radiation-exposed tumors and sporadic cases appeared to correlate with the nature of underlying drive mutations, i.e., *ETV6-NTRK3* was mainly found in FVPTC. Finally, all tumors with *ETV6-NTRK3* fusion were from patients older than 13 years of age at surgery.

ETV6-NTRK3 was later detected in 14.5% post-Chernobyl PTCs (age range from 14 to 32 years) and in 2% of sporadic (age range from 15 to 97 years) (Leeman-Neill *et al*. 2014). *ETV6-NTRK3* was the second most common rearrangement, after *RET/PTC*, in radiation-induced PTCs. One of the tumors with *ETV6-NTRK3* was from a patient who was aged 1 year at the time of the Chernobyl accident and another tumor was from a patient who was aged 10 years at the time of exposure. All radiation-induced PTCs in which *ETV6-NTRK3* fusion was identified had some component of a solid growth pattern and most were classified as FVPTC (Leeman-Neill *et al*. 2014). Importantly, the authors demonstrated that the presence of *ETV6-NTRK3* rearrangement, as well as *RET/PTC* and *PAX8-PPARγ* positive tumors, was significantly more common in tumors associated with higher dose exposure to ^{131}I than tumors that had point mutations (*NRAS*, *HRAS* and *BRAF*).

The prevalence of *ETV6-NTRK3* in pediatric sporadic PTC, its prognosis significance and whether in pediatric cases it is associated with older age (>10–18 years old) remains uncertain.

Other fusions transcripts

Other less prevalent fusion transcripts have been described in pediatric radiation-exposed PTC. The overall prevalence of these other fusion transcripts was 6% in a pediatric radiation-exposed PTC range from 3% to 19% (Ciampi *et al*. 2005, Sassolas *et al*. 2012, Ricarte-Filho *et al*. 2013) and 0% in sporadic (Ricarte-Filho *et al*. 2013).

The *PAX8-PPARG* and *CREB3L2-PPARG* fusions were previously identified in follicular thyroid cancer (Kroll *et al*. 2000, Lui *et al*. 2008). *PAX8-PPARG* rearrangement is predominantly identified in FTC and less often in FVPTC (Placzkowski *et al*. 2008). In adults, the *PAX8-PPARG* rearrangement occurs in up to 45–55% of FTC (Sahin *et al*. 2005, Castro *et al*. 2006), whereas the occurrence in follicular variant of PTC ranges from 0% to 35% (Zhu *et al*. 2003, Castro *et al*. 2006). In pediatric patients, the occurrence of *PAX8-PPARG* rearrangement was assessed only in one cohort of sporadic and radiation-exposed PTC patients. The authors did not find *PAX8-PPAG* in the sporadic group, whereas its prevalence was nearly 4% in the radiation-exposed group (Ricarte-Filho *et al*. 2013).

BRAF fusions have also been described in post-Chernobyl thyroid cancer, suggesting that this is a new mechanism of BRAF activation in human cancers (Ciampi *et al*. 2005, Ricarte-Filho *et al*. 2013). As far as we known, *AGK-BRAF* fusion was described in a tumor from one radiation-exposed PTC case who was 13 years old at surgery (Ricarte-Filho *et al*. 2013), while *AKAP9-BRAF* was identified in three tumors from radiation-exposed patients. Fuctional analyses revealed that both fusion oncogenes are able to activate the MAPK pathway. None of the pediatric sporadic PTC evaluated presented the *AGK-BRAF* fusion transcript (Ricarte-Filho *et al*. 2013).

Is the expression of iodine uptake and metabolism proteins higher in pediatric DTC than in adults?

It is well known that iodine uptake is a result of an active transport mechanism mediated by the sodium iodide symporter (*NIS*) protein, which is found in the basolateral membrane of thyroid follicular cells. It has served as an effective means for therapeutic doses of radioiodine to target and destroy cancer cells in which endogenous NIS is functionally expressed (Dadachova & Carrasco 2004). However, NIS-mediated radioiodine accumulation is often reduced in thyroid cancers due to decreased *NIS* expression/function (Liu *et al*. 2012, Xing 2013).

An important difference between pediatric and adult DTC is the high prevalence of functional metastases and the greater differentiation and radioiodine responsiveness in pediatric DTC. Accordingly, it has been suggested that the expression of *NIS,* as well as other proteins involved in iodine uptake and metabolism in pediatric patients, is higher than their expression in adults (Patel *et al*. 2002, Faggiano *et al*. 2004, Espadinha *et al*. 2009). Nonetheless, in some series, there is a higher prevalence of extrathyroidal extension, regional lymph node involvement and distant metastases in younger children than in adolescents (Alessandri *et al*. 2000, Jarzab *et al*. 2005, Dinauer *et al*. 2008, Lazar *et al*. 2009, O'Gorman *et al*. 2010, Rivkees *et al*. 2011, Vaisman *et al*. 2011, Francis *et al*. 2015). Therefore, one could postulate that the expression of *NIS* in children

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is lower than its expression in adolescents and, therefore, treatment of pediatric DTC should be stratified into more than one group.

In fact, the hypothesis that DTC from pediatric patients usually has a higher expression of iodine-metabolizing genes than DTC from adults and older patients has little support in the available literature, especially for young children (<0 years old). Either younger children were commonly underrepresented and/or patients over the age of 18 years at diagnosis were also included into the pediatric group. Moreover, only two studies specifically addressed the expression of iodine-metabolizing genes in pediatric patients (Patel *et al*. 2002, Espadinha *et al*. 2009). The former study assessed the expression of *NIS* in the malignant tumor and compared to benign lesions as a substitute of normal thyroid. The authors did not find a significant difference between benign and malignant thyroid lesions (Patel *et al*. 2002). Because the overall recurrence risk was increased for those tumors that had undetectable *NIS* expression, the authors suggested that *NIS* expression is a favorable prognostic indicator for DTC in children and adolescents (Patel *et al*. 2002). Additionally, the authors studied patients up to 21 years of age and only two cases under the age of 10. No comparison was made between children and adolescents. The subsequent study suggested that the expression of *PDS*, *TPO* and *TSHR* mRNA is higher in the pediatric group compared to adult (22–59 years) and elderly patients (>60 years). Nevertheless, among the 15 pediatric patients, only three cases were under 10 years of age, and there was no specific information regarding the expression of iodine-metabolizing genes in these patients (Espadinha *et al*. 2009).

Finally, it has been suggested that overactivation of the MAPK pathway, mainly through BRAF V600E mutation, leads to tumor dedifferentiation and, hence, reduced expression of proteins involved in iodine uptake and metabolism in PTC of adults (Romei *et al*. 2008, The Cancer Genome Atlas Research Network 2014, Zhang *et al*. 2014). However, it is becoming clear that the BRAF V600E-mutated group consists of distinct subgroups with variable degrees of thyroid differentiation (The Cancer Genome Atlas Research Network 2014), which suggests that additional genetic events may be associated with dedifferentiation status of the thyroid.

Of note the prevalence of BRAF V600E mutation in pediatric PTC is much lower than the prevalence observed in adults (Figs 1 and 2). Whether other genetic alteration that activates the MAPK pathway may modulate the expression of *NIS* in pediatric groups is still uncertain.

Therefore, the data are unclear as to whether younger age indicates a greater risk for extensive disease or recurrence, and the hypothesis of a greater expression of genes such as *NIS, TPO* and other proteins associated with iodine metabolism in pediatric patients would be associated with greater radioiodine responsiveness and overactivation of the MAPK pathways needs further evaluation.

Future plans

After the identification of new driver genes that are altered in radiation-exposed pediatric PTC cases lacking known genetic events (*RET/PTC, RAS, BRAF* mutations, *AKAP9-BRAF, TPR-NTRK1* and *PAX8-PPARG*), significantly reduced the so-called dark matter. Nearly 84% had fusion, most oncoproteins activate MAPK pathways, suggesting that pediatric PTC are also MAPK-driver cancer. Conversely, the prevalence of drive fusion oncogenes in sporadic pediatric PTC was much lower. Nearly 30% of cases are negative for the fusion events and/or point mutations found in radiation-induced pediatric cohort (Ricarte-Filho *et al*. 2013). As the risk factor to the development of sporadic pediatric thyroid carcinoma is not known and the landscape of sporadic pediatric cancer likely differs significantly from the landscape of the radiation-exposed pediatric cases, it is expected that sporadic cases might have higher prevalence of point mutations than radiation-induced pediatric thyroid carcinomas. Further in-depth genome analysis of sporadic pediatric thyroid carcinoma is necessary to address and clarify this issue. Furthermore, such analysis may also help define whether pediatric tumors from children and adolescents represent different molecular subgroups.

The use of molecular diagnostic testing in thyroid nodules became a reality and aims to improve the accurate diagnosis in cytologically indeterminate thyroid nodules and, consequently, to avoid unnecessary surgical procedures. Although the evaluation and treatment of thyroid nodules in children should be the same as in adults (Francis *et al*. 2015), the molecular tests that are available for indeterminate thyroid nodules have not been validated in the pediatric patients. Although two studies have suggested a molecular test might improve the diagnosis of an indeterminate cytology in pediatric patients (Monaco *et al*. 2012, Buryk *et al*. 2013), it is still uncertain its usefulness. Although positive results may be associated with malignancy, the insufficient data associated with the fact that the 'dark matter' of sporadic pediatric thyroid carcinomas has not yet been well

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characterized suggest that is too early to rely on negative genetic tests to exclude malignancy. The in-depth genome analysis of the sporadic pediatric cases that had no known driver mutations will help define a panel of mutations/fusions that may be better applied to the diagnosis of pediatric thyroid nodules.

In conclusion, most of the efforts to determine the landscape of pediatric cases have been focused in radiation-exposed pediatric thyroid cancer, while most routine cases of thyroid nodules/cancer are indeed sporadic cases. As PTC is the most prevalent histological type of pediatric thyroid carcinoma, further efforts should be undertaken to define the genomic landscape of pediatric sporadic PTC.

Regarding treatment, although children with DTC have high rates of regional lymph node involvement and distant metastasis, the overall survival is good. Therefore, the extent of surgery and proper dose of ^{131}I should be better defined based on the risk of recurrence. Whether molecular classification will help better classify pediatric thyroid carcinomas into subgroups and, therefore, refine diagnosis, prognosis and treatment, it is still a 'dark matter.'

Supplementary data

This is linked to the online version of the paper at http://dx.doi.org/10.1530/ERC-15-0381.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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