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Thirty-Five Years of Thyroid Cancer Experience in a Paediatric Population: Incidence Trends in Lithuania between 1980 and 2014

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Key Words
Thyroid cancer · Children · Paediatrics · Chernobyl accident · Radiation · Secondary cancer

Abstract
Background: Thyroid cancer (TC) is a rare condition in children. It may be associated with radiation, iodine deficiency or familial inheritance. ***Aims:*** The objectives of this study were to analyse the prevalence and incidence trends over 3 decades and clinical features of TC in the paediatric population in Lithuania. ***Methods:*** We reviewed all TC cases diagnosed in children aged less than 18 years during the period 1980–2014 using medical records from 3 main hospitals in Lithuania where such TC cases are managed. ***Results:*** During the 35-year period (1980–2014) there were 57 cases (45 females) of TC in children in Lithuania. The mean age at the time of diagnosis was 14.51 ± 0.52 years. The crude incidence rate of TC ranged from 0 to 0.93 cases per 100,000 children per year and the mean annual increase was 5.26% ($p < 0.001$). Papillary carcinoma was the most common histological type (73.7%). No association was found between the incidence of TC and the reported areas of radioactive contamination after the Chernobyl accident. In total, 8.8% of patients had secondary TC after initial radiotherapy of a primary oncologic disease. ***Conclusion:*** The incidence of TC in the Lithuanian paediatric population between 1980 and 2014 ranged from 0 to 0.93 cases per 100,000 children per year and there was a 5.26% annual increase ($p < 0.001$), most probably related to the increased use of ultrasound testing.

Introduction

Thyroid cancer (TC) is a rare condition among paediatric patients, affecting between 0.1 and 2.2 children per million [1] and representing between 1.5 and 3% of all paediatric tumours [2]. Well-differentiated TC is the most common endocrine tumour in children, representing 0.5–3% of all malignant diseases in children. Of all TC, papillary carcinoma accounts for 70–80% and follicular carcinoma represents 16–20% [3].

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Table 1. Incidence rates of TC in Lithuanian children between 1980 and 2014

Year	Cases	Adolescent population	Incidence rate	95% CI
1980	1	974,139	0.103	0–0.588
1981	2	971,855	0.206	0.019–0.757
1982	1	971,766	0.103	0–0.590
1983	1	964,869	0.104	0–0.594
1984	3	976,392	0.307	0.058–0.910
1985	1	980,476	0.102	0–0.585
1986	2	985,738	0.203	0.019–0.746
1987	1	991,768	0.101	0–0.578
1988	1	998,394	0.100	0–0.574
1989	0	1,000,088	–	–
1990	2	996,710	0.201	0.019–0.738
1991	0	992,166	–	–
1992	2	988,829	0.202	0.019–0.744
1993	1	981,331	0.102	0–0.584
1994	0	968,239	–	–
1995	2	950,369	0.210	0.020–0.774
1996	1	934,323	0.107	0–0.614
1997	0	918,173	–	–
1998	2	902,396	0.222	0.021–0.815
1999	3	886,749	0.338	0.064–1.001
2000	0	871,340	–	–
2001	2	851,715	0.235	0.022–0.864
2002	2	821,813	0.243	0.023–0.900
2003	1	790,512	0.127	0–0.725
2004	0	759,025	–	–
2005	0	726,333	–	–
2006	1	691,793	0.145	0–0.829
2007	2	667,579	0.300	0.028–1.102
2008	6	645,452	0.930	0.335–2.037
2009	1	624,787	0.160	0–0.917
2010	5	602,618	0.830	0.262–1.952
2011	3	574,943	0.522	0.098–1.545
2012	4	556,263	0.719	0.187–1.859
2013	3	543,756	0.626	0.123–2.192
2014	1	53,924	0.128	0.001–0.732

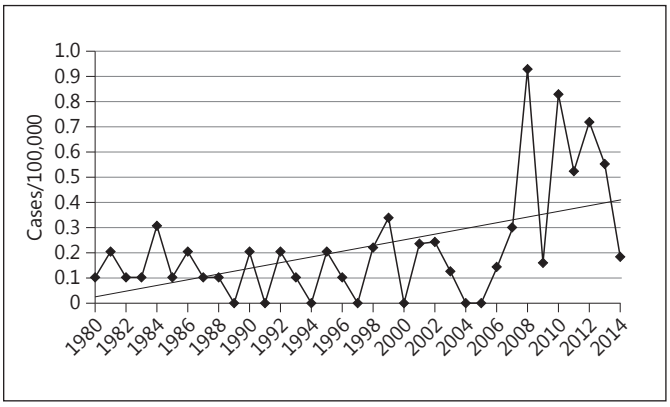

Fig. 1. Incidence trends of TC in Lithuanian children between 1980 and 2014.

Differentiated TC varies by its clinical presentation and outcome in children and adults. At diagnosis, TC in children is often more advanced, with metastases in the lymph nodes and lungs [4]. Lymph node metastases are found in up to 90% of cases in children, compared with 35% among adults [3]. Childhood TC often presents with multifocal growth, extra glandular invasion and distant metastases [1], indicating that TC in children has a more aggressive clinical course, despite the overall survival rate exceeding 95% in children [4] compared to 80–90% in adults [5].

A decade after the Chernobyl accident in 1986, the incidence of TC in children had increased dramatically, especially in the most radiation-contaminated areas of Belarus, Ukraine and Russia [6]. The Chernobyl accident demonstrated a clear relationship between radiation dose and the incidence of papillary carcinoma [7]. However, follicular cancer is thought to be more likely associated with iodine deficiency [8] and is more frequently diagnosed in regions with an iodine deficiency [9]. Both of these risk factors were present in Lithuania at certain time periods, i.e. the radioactive cloud after the Chernobyl accident passed over the territory, and Lithuania was considered to be a mild to moderate iodine-deficient zone up to 2005 [10]. The aim of this study was to analyse the incidence trends of TC in paediatric patients in Lithuania during the period between 1980 and 2014, and evaluate its association with the effect of the Chernobyl accident.

Materials and Methods

Data of 57 children and adolescents (aged under 18 years) operated on for TC in Lithuania during the period between 1980 and 2014 were reviewed and analysed from medical records from 3 main hospitals in Lithuania: the Hospital of the Lithuanian University of Health Sciences Kauno klinikos, Vilnius University Hospital Santariskiu Klinikos, and Klaipedos University Hospital. These are the only medical institutions in Lithuania that manage paediatric TC, thus all paediatric TC cases that were diagnosed in Lithuania during the study period were included in the review. The demographic data of this time period were obtained from Statistics Lithuania. The hypotheses of differences between categorical variables were confirmed using the χ^2 test. The means of continuous variables were compared using the Mann-Whitney U test. $p < 0.05$ was considered to be statistically significant.

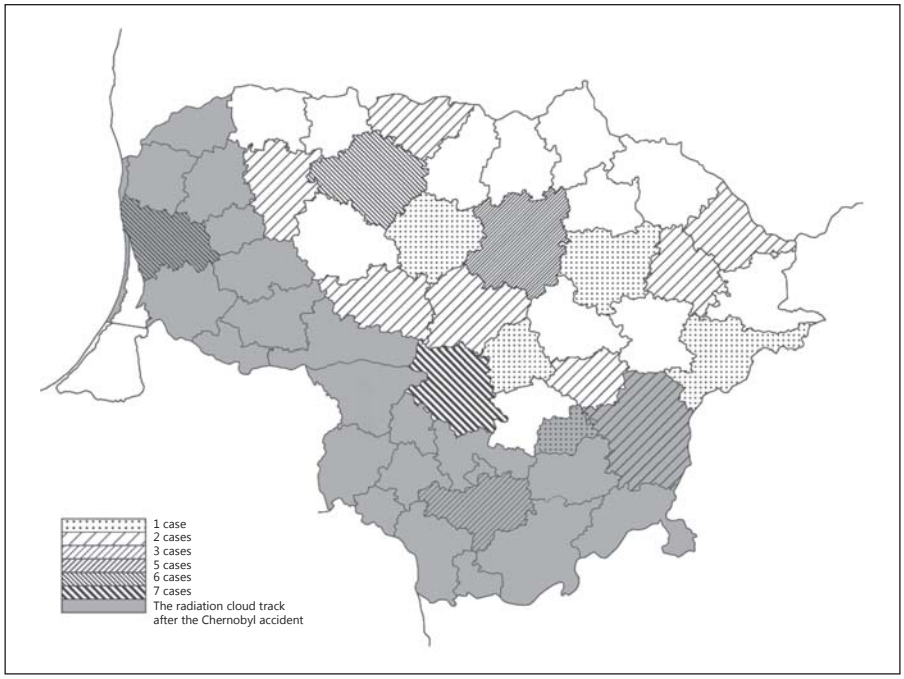

Fig. 2. The prevalence of TC in paediatric patients in Lithuania between 1980 and 2014.

Results

During the period from 1980 to 2014, 57 patients were diagnosed and underwent surgery due to TC; of these, 45 (78.91%) were females. The age of the patients ranged from 7 to 17 years, and the mean age was 14.51 ± 0.52 years. Five patients (8.83%) were younger than 10 years, 17 (29.82%) were 10–14 years old, and 35 (61.44%) were 15–17 years old. Five patients (8.83%) had previously been treated with radiotherapy for primary cancer.

Incidence

The incidence of TC among children in Lithuania between 1980 and 2014 ranged from 0 to 0.93 cases per 100,000 children per year, and there was an annual increase of 5.26% ($p < 0.001$) during this time period (fig. 1; table 1).

Relationship of Regional Incidence of TC in Children with Radioactive Cloud Exposure after the Chernobyl Accident

The prevalence of TC in the paediatric population in various regions of Lithuania during the study period is shown in figure 2. There was no association between the prevalence of TC in children with the officially reported areas of radioactive contamination after the Chernobyl accident.

Clinical Features

All children with suspected and later confirmed TC presented with neck masses. Two medullary carcinoma cases were diagnosed due to family history and confirmed MEN2A (multiple endocrine neoplasia type 2) syndrome.

The median TSH (thyroid-stimulating hormone) level was 1.37 mU/l (range 0.01–5.98 mU/l), the mean FT_4 level was 13.87 ± 1.28 pmol/l (median 14.8, range 1.2–23.9) at diagnosis. Subclinical hypothyroidism [TSH values from 4.2 to 10 mU/l with normal FT_4 and positive antithyroid autoantibodies (anti-TPO) levels] was found in 8 patients (14.04%). One patient with medullary carcinoma had an increased level of calcitonin (8.45 pmol/l).

Ultrasound Findings

Ultrasound (US) scans revealed a hypoechogenic nodule in 45 patients (78.95%). Three patients (5.26%) had an isoechogenic nodule and another 3 (5.26%) had a hyperechogenic nodule. In 4 children (7.02%) a cyst with endocystic proliferation was observed. In 2 cases (3.51%) the thyroid gland tissue had an appearance of autoimmune thyroiditis. Forty-nine patients (85.96%) had a single nodule and 8 children (14.04%) had multiple nodules. Thyroid nodules were found with the same frequency in both thyroid lobes without a significant difference [30 in the right lobe (52.63%) and 27 in the left lobe (47.37%), $p = 0.73$]. Nodule microcalcification was seen in 14 cases

Table 2. Distribution of Lithuanian patients according to gender and histological type

Histological type	Female		Male		p value
	n	%	n	%	
Papillary	33	73.3	9	75.0	0.45
Follicular	6	13.3	2	16.7	0.38
Poorly differentiated (insular)	2	4.5	0	0	–
Anaplastic	1	2.2	0	0	–
Medullary	3	6.7	1	8.3	0.42

$\chi^2 = 0.142$, d.f. = 4, p = 0.257.

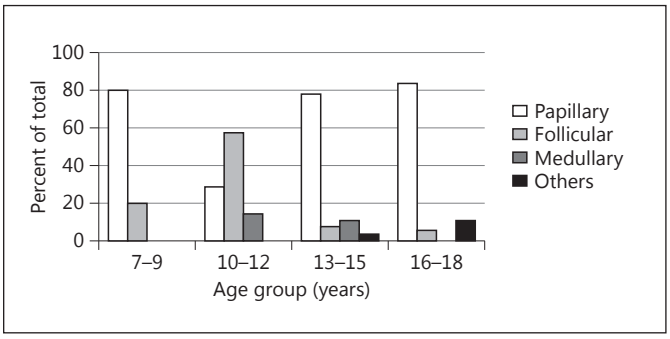

Fig. 3. The histology of TC according to age group among Lithuanian patients.

(24.56%), irregular margins in 47 cases (82.46%), active blood flow in 38 cases (66.67%), and reactive regional lymph nodes in 4 cases (7.02%).

Fine-Needle Aspiration

Fine-needle aspiration (FNA) was performed in 40 children (70.18%). Seventeen (29.82%) were operated without FNA since the US and clinical findings were typical for malignancy. The results of FNA were reported as suspicious for malignancy or as malignancy in all cases.

Histology

Based on the postoperative pathology, papillary carcinoma was confirmed in 42 patients (73.68%), follicular carcinoma in 8 (14.04%), medullary carcinoma in 4 (7.02%), poorly differentiated (insular) carcinoma in 2 (3.51%), and anaplastic carcinoma in 1 (1.75%; table 2; fig. 3). The cancer was surrounded by healthy thyroid tissue in 45 cases (78.95%), while signs of autoimmune thyroiditis were present in 11 cases (19.30%; all cases with papillary carcinoma). Adenomatous goitre was present in 1 patient (1.75%) with follicular TC.

Surgery

Total thyroidectomy together with lymphadenectomy was performed in 15 cases (26.32%), thyroidectomy in 35 cases (61.40%), and hemithyroidectomy in 7 cases (12.28%). Three children (5.26%) with an initial hemithyroidectomy eventually underwent total thyroidectomy as a result of a false negative urgent histological evaluation. Lymph node metastases were diagnosed in 15 patients (26.32%), distant metastases in 5 (8.77%), and thyroid capsule invasion in 31 (54.4%). The mean tumour size was 19.7 ± 3.8 mm (median 17, range 3–46). There was a trend towards a decrease in thyroid tumour size over time, as shown in figure 4.

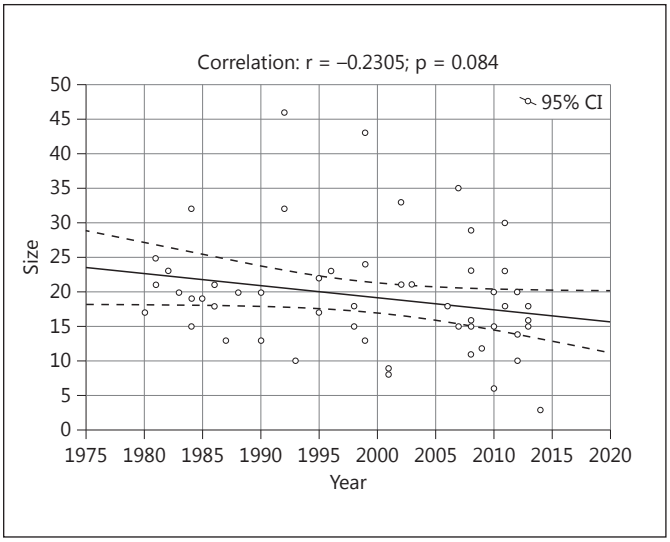

Fig. 4. The distribution of thyroid tumour size in Lithuanian children between 1980 and 2014.

Complementary Treatment

Radioactive iodine therapy was used in 33 cases (57.89%), including 2 children (3.51%) who received external beam therapy and another 2 (3.51%) who received telegamma therapy.

Complications

Acute postoperative complications were observed in 5 cases (8.77%): 3 patients developed vocal cord paresis and 2 subjects had transient hypocalcaemia due to transient hypoparathyroidism. There were 2 fatal cases (3.51%): 1 patient with anaplastic carcinoma died 2 months after surgery and the second patient died 2 years after diagnosis from an end-stage poorly differentiated (insular) carcinoma.

Table 3. Lithuanian cases of secondary TC

Case No.	Year of birth	Age at diagnosis of primary cancer, years	Gender	Primary cancer	Radiotherapy dose, Gy	Years to secondary TC diagnosis	Type of TC
1	1984	2	Female	Acute leukaemia	12	10	Papillary
2	1985	6	Male	Acute leukaemia	12	7	Papillary
3	1986	6	Female	Acute leukaemia	12	6	Papillary
4	1994	8	Female	Cerebellar medulloblastoma	54	8	Papillary
5	1995	4	Male	Acute leukaemia	12	10	Papillary

TC as a Secondary Malignancy

Secondary TC was observed in 5 patients (8.77%): 2 boys and 3 girls (table 3). These patients had an oncological disease and were treated with chemotherapy and radiotherapy between the ages of 2 and 8 years. All of them were diagnosed with papillary TC within 6–10 years (median 8 years) after the original cancer treatment.

Discussion

Several studies performed in Ukraine and Belarus addressed the effect of radiation related to the Chernobyl accident on the TC incidence trends in children and adults. According to 1 study conducted in Ukraine, the relationship between the ^{131}I radiation dose and TC risk 20 years after the Chernobyl accident remained stable [11]. The study from Belarus demonstrated that 10–15 years after radiation exposure, the relation between radiation dose and increased risk of TC in children and adults remained present [12]. Niedziela et al. [13] suggested that an increasing incidence of TC in children and adolescents in Poland might be a result of iodine deficiency and radiation from the Chernobyl disaster.

The radioactive cloud after the Chernobyl accident also passed over Lithuania. The information on radioactive contamination was very limited and no timely preventive measures were implemented to avoid hazardous radiation effects. According to available information, the level of radiation in Lithuania after the Chernobyl accident was mild: on April 27 and 28, 1986, it was reported to be 100 Bq/l [14], which was similar to other countries in Eastern Europe and Finland [15].

The incidence of paediatric TC during the period between 1986 and 1997 increased dramatically in countries with radiation contamination, such as Belarus, Ukraine, and Russia [16]. In contrast, the number of new TC cases during the same period in the Lithuanian paediatric population remained stable at only 0–2 per year (table 1). However, analyses of childhood TC incidence over a longer period from 1980 to 2014 have shown a persistently rising incidence, with a 5.26% annual increase, although without a link to the level of radiation after the Chernobyl accident in different regions of the country (fig. 2).

Iodine deficiency is a well-known risk factor for the development of TC [17, 18]. Before the national iodization program was initiated in 2005, Lithuania was considered a zone of mild iodine deficiency. However, the previously performed research in Lithuania failed to demonstrate a relationship between the severity of iodine deficiency and incidence of follicular or anaplastic TC [10]. Furthermore, in this analysis, the incidence of TC continued to rise after 2005, when the iodization program was already implemented.

It is highly probable that the increasing incidence of TC in the Lithuanian paediatric population is related to improved diagnostics, i.e. the higher availability of thyroid US in recent years. This hypothesis is further supported by findings showing a tendency towards a decrease in tumour sizes over the reported years of investigation. It has been shown that the detection of thyroid nodules increases dramatically when US is used for thyroid assessment compared to palpation alone [19]. With the increasing use of imaging and FNA, TC has one of the fastest growing incidence rates [20]. However, a large number of cases are diagnosed as subclinical, low-risk cancer, which creates a dilemma for management [19]. On the other hand, some authors suggest that the occurrence of chronic effects may never be entirely validated because such relatively small increments are statistically indistinguishable in the face of the great variability of spontaneous cancer rates [21, 22].

Solid secondary malignancies represent the most common malignant neoplasm developing in aging survivors of childhood cancer [23]. TC is responsible for approximately 6% of secondary malignancies among child-

hood cancer survivors [24]. Some authors found that long-term survivors of childhood malignancy who underwent radiotherapy have an increased incidence of secondary TC, and this association depends on the dose of irradiation received [25, 26]. Gender, age at exposure and time since exposure were found to be significant modifiers of the radiation-related risk of TC, and as such are important factors to take into account for clinical follow-up [27]. The effect of chemotherapy drugs on TC risk still remains unclear, but it has been shown that alkylating agents increase the risk of TC together with radiotherapy under the dose of 20 Gy [28]. Childhood cancer survivors who were treated for leukaemia and CNS tumours at a younger age were at the highest risk for thyroid tumours [29, 30]. All 5 patients with secondary TC in our study had previously been treated for leukaemia or a CNS tumour.

Conclusions

The incidence of TC in the paediatric population in Lithuania between 1980 and 2014 ranged from 0 to 0.93 cases per 100,000 children per year, with an annual increase of 5.26% ($p < 0.001$). This increase in incidence is most likely related to improved diagnostic methods. No relationship was found between TC incidence rates and radiation exposure following the Chernobyl accident in Lithuania. Papillary carcinoma was the most common cancer in this population and it was found in all cases with secondary TC.

Disclosure Statement

The authors declare no conflicts of interest.

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