Incidence and Prognosis of Thyroid Cancer in Children: Based on the SEER Database

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Research Article

Keywords: Childhood thyroid cancer, Incidence trend, Prognosis factors

Posted Date: August 4th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-743194/v1>

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Version of Record: A version of this preprint was published at Pediatric Surgery International on January 29th, 2022. See the published version at <https://doi.org/10.1007/s00383-022-05069-3>.

Abstract

Background: Studying the incidence trend and prognosis factors of childhood Thyroid cancer (TC) may better reflect the prevalence of this disease.

Objectives: To explore the trends in the incidence of childhood thyroid cancer and the prognosis.

Material and Methods: Join-point regression model was used to analyze incidence trend of TC. Cox regression model was applied to explore the survival situation and prognostic factors.

Results: The incidence rate of childhood TC increased between 1975 and 2016 from 3.8/million (95%CI: 2.6-5.5) to 11.5/million (95%CI: 9.2-14.1), AAPC = 2.38 (95%CI: 1.98-9.65)) and could be divided into two stages of increasing trends. The incidence rate of Trend1 (1975-2005) increased slowly but Trend2 (2005-2016) increased dramatically. And annual rates of small size tumor (<4cm) and local stage TC in children increased significantly. The overall cumulative survival rate for childhood TC was high up to 97%-99%. Males, the black people, MTC type, distant metastasis, tumor size ≥ 4 cm, non-primary cancer were the independent risk factors of prognosis of childhood TC.

Conclusions and Significance: A contribution of over detection to rising pediatric TC rates might not be able to rule out. Over-treatment to small size and local stage TC in children should be avoided.

1. Introduction

Thyroid cancer (TC) is a common endocrine malignant tumor in both adults and children whose incidence has been increasing steadily for decades in the world [1]. Due to advancements in diagnostic methods, with the implementation of advanced imaging modalities in the past decades, the diagnosis of micro-TC (< 1 cm) has been promoted [2]. Although TC is likely to be over diagnosed in adults, children are less likely to receive thyroid screening or imaging examinations of the neck [3, 4]. Therefore, studying the incidence trend of childhood TC may better reflect the prevalence of this disease in the population. In addition, some types of childhood TC are more prone to have lymph node metastasis than in adults, with a wider range of lesions and leading a worse prognosis [5]. Currently, on account of low incidence, very low mortality and few prognostic analysis using large samples, little knowledge is recognized about the prognostic factors of children's TC [6, 7].

This study intended to explore the trends in the incidence of childhood TC and the prognosis in children using a large and public population-based cohort. First, the incidence of childhood TC was fitted through the join-point regression (JPR) model to explore its changing trend and its distribution in the population. Then, univariate and multivariable Cox regression model analysis were applied to explore the survival situation and prognostic factors of childhood TC. From epidemiological perspective, we aimed to provide suggestions for further investigations into descriptive and etiological epidemiology of TC. For clinical implications, we intended to provide constructive advice for therapy to childhood TC more precisely and specifically.

2. Materials And Methods

Data resource

Data in this study was attained from the Surveillance, Epidemiology, and End Results (SEER) program, one of the most representative databases of large oncology registries worldwide. As an ongoing longitudinal program proceeding for decades, the SEER research reports annual national cancer statistics on incidence and survival and provides population data associated by age, sex, race, year of diagnosis, geographic areas, etc. on its website (<https://seer.cancer.gov/data-software/>), serving as a platform for offering systematic evidence to studies of cancer-related health disparities [8]. Information of childhood TC was collected from “Incidence-SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub (1975–2016)”.

TC patients were classified into histology types according to the histology codes in the International Classification of Disease for Oncology, 3rd edition (ICD-O-3) SEER site/histology validation list 2015 [9], including differentiated TC (DTC) and undifferentiated TC (UTC) and were specifically identified using the following ICD-O-3 codes: Classic Papillary Thyroid Cancer (C-PTC): 8050/3, 8260/3, and 8343/3; Variant Papillary Thyroid Cancer (V-PTC): 8340/3, 8350/3, 8344/3, 8052/3, 8130/3, and 8342/3; FTC (Follicular Thyroid Cancer): 8330/3, 8331/3, 8332/3, and 8335/3; MTC (Medullary Thyroid Cancer): 8345/3, 8510/3, 8346/3, and 8347/3; and ATC (Anaplastic Thyroid Cancer): 8021/3 [9]. C-PTC, V-PTC, and FTC were classified as DTC while MTC and ATC were recognized as UTC. In this study, we collected types of C-PTC, V-PTC, FTC and MTC.

For cancer-directed surgery status, the “Subtotal or Near Total Thyroidectomy” and “Total Thyroidectomy” groups were combined to form “Total Thyroidectomy” group. The “Lobectomy” group consisted of TC patients who underwent lobectomy, with or without subsequent isthmusectomy. If a patient initially underwent a thyroid lobectomy and then went on to have a completion thyroidectomy, his/her surgery status in SEER was coded as “Total Thyroidectomy” [9].

In this study, we used its software SEER*Stat (version 8.3.9) to retrieve the complete TC cases with an age under 20 from 1975 to 2016 in the SEER database. A total of 4,343 eligible patients were finally extracted according to pathologically confirmed diagnosis and integrated survival information. And annual standardized TC incidence rates were obtained. The following demographic and clinicopathological variables were included in our analysis: age, sex, race, histologic type, metastasis, radiation, chemotherapy, grade, surgery, AJCC stage, TNM stage, tumor size, primary cancer and survival information. Age groups were divided by 5 years per group. Due to the small number of patients aged 0–9 years, they were combined into one group. Race was aggregated into White, Black and others (American Indian/Alaskan Native or Asian/Pacific Islander). The primary outcomes in our study were overall survival (OS). OS was calculated as the time from diagnosis to death regardless of any cause.

Join-point regression model

The traditional regression analysis mainly reflects the overall trend of global data, but may not reveal the specific trend of local data. Therefore, the piecewise regression model comes into being. The basic idea of the JPR model proposed by Kim et al. is to divide a long-term trend line into several statistically significant trend segments by model fitting, and each segment is described by continuous linearity, which could be linear data model or log-linear data model [10]. Based on the annual incidence, this model mainly provides two outcome indicators: annual percent change (APC) and average annual percent change (AAPC) and corresponding confidence intervals (CIs). As a trend analysis of time series data, JPR model has been widely used in the field of epidemiological trends of cancer and chronic diseases, mainly to analyze the characteristics of temporal trends of morbidity and mortality [11].

Statistical methods

Summary statistics was used to describe the demographic characteristics and clinical data at baseline. The measurement data of normal distribution were described by means $\pm$ SD), the non-normal data were described by median and quartile range [M(Q1,Q3)]; and the enumeration data were described by number of cases and composition ratio [N(%)]. The incidence rates were calculated per 100,000 persons and age-adjusted to 2000 US Standard Population using SEER*Stat (version 8.3.9). The JPR model analysis was performed using Join-point Regression Program4.8 and trend curves were presented using three-year rolling average for each calendar year. Survival analysis using Cox proportional hazard regression model and K-M survival curve analysis with log-rank test were performed using R4.0.2. Bilateral tests were used for all statistical tests. A value of $P < 0.05$ was considered statistically significant. All other statistical analyses were performed using R4.0.2.

3. Results

3.1. Demographics and incidence of childhood TC

3.1.1. Demographics of childhood TC

A total of 4,343 TC cases under 20 years old were included. Age 0-9 group consisted of 213 cases, accounting for 4.90% of the overall subjects; age 10-14 group consisted of 904 cases (20.82%); and age 15-19 group was 3,226 cases (74.28%). Male subjects were 824 cases accounted for 18.97% while female subjects were 3,519 cases accounted for 81.03%. Black people were 233 cases (5.23%), white people were 3,602 cases (84.44%), and others were 441 cases (10.34%). The median follow-up time was 104.00 (Q1:46.00, Q3:193.00) months. The characteristics of demographics and clinic information at baseline are displayed in **Table1**.

3.1.2. Overall incidence of childhood TC

Table2 and **Figure1** show the JPR analysis of trends in incidence. From 1975 to 2016, the overall incidence of childhood TC increased with an age-standardized incidence rate (ASR) = 3.8/million (95%CI: 2.6-5.5) to 11.5/million (95%CI: 9.2-14.1), AAPC = 2.38 (95%CI: 1.98-9.65), which could be divided into

two increasing stage of trends. Between 1975 and 2005, the ASR of childhood TC increased slowly with APC = 1.08 (95%CI: 0.38-1.82, $P < 0.05$). But the ASR had increased significantly since 2005 with APC = 6.77 (95%CI: 4.30-9.28, $P < 0.001$). See **Figure1A**.

3.1.3. Distribution of incidence of childhood TC

We performed subgroup analysis of incidence by some interested population groups. Due to lack of data, the results of “0-9 years” group in “Age”, “Other” group in “Race” and “<1” group in “Tumor size” were not applicable. From **Table2** and **Figure1**, the incidence of “10-14 years” group had no “join-point” and increased gradually from 1975 to 2016 ($P < 0.05$) and so as “Male” group and “1-4 cm” ($P < 0.05$). Differently, note that the incidence of “15-19 years” group, “Female” group, “White” group, “Differentiated” group and “Regional” group increased gradually from 1975 to 2005 ($P < 0.05$) but sharply increased after 2005 ($P < 0.05$), just as the tendency of overall incidence. And the incidence trend of “Localized” group was also similar to the overall incidence trend. Besides, incidence of “Black”, “Distant” and “Undifferentiated” had no significantly increasing ($P > 0.05$).

3.2. Risk factors for the prognosis of TC in children

3.2.1. Univariate risk factors analysis

Table3 showed the results of single risk factors analysis of prognosis in childhood TC. As shown in **Table3**, there were no significant differences in risk of death between age groups. Male patients had 2.595 times of death risk compared to females (hazard ratio, HR = 2.595, 95%CI: 1.776-3.790). The black patients had 3.029 times of death risk compared to the white (HR = 3.029, 95%CI: 1.749-5.245).

In terms of clinic factors, because of a large amount of missing data (20%-80%) of “grade”, “surgery”, “AJCC stage” and “TNM stage”, we keep cautious of these results. And because few subjects (19 cases, 0.44%) received chemotherapy, its result had bias. In “Histologic type” group, compared to “MTC”, other histologic types had lower death risk ($P < 0.001$). The distant metastasis patients had much high death risk compared to localized patients (HR = 4.209, 95%CI: 2.540-6.975). The patients who were “First malignant” had much lower death risk compared to those who were not “first” (HR = 0.186, 95%CI: 1.776-3.790). Besides, whether received radiotherapy or not and tumor size had no significant difference for death risk ($P > 0.05$).

3.2.2. Multivariate risk factors analysis

Variables that were statistically significant in the univariate factor analysis such as sex, race, histologic type, metastasis and primary cancer and the common influencing factor like age and tumor size [12] were included in the multiple factors Cox regression model analysis. Finally, factors that were included in the regression model are presented in **Table4**. Males (HR = 2.659, 95%CI: 1.524-4.641), the black people (HR = 2.345, 95%CI: 1.027-5.355), MTC type (C-PTC, HR = 0.160, 95%CI: 0.072-0.355; FTC, HR = 0.185, 95%CI: 0.058-0.586; V-PTC, HR = 0.127, 95%CI: 0.050-0.323), distant metastasis (HR = 2.884, 95%CI: 1.296-

6.419), tumor size ≥ 4 cm (HR = 3.071, 95%CI: 1.141-8.264), non-primary cancer (HR = 0.089, 95%CI: 0.043-0.185) were the independent risk factors of prognosis of childhood TC.

3.2.3. K-M survival curves analysis

K-M survival curves for the above independent risk factors as well as the overall survive are shown in **Figure2**, Log-rank test see in **TableS1**. The overall cumulative survival rate for childhood TC from 1975 to 2005 was 97.70% and with a promotion to 99.27% from 2006 to 2016 ($P = 0.030$). From 1975 to 2016, the survival rate for female was 97.98% and higher than that of male with 94.78% ($P < 0.001$). The cumulative survival rate for the white, black and others was 97.64%, 93.27% and 96.83% respectively, and had a difference ($P < 0.001$). The cumulative survival rate for DTC was up to 98.88% and higher than that of UTC with 94.65% ($P < 0.001$). The cumulative survival rate for tumor size < 4 cm was around 99.15% and 97.80% for size ≥ 4 cm with a difference ($P = 0.035$). The cumulative survival rate for localized, regional and distant metastasis was 97.78%, 97.91% and 89.40% with a difference ($P < 0.001$). The cumulative survival rate for primary cancer was 97.63% and much higher than that of non-primary cancer with 88.62% ($P < 0.001$).

Discussion

The pattern of TC incidence in children and adolescents is similar to that in adults. Compared to being over diagnosed in TC in adults often, children and adolescents are less likely to have over detection effects from a clinical perspective [4, 8, 13]. Therefore, studying the incidence trend and exploring the prognostic factors of childhood TC may better reflect the prevalence of this disease in the population and offer clinical treatment suggestions. This study analyzed the trends in the incidence of childhood TC with distribution and explored the prognosis factors based on large samples and longitudinal data from the SEER database between 1975 and 2016 using JPR model and survival analysis.

The overall ASR of childhood TC increased from 3.8/million (95%CI: 2.6-5.5) in 1975 to 11.5/million (95%CI: 9.2-14.1) in 2016, with AAPC = 2.38 (95%CI: 1.98-9.65) and could be divided into two stages of increasing trends. Between 1975 and 2005 (Trend1), the ASR of childhood TC increased slowly with APC = 1.08 (95%CI: 0.38-1.82) but had increased significantly since 2005 (Trend2) with APC = 6.77 (95%CI: 4.30-9.28). In the same time period, the overall incidence of childhood TC in Denmark increased significantly from 3.6/million in 1980 to 9.7/million in 2014 with an AAPC of 2.9% [7]. The growth trend was roughly the same. Trend1 was lower than incidence trend of childhood TC in Europe of 3% per year during 1978-1997 [14]. A national study [4] of trends in pediatric DTC incidence in the United States from 1998 to 2013 only reported one trend that pediatric DTC incidence rates significantly increased from 4.77/million (95% CI: 4.26, 5.33) in 1998 to 8.82/million (95% CI: 8.13, 9.56) in 2013 whose incidence trend was similar to that of the present study during the same period (see **Figure1A**). The advantage of this study is that we provided a longer time line to observe the incidence trend of TC in children more comprehensively so that a fast-growing period was found (since 2005).

The incidence of TC is known to vary widely according to age, gender and race/ethnicity. Low in the first years of age, the incidence rates increase dramatically in adolescence, and are higher in girls than boys [7, 15]. This study is consistent with prior findings. In the analysis of distribution of incidence (**Figure1**), we found that the trends reported for overall incidence were largely driven by “15-19 years” group, “Female” group, “White” group, “Localized” group, “Regional” group and DTC types (papillary TC, 87%). Physiologically, this can be explained by differences in developmental status, hormone levels and race [16, 17]. However, we observed that the annual increase rates of distant TC are lower than those observed for localized or regionally, which contradicted the findings of a previous study [2]. The significant annual increases in the rates of small size tumor (<4cm) and local stage TC in children suggests that we might not be able to rule out a contribution of over detection to rising pediatric DTC rates. A global study [17] shows that there is over-diagnosis among childhood TC, too. Because patients undergoing detection are younger and healthier and are diagnosed with lower-risk TC, they are less likely to die [18]. However, considering over-diagnosis can lead to over-treatment, lifelong medical care, and side effects, we once again appeal to explicitly recommend against screening for thyroid cancer in children and adolescents.

We then explored survive and prognosis factors of childhood TC. Generally, the overall cumulative survival rate for childhood TC was high, of 97.70% from 1975 to 2005 and with a promotion to 99.27% from 2006 to 2016 ($\chi^2 = 4.733$, $P = 0.030$). Female, white people, DTC, all sizes of tumor, localized, regional and primary cancer had a much higher cumulative survival rate above 97% while the cumulative survival rate of distant metastasis and non-primary cancer was lower than 90%. The overall high survival rate for childhood TC was consistent with previous studies [7, 14]. Males, the black people, distant metastasis, MTC histological subtype, tumors size ≥ 4 cm and non-primary cancer were the independent risk factors of prognosis of childhood TC. A study of analysis of prognosis of geriatric DTC showed that male, African-American, tumors sized over than 4 cm, lymph node metastasis, and distant metastasis, were strong risk factors in elderly DTC patients prognosis [19]. Prognostic factors of TC for children were similar to those for the elderly. However, we are cautious about the result of surgery method due to the absence of data. A study about total thyroidectomy vs thyroid lobectomy for localized papillary TC in children showed that both two methods had a good prognosis for children [20].

This study has its merits. First, this study is based on a large sample of public databases which can provide reliable and powerful evidence. Second, we used JPR model to analyze a long time line database to observe the incidence trend of TC in children more comprehensively so that a fast-growing period was found. Also, still some limitations need to be considered. Due to insufficient baseline information of the public database, we did include limited potential risk factors into survival prognosis analysis. More additional potential factors including demographic characteristics, life behavior pattern, and clinical treatment information need to be considered in further researches.

Conclusion

Analysis Based on SEER database revealed that the incidence rate of childhood TC increased between 1975 and 2016 and could be divided into two stages of increasing trends. The incidence rate of Trend1 (1975-2005) increased slowly but Trend2 (2005-2016) increased dramatically. A contribution of over detection to rising pediatric TC rates might not be able to rule out. The overall cumulative survival rate for childhood TC was high. Several risk factors of prognosis of childhood TC were identified. For clinical implications, over-treatment to small size and local stage TC in children should be avoided. Still, more additional potential factors including life behavior pattern, demographic characteristics and clinical treatment information need to be considered in further researches.

Declarations

Ethics approval and consent to participate

The authors declare that there is no ethics problem.

Consent for Publication

Not Applicable.

Availability of data and material

The datasets generated and/or analysed during the current study are available in the [SEER] repository, [<https://seer.cancer.gov/data-software/>]

Competing interests

The authors declare that they have no competing interests.

Funding

This study has no funding information.

Authors' contributions

Study conception and design: Liang Zong

Data collection and clean: Wenming Wu and Xiaofei Shang

Real data analysis and interpretation: Deliang Huang and Mingbo Liu

Drafting of the manuscript: Bing Zhang

All authors reviewed the manuscript.

Acknowledgements

We acknowledge all participants and staff in the collection of participants.

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Tables

Due to technical limitations, table 1-4 is only available as a download in the Supplemental Files section.

Figures

Figure 1

Distribution of childhood TC incidence trend chart (A. Overall, B. Age, C. Sex, D. Race, E. Histologic subtype, F. Extent of disease, G. Tumor size)

Figure 2

Factors affecting the grouping of KM curve (A. Year, B. Sex, C. Race, D. Tumor size, E. Histologic subtype, F. Extent of disease, G. Primary lung cancer)

Supplementary Files

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