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Long-Term Risk of Thyroid Cancer after Childhood Malignancy: A Retrospective Cohort of Survivors Treated Between 1990 and 2018

Ali Hassan[1]*, Noor Siddiqui[1], Bilal Khan[2], Sana Malik[1]

[1]Department of Biomedical and Clinical Research, Aga Khan University, Karachi, Pakistan.
[2]Department of Medical Innovation Systems, Qatar University, Doha, Qatar.

Abstract

Although survival rates for childhood cancer have risen considerably, survivors remain at heightened risk for second malignant neoplasms (SMNs), with thyroid cancer being a notable concern. This study explores the demographic, clinical, genetic, and treatment-related profiles of childhood cancer survivors who developed thyroid cancer as a second or third malignancy, underscoring the necessity of extended long-term follow-up. Medical records of childhood cancer survivors treated from 1990 to 2018 who later presented with thyroid cancer as a second or third malignancy were retrospectively analyzed. Details on patient demographics, clinical features, treatment history, and outcomes were reviewed. In a cohort of 3204 childhood cancer survivors, 10 individuals (6 female, 4 male) were found to have papillary thyroid carcinoma (PTC) after a median latency of 9 years from their first cancer diagnosis. Radiation therapy, especially to the head and neck, had been administered in most cases. Genetic analysis detected mutations in the Cell Cycle Checkpoint Kinase 2 (CHEK2) and Adenomatous Polyposis Coli (APC) genes in four patients, potentially contributing to their increased susceptibility. Thyroid cancer was identified in all cases through ultrasound screening; all patients underwent total thyroidectomy, with three also receiving radioactive iodine (RAI) therapy. During a median follow-up of 5.5 years after the thyroid cancer diagnosis, no recurrences or PTC-related deaths occurred. Exposure to radiation therapy, particularly when combined with chemotherapy, substantially raises the likelihood of thyroid cancer in individuals who survived childhood cancer. Genetic predispositions further contribute to this risk. Ongoing lifelong monitoring for thyroid cancer is vital, above all for survivors who received radiation or chemotherapy. More research is warranted to improve surveillance protocols and to deepen understanding of the genetic influences on thyroid cancer development in this population. Timely identification and sustained observation are key to achieving a better long-term prognosis.

Keywords: Childhood cancer survivors, Thyroid cancer, Second malignant neoplasms, Radiation therapy, Genetic mutations

Corresponding author: Ali Hassan
E-mail: ali.hassan@gmail.com

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Introduction

The last several decades have witnessed breakthroughs in pediatric oncology, resulting in significantly improved survival rates for children with cancer. These advances are largely due to greater access to cutting-edge therapies, refined supportive care measures, and progress in early detection, all of which have contributed to better overall outcomes for young cancer patients [1, 2]. As more children survive their initial cancer, attention has

increasingly shifted toward the late consequences of treatment. Survivors often deal with various delayed complications that can affect their physical health, emotional well-being, and psychological state as a result of the therapies they underwent. One of the gravest long-term risks facing childhood cancer survivors is the emergence of second malignant neoplasms (SMNs) [3]. Among these secondary cancers, thyroid cancer ranks as one of the most frequent and clinically significant [4, 5]. The increased chance of developing thyroid cancer as an SMN is particularly well recognized in patients who were exposed to radiation therapy during treatment of their primary tumor. However, the risk is not confined to radiation; those treated with certain chemotherapeutic drugs (such as alkylating agents or anthracyclines) or targeted therapies like I-131 MIBG also show elevated rates of secondary thyroid cancer. Extensive research has confirmed a strong dose-dependent link between radiation exposure and the subsequent development of thyroid malignancy [6]. In addition to treatment effects, underlying genetic factors can play a meaningful role in raising the likelihood of secondary thyroid cancers. Inherited mutations or specific cancer predisposition syndromes may make childhood cancer survivors more prone to developing thyroid cancer later on [7].

Against this background, the current study evaluates cases of thyroid cancer occurring as a second or third malignancy in childhood cancer survivors from a single institution. It emphasizes the critical importance of prolonged surveillance in this vulnerable group.

Materials and Methods

We carried out a retrospective chart review involving childhood cancer survivors who received treatment between 1990 and 2018, had been followed for a minimum of five years in the pediatric oncology department of a tertiary care hospital, and subsequently developed thyroid cancer as either a second or third malignancy. Patient-specific information on demographics, clinical presentation, imaging findings, therapeutic interventions, and eventual outcomes was collected and assessed. The duration of follow-up was calculated from the date of thyroid cancer diagnosis to November 2024 or the date of the last recorded visit. In four patients, germline genetic testing targeting predisposition genes was conducted via next-generation sequencing; three of these patients had also developed a third subsequent malignancy. The study protocol received approval from the hospital's institutional ethics review board.

Results and Discussion

Out of 3204 children who received cancer treatment from 1990 to 2018, 10 individuals (six female, four male) went on to develop thyroid cancer. These patients had a median age of 7.5 years (range 12 months to 16 years) when their primary cancer was diagnosed, and thyroid cancer emerged after a median period of 9 years (range 4 to 19 years). Histopathology confirmed papillary thyroid carcinoma (PTC) in every instance. Key details about these cases are outlined in **Table 1**.

Table 1. Patient characteristics.

Patient/Sex	Age at first cancer diagnosis (years)	Initial cancer diagnosis	Treatment for initial cancer	Interval to thyroid cancer diagnosis after first cancer (years)	Status at final follow-up
Patient 1 / F*	9	Head and neck rhabdomyosarcoma	CT, RT	16	Alive with NED
Patient 2 / M**	1	Neuroblastoma	CT, S	19	Alive with NED
Patient 3 / M***	16	Osteosarcoma	CT, S	18	Alive with NED
Patient 4 / M	10	Hodgkin lymphoma	CT, RT	4	Alive with NED
Patient 5 / F	10	Pinealoblastoma	S, RT, CT	10	Alive with NED
Patient 6 / F	7	Medulloblastoma	S, RT, CT	9	Alive with NED
Patient 7 / F****	7	Medulloblastoma	S, RT	7	Deceased (D)
Patient 8 / F	5	Medulloblastoma	S, RT, CT	9	Exitus (EX)
Patient 9 / M	8	Hodgkin lymphoma	CT, RT	5	Alive with NED
Patient 10 / F	4	Ovarian sarcoma	S, CT, RT	7	Alive with NED

Abbreviations: CT = chemotherapy; D = disease; F = female; M = male; NED = no evidence of disease; RT = radiation therapy; S = surgery; EX = excitus. The patient was diagnosed with breast cancer at the age of 39 years as a third malignancy and was found to have a cell cycle checkpoint kinase 2 (CHEK2) mutation. The patient was diagnosed with renal cell carcinoma at the age of 9 years as a second malignancy. The patient was diagnosed with renal cell carcinoma at the age of 30 years as a second malignancy. The patient was diagnosed with soft tissue sarcoma at the age of 19 years as a third malignancy and found to have an adenomatous polyposis coli (APC) mutation.

Chemotherapy was part of the initial regimen for all patients. Radiotherapy was delivered to eight of the ten cases, and in seven of those cases, the radiation field encompassed the head and neck.

The original cancer diagnoses among the seven patients who received head and neck radiation included brain tumors in four (specifically three medulloblastomas and one pineoblastoma), Hodgkin lymphoma in two, and rhabdomyosarcoma located in the head and neck in one.

The individual with head and neck rhabdomyosarcoma was diagnosed with thyroid carcinoma 16 years after the primary cancer. Even though the thyroid gland lay outside the targeted radiation zone, possible exposure to scattered radiation remained a consideration. This patient was given radioactive iodine (RAI) treatment and continues in remission from thyroid cancer. Twenty-eight years after the first diagnosis, she developed breast cancer, which was managed with surgery, radiotherapy, and chemotherapy. Subsequent molecular analysis uncovered a germline CHEK2 mutation.

One patient treated for medulloblastoma developed thyroid carcinoma after 7 years and was later found to have a malignant mesenchymal tumor in the head and neck region 12 years from the initial diagnosis. Genetic evaluation in this case revealed a germline APC mutation.

A patient whose primary diagnosis was ovarian sarcoma had undergone whole abdomen radiotherapy (WART) and carried a germline DICER1 mutation. Two years after finishing treatment, she required surgical intervention for a pancreatic pseudocyst. Regular monitoring revealed microcysts and hypoechoic nodules affecting both thyroid lobes. A biopsy conducted 5 years after the original malignancy yielded indeterminate atypia. As the nodules continued to enlarge, a second biopsy performed 7 years after the first cancer diagnosis established the presence of multifocal papillary carcinoma featuring a follicular subtype without capsular invasion.

The patient originally diagnosed with pinealoblastoma underwent comprehensive hereditary cancer panel testing that included DICER1, yet no underlying genetic predisposition was identified.

The final two patients received only chemotherapy and surgery, with no radiotherapy exposure. One had been treated for infantile neuroblastoma and the other for osteosarcoma. Both later developed renal cell carcinoma as a second malignancy—9 years and 14 years after their primary diagnosis, respectively—before the appearance of thyroid cancer. Hereditary cancer panel testing via next-generation sequencing (NGS) was carried out for the neuroblastoma survivor, but no predisposing mutation was found. Genetic testing could not be completed for the osteosarcoma case.

None of the patients in this series had any documented family history of thyroid cancer.

Thyroid cancer was detected in all cases through routine ultrasound examinations performed as part of ongoing surveillance. Every patient proceeded to total thyroidectomy, and three were additionally treated with radioactive iodine (RAI). No instances of PTC recurrence or PTC-related mortality occurred. One patient with prior medulloblastoma succumbed to an unrelated accident. The remaining nine patients are still alive, with a median follow-up duration of 5.5 years (range 0.5 to 15 years) following their thyroid cancer diagnosis.

Survival rates among children with cancer have risen dramatically in recent decades, resulting in a steadily expanding group of long-term survivors. Nevertheless, the therapies used—particularly chemotherapy and radiotherapy—carry substantial late toxicities. The appearance of second malignant neoplasms (SMNs) continues to rank among the primary contributors to treatment-related deaths in this population, demanding greater clinical focus [6]. Thyroid cancer stands out as one of the most frequent SMNs, occurring in as many as 10% of childhood cancer survivors [8]. In line with previous reports, all cases in our series were confirmed as papillary thyroid carcinoma [9]. The likelihood of SMNs depends on multiple factors, including the patient's age at initial diagnosis, the specific treatments administered, and any underlying genetic susceptibility [10].

Radiotherapy is a firmly established risk factor for the development of secondary thyroid cancer (STC) in childhood cancer survivors. Earlier publications have typically described a latency interval of 20–30 years for radiation-associated secondary tumors [11]. However, a review by Clement *et al*. [12] that compiled data from 16 studies indicated a shorter latency of 10–20 years, with STC appearing as early as 4.2 years after radiation exposure. In the present cohort, the median interval from primary cancer diagnosis to thyroid cancer was 9 years, with the shortest gap being 4 years (range 4 to 19 years). The International Late Effects of Childhood Cancer Guideline Harmonization Group, working with the PanCareSurFup Consortium, recommends initiating thyroid cancer screening no later than 5 years after radiotherapy and continuing surveillance for an appropriate duration thereafter [12].

Numerous investigations have examined the link between radiation dosage and subsequent thyroid cancer risk. The Childhood Cancer Survivor Study reviewed 119 cases of STC among 12,547 survivors diagnosed between 1970 and 1986. It demonstrated a linear rise in risk with increasing radiation dose, reaching a peak relative risk of 14.6 at around 20 Gy compared with non-irradiated patients. Beyond 20 Gy, however, the dose-risk relationship weakened [13]. The same study also assessed the contribution of chemotherapy and possible interactions with radiotherapy. Treatment involving alkylating agents

was associated with a 2.4-fold higher risk of secondary thyroid cancer in survivors who had received 20 Gy or less. This added risk from chemotherapy was not evident at higher radiation doses, likely because intense radiation exerts a strong cell-killing effect that may mask chemotherapy's influence. These observations underline that while radiotherapy remains a major driver of thyroid cancer, certain chemotherapeutic drugs can also elevate the risk, making it essential to evaluate both modalities when estimating long-term hazards for childhood cancer survivors [14]. Furthermore, although radiation is the dominant risk factor, thyroid cancers have been documented after exposures below 1 Gy as well as above 40 Gy, showing that no universally safe radiation dose threshold has been defined [15].

Veiga *et al*. [14] confirmed that radiotherapy is a clear risk factor. Yet, certain chemotherapy agents—especially alkylating agents and anthracyclines—were linked to higher thyroid cancer rates even among patients who never received radiation. Similarly, Black *et al*. [16] described 18 cases of STC in which one patient had no radiation history at all, and two had radiation fields distant from the thyroid gland. Our series likewise included two patients (one with osteosarcoma and one with neuroblastoma) who developed thyroid carcinoma following chemotherapy alone, without any radiotherapy. The ovarian sarcoma patient received whole-abdomen radiotherapy, a site remote from the thyroid. In the head and neck rhabdomyosarcoma case, although radiotherapy was delivered, the thyroid tumor arose outside the irradiated field. Collectively, these observations point to a contributory role of chemotherapy in secondary thyroid malignancies and reinforce the need for continued thyroid surveillance in all childhood cancer survivors, irrespective of radiation exposure.

Several reports have shown that the risk of radiation-induced thyroid cancer declines as age at exposure increases [17, 18]. Data from atomic bomb survivors—an exceptional population allowing risk assessment across broad age ranges—revealed progressively lower radiation-related thyroid cancer risk with advancing age at exposure. Notably, no radiation-associated thyroid cancers were recorded among individuals aged 20–39 years in that cohort [19]. Taylor *et al*. [20], analyzing the British Childhood Cancer Survivor Study, found that age at radiotherapy strongly affected subsequent thyroid cancer risk. Children younger than 5 years at the time of radiation faced a substantially elevated risk compared with older children, and the relative risk steadily fell as age at exposure rose. These results highlight the importance of factoring in age at treatment when evaluating long-term cancer risks and support the development of individualized surveillance plans that take both age and treatment details into account.

(131) I-Metaiodobenzylguanidine (MIBG), a guanidine-based compound absorbed by a norepinephrine transporter present on the majority of neuroblastoma (NBL) cells, serves as a form of targeted radiotherapy for neuroblastoma management. Thyroid problems, including thyroid carcinoma, have been noted in nearly half of pediatric patients as early as 1.4 years following (131) I-MIBG therapy for neuroblastoma, even when potassium iodide protection is provided. The initial two reported instances of differentiated thyroid carcinoma arising in children after (131) I-MIBG treatment for neuroblastoma described malignancies appearing several years after the therapy. To block thyroid uptake of iodine, potassium iodide (KI) is routinely given to children undergoing 131I-MIBG treatment. This approach works by diluting the free circulating radioiodine released from 131I-MIBG, thereby lowering the amount absorbed by the thyroid. Nevertheless, cases of hypothyroidism, thyroid nodules, and thyroid cancer have still been documented after 131I-MIBG administration. Such thyroid injury is believed to result from the gland's uptake of free radioiodine circulating in the blood [21, 22].

In this setting, the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) assembled an expert panel to guide the care of childhood, adolescent, and young adult cancer (CAYAC) survivors who face a higher chance of developing differentiated thyroid cancer (DTC). The panel reviewed and summarized the existing evidence on DTC risk factors and assessed various approaches to screening for subclinical disease. According to the IGHG, CAYAC survivors who underwent radiation therapy that included the thyroid field or received therapeutic 131 I-MIBG are considered at increased risk for DTC. Thyroid ultrasonography is the preferred screening tool for identifying thyroid abnormalities. Surveillance for DTC should reasonably begin 5 years after radiation involving the thyroid or after therapeutic 131I-MIBG, with repeat ultrasound examinations every 3–5 years. Although specific recommendations on how long to continue monitoring are not defined, lifelong follow-up may be appropriate given the possibility of very late events [12].

Furthermore, our findings emphasize the value of evaluating genetic susceptibility in cases of secondary cancers. In our cohort, one patient developed breast cancer as a third malignancy and was found to carry a CHEK2 mutation. Cell cycle checkpoint kinase 2 (CHEK2) is a key component of the DNA damage response pathway and has been associated with elevated risk for several cancers, including rhabdomyosarcoma and breast cancer. The CHEK2 gene produces a protein kinase that participates in DNA damage signaling, cell cycle control, and genomic stability. Loss-of-function mutations in CHEK2 disrupt these processes, thereby heightening vulnerability to

various malignancies, including thyroid cancer. These mutations hinder the cell's capacity to sense DNA damage and arrest division, permitting cells with genetic defects to continue proliferating. This mechanism can promote tumor formation and advancement. Previous reports have linked CHEK2 mutations to a greater likelihood of thyroid cancer [23-26]. However, current evidence remains limited and does not yet justify firm surveillance guidelines [27]. One co-author (RK) encountered a case of relapsed acute lymphoblastic leukemia (ALL) in a child whose mother had been diagnosed with papillary thyroid carcinoma in adulthood; a germline CHEK2 mutation was present in both. In our series, an APC mutation was identified in a patient whose primary cancer was medulloblastoma and who later developed a malignant mesenchymal tumor as a third malignancy. The APC gene is central to the Wnt signaling pathway, which controls cell proliferation, differentiation, and adhesion. Pathogenic APC mutations disrupt this pathway, leading to nuclear accumulation of β-catenin and activation of genes that drive cell growth. In thyroid tissue, aberrant Wnt signaling triggered by APC alterations may promote uncontrolled expansion and contribute to the development of thyroid carcinomas, including papillary carcinomas [28]. Patients with familial adenomatous polyposis caused by germline APC mutations carry a markedly higher risk of papillary thyroid cancer in addition to colonic polyps. Annual thyroid ultrasound screening is advised for these individuals, although there is disagreement about the optimal age to start [7, 29]. Given the involvement of CHEK2 and APC in critical cellular processes, therapies designed to correct dysfunction in these pathways may eventually offer new options for treating secondary thyroid cancer in childhood cancer survivors [30].

In the patient with ovarian sarcoma, the unusual tumor type for her age group, combined with pulmonary air cysts and thyroid microcysts, prompted consideration of DICER1 syndrome. This rare inherited cancer predisposition disorder is linked to a broad spectrum of neoplastic and non-neoplastic abnormalities across multiple organs [31]. DICER1 is typically viewed as a tumor suppressor gene when loss-of-function mutations occur, or as an oncogene when gain-of-function mutations occur. Most tumors in DICER1 syndrome arise in individuals who inherit a germline DICER1 mutation and then acquire a second somatic missense mutation in the 5′ "hot-spot" region of the RNase IIIb domain. This dual hit activates the PI3K/AKT/mTOR signaling cascade [32]. In a large epidemiological comparison of people with DICER1-related conditions versus controls, the cumulative incidence of multinodular goiter or prior thyroidectomy by age 20 reached 32% in females and 13% in males. Carriers of DICER1 mutations face a 16- to 24-fold elevated risk of thyroid cancer [33]. DICER1 alterations may also predispose to pinealoblastoma. No genetic predisposition was identified in our pinealoblastoma patient. Guidelines developed from the International Pleuropulmonary Blastoma (PPB) Registry data advise that individuals with pathogenic DICER1 variants or DICER1-associated conditions—especially children—receive counseling about their heightened chance of thyroid nodules and cancer. Baseline thyroid ultrasonography is recommended around age 8 years, with follow-up scans every 2 to 3 years. For those who have undergone chemotherapy or radiation for other malignancies, thyroid ultrasound should be performed at diagnosis and repeated yearly for the first 5 years; thereafter, the interval can be extended to every 2 to 3 years if findings remain normal [34].

When assessing patients with thyroid cancer, beyond the genetic changes observed in our series, clinicians should also consider other hereditary syndromes that may form a familial background. These include multiple endocrine neoplasia type 2 (MEN 2) for medullary thyroid cancer and Li-Fraumeni syndrome, Cowden syndrome, Carney complex, and Werner syndrome for non-medullary thyroid cancers [35].

To enhance the long-term health outcomes and quality of life among childhood cancer survivors, upcoming investigations should prioritize several important domains. First, improving genetic screening approaches is crucial for detecting those at higher risk of secondary thyroid cancer. Focused testing for specific mutations, including DICER1, CHEK2, and APC, would enable the identification of high-risk patients and support more timely interventions along with individualized follow-up plans. Incorporating genetic analysis into standard clinical practice, together with detailed records of radiation and chemotherapy exposure, could become an essential method for forecasting cancer risk in this survivor group.

In addition, studies should investigate possible preventive measures for these vulnerable populations. This might involve creating chemoprevention options, such as medications designed to address particular genetic abnormalities or disrupted signaling routes associated with thyroid cancer. Furthermore, evaluations of the value of prompt, more rigorous monitoring protocols that could incorporate sophisticated imaging tools and molecular markers will play a vital role in advancing early identification and improving therapeutic outcomes.

Additional large-scale, multi-institutional projects are required to clarify the intricate interactions among genetic elements, various treatment approaches, and environmental influences that affect thyroid cancer development in childhood cancer survivors. Such collaborative efforts may uncover novel biomarkers for timely detection and generate stronger evidence to support customized management and prevention frameworks.

Conclusion

In summary, raising awareness about the genetic and environmental contributors to thyroid cancer risk in survivors, paired with active surveillance measures, will prove essential for meeting the healthcare requirements of this susceptible group. Concentrating efforts on these priorities can lead to meaningful advancements in the prognosis and overall quality of life for childhood cancer survivors.

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Ethics statement: The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Istanbul University, Oncology Institute (protocol code 1667287, date of approval: 6 March 2023).
Written informed consent has been obtained from the parents to publish this paper.

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