

DOI: 10.4274/tpa.46.566

## Second malignant tumors in childhood cancer survivors

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### Summary

The growing incidence of individuals surviving childhood cancer has increased the awareness of adverse long-term sequelae. One of the most unpleasant complications after cancer therapy is development of second malignant neoplasms. The risk of second malignancies is 2-3 times higher in childhood cancer survivors. The 20 year cumulative risk of secondary malignancies in 14193 childhood cancer survivors followed for >5 years was 3.2 % . In this paper, the risk factors and development of improved therapies for second malignant neoplasms in childhood cancer survivors were reviewed. (*Turk Arch Ped 2011; 46: 261-5*)

**Key words:** Childhood cancers, secondary malignancy, late effects

### Introduction

With the developments in cancer treatment very disciplined treatment approaches have achieved significant milestones in the last 30 years. Currently, survival rates in pediatric cancers have reached the levels of 70-80% (1). In some cancer forms and especially in early stage tumors, survival rates have increased further and reached a level of 90%. However, attention has been started to be intensified on early and/or especially late side effects related to treatment with the increase in survival rates (1,2). Secondary cancers are a rare, but significant late side effect of cancer treatment. The most important cause of death in cancer survivors is secondary cancers (3,4) The risk of secondary cancer in survivors of pediatric cancer is 2-3 fold higher compared to the risk of cancer development in healthy children (5).

The frequency and type of secondary cancers may vary depending on the first diagnosis, the treatment administered and genetic factors. Therefore, in follow up of survivors of pediatric cancers, it is important to know the primary tumor, the properties and cumulative doses of the chemotherapeutic drugs and the dose and area of action of radiation therapy. Hematologic secondary cancers are generally observed during the first 2-5 years after treatment especially with alkalinizing agents and topoisomerase enzyme inhibitors. Solid tumors occur in the later period.

In this article, the risk factors in development of secondary cancer in survivors of pediatric cancers and their differences by cancer type and treatment method were examined considering the properties of the patients in follow-up.

### Etiology

The frequency and type of secondary cancers is affected by the diagnosis of primary cancer, the treatment administered, the time passed after treatment and genetic factors.

In a study about pediatric cancer survival including 14193 children who received treatment between 1970 and 1986 and who survived at least more than 5 years performed by Robison et al. (6), the risk of secondary cancer for 20 years was reported to be 3.2%. The risk of secondary cancer was found to be 6 fold higher in cancer survivors compared to the normal population. The risk of development of secondary cancer at the 20th year by the first diagnosis shows variance (6) (Table 1).

When the risks of secondary cancers are examined, the risk of bone cancer is 19 fold higher, the risk of breast cancer is 16 fold higher, the risk of central nervous system cancer is 10 fold higher and the risk of thyroid cancer is 10 fold higher compared to the normal population. In addition, female gender, treatment at a young age, use of alkalinizing agents for chemotherapy, a primary diagnosis of Hodgkin lymphoma or soft tissue cancer are included in the factors which increase the risk of secondary

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*Turkish Archives of Pediatrics, published by Galenos Publishing*

cancers (6). It is known that some secondary cancers are observed more frequently in certain cancer types (7) (Table 2). This is thought to be related to the treatment administered rather than the characteristics of the primary disease.

The addition of radiotherapy (RT) to treatment increases the risk in terms of secondary cancers. The age at the time of radiation therapy, the dose of radiation and the time passed after RT are significant. The risk of breast cancer and lung cancer has been reported to be increased in Hodgkin lymphoma patients who received RT in childhood, the risk of brain tumors has been reported to be increased in leukemia patients who received cranial prophylaxis or therapy and the risk of osteosarcoma has been reported to be increased in patients with retinoblastoma in many studies (7-9).

In our country, two different studies were performed about the frequency of secondary cancer in survivors of pediatric cancer after chemotherapy by Hacettepe University Medical Faculty and

Istanbul University Oncology Institute. In the study performed by Çağlar et al. (10), secondary cancer was observed to be developed in 26 (1.7%) of 1511 children who survived for three years or longer after chemotherapy performed between 1971 and 2000 in Hacettepe University Medical Faculty. In our study, secondary cancer was found in 8 (0.6%) of 1300 children who survived for three years after chemotherapy performed between 1989 and 2005 in Istanbul University Oncology Institute, division of Pediatric Hematology-Oncology (11). In the evaluation performed in 2011, 18 secondary cancers were found in 19 patients (individual communication with Kebudi R). As the follow up time increases, increase in these rates may be observed.

### Facilitating factors

In many studies, the risk of secondary cancer is increased in Li-Fraumeni syndrome, hereditary retinoblastoma, Wilms tumor of genetic origin, neurofibromatosis (NF-1) (Von Recklinghausen), xeroderma pigmentosum, Klinefelter disease and immun deficiency syndromes (12-15). Especially in these patients, late effects of chemotherapy and radiation occur more prominently. When 58 patients with neurofibromatosis type 1 and optic glioma were evaluated, 12 secondary malign neoplasms (SMN) were found in 9 of 18 patients who received radiotherapy and 9 SMNs were found in 8 of 40 patients who did not receive RT. The relative risk of SMN was found to be 3.04 in patients who received radiotherapy and it was concluded that RT should not be used unless very necessary (15).

Secondary cancers developing as a result of genetic predisposition:

- Hereditary retinoblastoma
- Li Fraumeni syndrome
- Some genetic polymorphisms types observed in the enzymes which are responsible for metabolic activation/detoxification of anticancer drugs
  - The risk of development of t-MDS and acute myeloid leukemia (AML) increases as a result of NADPH: Quinone-oxidoreductase-NQO1 polymorphism
    - In CYP3A4-W genotype, the substances which increase DNA damage increase
    - Studies on glutathione-S transferase (GST)M1 T1 are going on (16-18).

In survivors of pediatric cancers, smoking is an external factor increasing especially the risk of Hodgkin disease and lung cancer (19). Alcohol is involved in development of mouth, esophagus and hepatic cancer (20). Wrong eating habits and hormonal factors have also been shown to be related to colon, breast, ovary, uterus and prostatic cancers. Therefore, attention should be paid to eating habits during and after treatment of children and adolescents.

### The most commonly observed secondary cancers

The most commonly observed secondary cancers in children who received cancer treatment include breast cancer,

**Table 1. Secondary cancer risk by the first diagnoses**

The first diagnosis	The risk of development of secondary cancer (%)
Hodgkin disease	7.6
Soft tissue sarcomas	4.0
Bone sarcomas	3.3
Central nervous system tumors	2.1
Neuroblastoma	1.9
Non-Hodgkin lymphoma	1.9
Leucemias	2.1
Renal tumors	1.6

**Table 2. Secondary cancer types by the primary diagnoses**

The first diagnosis	Secondary cancer type
Leukemia	Myelodysplastic syndrome (MDS), leukemia, skin cancer, meningioma, brain tumor
Brain tumor	Brain tumor, meningioma, skin cancer, MDS, leukemia
Hodgkin lymphoma	Thyroid cancer, breast cancer, lung cancer, upper gastrointestinal system cancer, sarcoma, skin cancer, colon cancer, genitourinary cancer, MDS, leukemia
Neuroblastoma	Skin cancer, sarcoma, breast cancer, thyroid cancer, MDS, leukemia
Wilm's tumor	Colon cancer, skin cancer, sarcoma, breast, thyroid, lung cancer
Sarcoma	MDS, leukemia, skin, bone cancer

bone sarcoma, thyroid cancer and treatment-related MDS and AML (21-23).

### **Breast cancer**

In children who survive cancer, the most commonly observed solid tumor is breast cancer. The frequency of breast cancer after radiotherapy has been investigated in different studies. The frequency of breast cancer was reported to be 17% in 30 years (24) in a study performed in girls who received radiotherapy with a diagnosis of Hodgkin lymphoma in childhood and 14% at the age of 40 and 20% at the age of 45 in another study (25). While there are studies reporting that the risk increases if the age at the time of radiation therapy is younger than 21 years, other studies have reported that there is no difference in terms of the risk between receiving radiotherapy before adolescence and in the adolescence period. It is generally emphasized that the risk is increased 8 years after radiotherapy, these patients are diagnosed before the age of 40 and early diagnosis has a significant effect on survival (25-28). In men who received RT to the chest area, the risk of breast cancer has not been shown to be increased.

### **Lung cancer**

In patients who received radiotherapy to the chest area during the childhood, the risk of lung cancer is higher compared to the normal population. The risk is increased with the dose of radiotherapy (29). Smoking has been reported to increase this risk (19). In patients who received RT because of pediatric Hodgkin disease, lung cancer is in the second order among secondary cancers just after breast cancer in terms of frequency. The frequency of non-asbestosis-related pleural mesothelioma increases in 20-24 years after radiotherapy.

### **Thyroid cancer**

Thyroid tissue is very sensitive to radiation. The risk of thyroid cancer which is very low during the childhood was increased in children who were exposed to radiation after Chernobyl nuclear accident in that area (30). Thyroid cancers may be observed as a result of exposure of the thyroid tissue to reflecting radiation during radiation of the head-neck region because of Hodgkin lymphoma, acute lymphoblastic leukemia and brain tumor or during radiation of the whole body (31-34). The risk is higher in children who are exposed to radiation at younger ages. In France and Great Britain, the risk of thyroid cancer was reported to be increased with dose in the ones who survived more than 3 years among 4076 children who received RT between 1942 and 1985. The risk was reported to be increased 35 fold in patients who received 0.5 Gy RT to the thyroid tissue and 73 fold in patients who received 3.6 Gy (34). In the study performed by Robison et al (6), the risk of thyroid cancer was found to be increased 18 fold in 1791 Hodgkin

disease survivors and a directly proportional dose-response relation was reported up to a dose of 20-29 Gy radiation. The frequency of thyroid cancer was found to be increased in patients who received craniospinal RT because of acute lymphoblastic leukemia (32). Secondary thyroid cancers which develop due to radiotherapy are generally of papillary type and have a good prognosis.

### **Bone tumor**

Tucker et al.(35) found the frequency of bone tumor to be 13.3 fold higher in 9170 cancer survivors compared to the general population. The cumulative risk in 20 years was reported to be 2.8+ 0.7% (35). The risk of development of bone tumors as secondary cancers is especially high for hereditary retinoblastoma, Ewing sarcoma and soft tissue sarcoma. Radiotherapy and use of alkalinizing agents increases this risk (36). This risk is reported to be increased 2,7 fold in patients who received radiotherapy (35). If the dose of radiotherapy is 60 Gy or higher, the risk is increased approximately 40 fold higher. Alkalinizing agents have been shown to increase the risk 4.4 fold depending on the cumulative dose (35).

According to the National Registry of Childhood Tumors in Britain, the cumulative risk of bone tumor in 20 years was found to be 0.9 in 13175 patients who received treatment because of pediatric cancer between 1940 and 1983 and who survived more than 3 years. These rates were found to be 7.2%, 5.4% and 2.4% for hereditary retinoblastoma, Ewing sarcoma and other malign tumors, respectively. A close directly proportional relation has been shown between secondary cancers and the cumulative radiation dose ( $p < 0.001$ ) and secondary cancers and the cumulative dose of alkalinizing agents ( $p = 0.04$ ) (36). In France and Great Britain (1942-1986), the risk of osteosarcoma was reported to be increased with radiation in 4400 patients who survived 3 years (37).

### **The risk of myelodysplastic syndrome and acute myeloid leukemia**

Alkalinizing agents and topoisomerase inhibitors (including etoposide) may increase the risk of treatment-related MDS (t-MDS) and AML. Secondary cancers related to alkalinizing agents usually develop after a period of 5-10 years. Damages to the 5th and 7th chromosomes are involved in the cytogenetic basis of the development of secondary cancers related to alkalinizing agents. 11q23 mutations are considered to be responsible for secondary cancers developing after treatment with topoisomerase II inhibitors.

Bhatia et al.(38) found that t-MDS and AML developed in 11 of 578 patients in 5 years after treatment of Ewing sarcoma family of tumors of the bone in the Child Oncology Group study conducted between 1988 and 1992 and the cumulative risk was found to be 2%. In the same study, the cumulative frequency of secondary cancers was found to be increased 16 fold according

**Table 3. The risk of secondary cancer after ESFT according to the study performed by Bhatia et al.**

Chemotherapy protocol	The drugs used	Dose (Total dose)	Cumulative frequency for 5 years (%)
Standard chemotherapy (VAdCA)	Doxorubicin Vincristine Cyclophosphamide Dactinomycine	75 mg/m <sup>2</sup> (total 375 mg/m <sup>2</sup> ) 2 mg/m <sup>2</sup> 1.2 g/m <sup>2</sup> (total 9.6 g/m <sup>2</sup> ) 1.25 mg/m <sup>2</sup>	0.4
Experimental treatment (Alternately; VAdCA/IE)	Doxorubicin Vincristine Cyclophosphamide Dactinomycine Ifosfamide Etoposide	75 mg/m <sup>2</sup> (total 375 mg/m <sup>2</sup> ) 2 mg/m <sup>2</sup> 1.2 g/m <sup>2</sup> (toplam 9.6 g/m <sup>2</sup> ) 1.25 mg/m <sup>2</sup> 90 g/m <sup>2</sup> (total 90 g/m <sup>2</sup> ) 100 mg/m <sup>2</sup>	0.9
High dose chemotherapy	Ifosfamide Cyclophosphamide Doxorubicin	(total 140 g/m <sup>2</sup> ) (total 17.6 g/m <sup>2</sup> ) (total 450 mg/m <sup>2</sup> )	11

to the total doses of chemotherapy drugs (especially alkalinizing agent including cyclophosphamide, ifosfamide) in the preferred chemotherapy protocol (Table 3) (38).

Bacci et al. (39) found the risk of development of secondary cancer to be higher in children and adolescents who received additional chemotherapy compared to the ones who received only RT in the study they performed in 597 patients who were treated for Ewing sarcoma without metastases followed up between 1972 and 1999 and who survived for long term.

### Growth hormone and secondary cancer

In a study performed by Ergun-Longmire et al. (40) in 14108 pediatric cancer survivors, 361 children had received growth hormone. Although the recurrence risk was not increased in the primary cancers in these patients, secondary cancers were found to be developed in 20 of them. The risk of development of secondary cancer in patients who received growth hormone was found to be 2.15 fold higher compared to the ones who did not receive growth hormone ( $p < 0.002$ ). Among 20 patients who developed secondary cancer, the most common tumor after growth hormone treatment was reported to be meningioma in 9 patients. It has been emphasized that as the follow up time increases, the risk of development of secondary cancer which is found to be higher in patients who received growth hormone compared to the ones who did not receive growth hormone may be decreased and long-term follow up is needed.

### Follow up in children who survive cancer treatment in terms of development of secondary cancer

Patients who receive cancer treatment should be followed up regularly because of the risk of development of secondary cancer. Secondary hematologic cancers are observed with a higher rate in the first 5 years. However, the increase in the risk

of AML continues for 10 years especially in patients who were treated with topoisomerase II inhibitors (epipodofilotoxin, anthracycline) and for 15 years in patients who were treated with alkalinizing agents. Therefore, children who survive after primary cancer treatment should be followed up in terms of the risk of development of AML by performing complete blood count and peripheral smear yearly at least for 15 years.

In addition to yearly evaluation of the skin and soft tissue performed during physical examination, patients should be checked with radiologic tests and screens as necessary against the risk of development of secondary cancers as a result of radiation.

The risk of breast cancer increases after mantle RT (mediastinum > 30 Gy), whole lung RT, spinal RT and whole body radiation. Patients should be educated about follow up by individual monthly breast examination from the puberty until the age of 25 years. Patients older than 25 years who received mantle RT and survived 8 years after RT should be followed up by clinical breast examination every 6 months and yearly mammography (41).

The risk of colorectal cancer increases in patients who receive whole body radiation and a radiation dose of 25 Gy and higher to the abdominal, pelvic and spinal regions. The increase in the risk of colorectal cancer starts after 35 years of age and 15 years after RT. During this period, all patients should be checked with colonoscopy every 10 years, double-contrast barium graphy every 5 years or occult blood test in the stool yearly and sigmoidoscopy every 5 years.

Since cirrhosis and hepatocellular carcinoma can develop as a result of chronic hepatitis, alpha-fetoprotein should be measured and ultrasonography should be performed yearly.

The risk of skin cancer (basal cell carcinoma, squamous cell carcinoma, melanoma) is increased in patients who received moderate voltage RT before 1970 for treatment of some diseases, who were exposed to additional sun beams and who were exposed to ultraviolet radiation from solarium lamps.

Cranial RT is involved in the etiology of secondary central nervous system tumors depending on the dose and age.

Conclusively, efficient protocols with less side effects should be selected considering late side effects, when planning treatment for children who are treated for cancer and these children should be followed up for a life time in terms of late side effects considering secondary cancers.

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