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Original Research

Second malignant neoplasms after childhood non-central nervous system embryonal tumours in North America: A population-based study

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Epidemiology

Abstract ***Background:*** Few studies in North America have quantified the risks of second malignant neoplasms (SMNs) among survivors of childhood non-central nervous system (non-CNS) embryonal tumours due to their rarity. We aimed to investigate these risks by combining population-based data from the United States of America and Canada.
Methods: We evaluated patients with childhood non-CNS embryonal tumours reported to the Surveillance Epidemiology and End Results program and eight Canadian cancer registries from 1969 to 2010. Standardised incidence ratio (SIR) and cumulative incidence of SMNs were calculated. Subgroup analyses were conducted by the type of first primary cancer, age at first primary diagnosis and follow-up duration.
Findings: Of the 13,107 survivors, 190 SMNs were reported over 134,548 person-years of follow-up. The SIR for all SMNs combined was 6.4 (95% confidence interval [CI]: 5.5–7.4). Most site-specific SIRs were significantly increased, ranging from 36 (95% CI: 26–49) for bone and joint cancer to 3.1 (95% CI: 1.5–5.2) for brain tumour. The risk for second malignancies declined as the time elapsed from the first primary diagnosis and was less prominent for patients first diagnosed at age 1–4 years. Notably, rhabdomyosarcoma survivors had a higher risk for SMNs than those with other first primaries. The overall cumulative incidence of SMNs was 1.0% at 10 years, increasing to 2.2% at 20 years and 4.1% at 30 years.

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Interpretation: Survivors with childhood non-CNS embryonal tumours faced an increased risk for SMNs compared to the general population. The risk variations observed in different patient categories may help target prevention strategies in high-risk subgroups.

1. Introduction

Embryonal tumours of the non-central nervous system (non-CNS) are a group of specialised paediatric tumours that form in embryonic cells and almost exclusively occur among infants and very young children. Five common types in children are neuroblastoma, nephroblastoma, retinoblastoma, hepatoblastoma and rhabdomyosarcoma (RMS). Non-CNS embryonal tumours accounted for approximately 20% of all new paediatric cancers in Canada from 2006 to 2010 and an even higher percentage among children under 5 years of age [1]. Neuroblastoma is the most commonly diagnosed cancer during the first year of life [2]. Nephroblastoma (Wilms tumour) comprises 92% of the kidney tumours diagnosed before age 5 years, whereas hepatoblastoma is the most commonly diagnosed liver cancer of childhood [2]. Retinoblastoma and RMS each account for about 3–5% of cancer cases among children aged 0–15 years in North America [3,4].

In the United States of America (USA) and Canada, the Children's Oncology Group (COG) protocol for Wilms tumour treatment favours immediate nephrectomy and subsequent radiotherapy and chemotherapy based on postsurgical pathological findings [5]. The treatment strategy for RMS and neuroblastoma is guided by COG risk stratification systems developed from clinical and tumour biological factors [6,7]. A major component of the treatment for this group of tumours is the use of anthracycline, seen in 35–40% of Wilms tumour patients and most RMS and neuroblastoma patients. A study of the Surveillance, Epidemiology and End Results (SEER) database showed the use of radiotherapy for paediatric Wilms tumour, neuroblastoma and retinoblastoma decreased from 73%, 60% and 30% in 1973–1976 to 53%, 25% and 2%, respectively, in 2005–2008 [8]. As a result of diagnostic advance and risk-adapted therapy, recent estimates of 5-year survival rates for non-CNS embryonal tumours are reported to be between 49% and 77% for RMS and 92–99% for retinoblastoma [1,4]. The prolonged survival coincides with the increased risk for second malignant neoplasms (SMNs), one of the most severe late effects of cancer treatment [9–11]. One of the largest studies of Wilms tumour shows over five times the population risk for SMNs in the survivors diagnosed before 15 years of age [12]. The cumulative risk of SMNs following retinoblastoma is reported to be as high as 47% at 50 years after the initial diagnosis [13].

Previous reports only explored the occurrence of SMNs after the most common types of childhood non-CNS embryonal tumours, such as neuroblastoma, Wilms tumour and retinoblastoma [12,14,15]. The overall risk of SMNs in these survivors has not been examined. Evidence is also lacking that quantifies the cumulative risk of SMNs, and how this varies over time and differs between the five tumour types. In Canada, little data has been reported on SMNs among childhood cancer survivors with few studies focussing on local cancer registries [11,16]. Therefore, we investigated the relative and absolute risks of SMNs in these survivors, and to maximise the study power, we combined population-based registry data from the USA and Canada.

2. Patients and methods

We identified children with a primary non-CNS embryonal tumour using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) site codes: 8960/8959 for nephroblastoma, 9500 for neuroblastoma, 8970 for hepatoblastoma, 9510/9513 for retinoblastoma and 8900/8901/8910/8920/8991 for RMS [17]. We obtained data on primary non-CNS embryonal tumours occurring among children under 15 years old from the SEER program in the USA and eight provincial cancer registries in Canada including: Alberta, Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia, Ontario, Quebec and Saskatchewan. The participating registries contributed data on age at diagnosis, sex, diagnosis of the first primary cancer and date and diagnosis of the SMN, if any, for different time periods in the years 1969–2010 as defined by each cancer registry (Table 1). Follow-up started at the first primary cancer diagnosis and ended at the date of SMN diagnosis, death, loss to follow-up or end date of available data per registry (whichever came first). Those who were followed for at least 2 months were eligible for the analysis. A second cancer qualified as SMN if it originated in a new primary site or tissue and was not an extension, a recurrence or a metastasis of the primary cancer. SMNs were coded using the site and histology coding rules proposed by the SEER [18]. Third and subsequent malignancies were not considered in this