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WUQING HUANG is a medical graduate from China. She completed her medical degree at China Medical University in 2015 and received a Master degree in Public health from Sun Yat-Sen University in 2018. Her research interests are cancer epidemiology and pharmaco-epidemiology. The main focus of this doctoral thesis was to investigate the potential impacts of central nervous system tumor diagnosed in early life on their children, including children's birth outcomes, physical and mental health, and academic performance.

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DOCTORAL DISSERTATION

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Abstract

Background: An increasing number of patients with central nervous system (CNS) tumor could survive to reproductive age and successfully have children, especially patients diagnosed at a younger age. However, it is largely unknown whether the history of CNS tumor and its treatments might affect their children. We aimed to explore the health status and school performance in offspring of survivors with CNS tumor before age of 20, including preterm birth, somatic and psychiatric diseases, and academic performance.

Methods: By linking several nationwide registers in Sweden, we identified children whose parents were previously diagnosed with CNS tumor in childhood or adolescence. Children, whose parents did not have CNS tumor, were matched randomly with a 5:1 ratio to generate the reference group. Outcomes included preterm birth, overall somatic diseases, mental disorders and final grade achieved after completing the compulsory years of education at age of 16. Odds ratio (OR), relative risk (RR), absolute excess risk (AER) or hazard ratio (HR) was calculated in this project.

Results: In Paper I, a total of 95 children among 1369 offspring of CNS tumor survivors were born preterm. As compared with 6845 comparison children, children of survivors were at an increased likelihood to be born preterm (adjusted OR=1.29, 95%CI=1.01-1.65). In Paper II and Paper III, after removing children dying within three months after birth, 1364 children born from survivors were included to estimate the risk of somatic or mental diseases. These children were not associated with a higher risk of overall somatic diseases (RR=1.02, 95% CI=0.98-1.07) or psychiatric diseases (adjusted HR=1.10, 95%CI=0.94, 1.28). In Paper IV, among these children of CNS tumor survivors, 655 children had the record of final grade which was used to measure academic performance. They experienced 1.39 times higher risk of achieving a poor academic performance as compared to the reference (95%CI=1.10-1.76).

Conclusions: Offspring of survivors with CNS tumor below age of 20 were at an increased risk of being born preterm and getting poor academic achievement. However, overall physical or mental health was comparable between these children and the general population.

Key words: central nervous system tumor, offspring, preterm birth, somatic diseases, psychiatric disorders, academic performance

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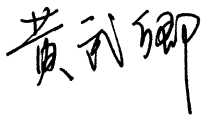
Signature  Date 2021-04-12

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“There is only one heroism in the world: to see the world as it is, and to love it.”

Romain Rolland

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List of papers included in the thesis

This thesis is based on the following four articles that are appended at the end of this thesis. Reprinted with permission from respective publishers.

Paper I

Huang W, Sundquist K, Sundquist J, Crump C, Ji J. Risk of being born preterm in offspring of survivors with childhood or adolescent central nervous system tumor in Sweden. International Journal of Cancer. 2020; 147(1):100-106.

Paper II

Huang W, Sundquist K, Sundquist J, Ji J. Risk of somatic diseases in offspring of survivors with childhood or adolescent central nervous system tumor in Sweden. International Journal of Cancer. 2021; 148(9):2184-2192.

Paper III

Huang W, Sundquist K, Sundquist J, Ji J. Psychiatric disorders in offspring of childhood or adolescent central nervous system tumor survivors: a national cohort study. Cancer Medicine. 2021; 10(2):675-683.

Paper IV

Huang W, Sundquist K, Sundquist J, Ji J. Poor academic performance in offspring of survivors with childhood or adolescent central nervous system tumor in Sweden. International Journal of Cancer. 2020; 147(10):2687-2694.

List of papers not included in thesis

1. **Huang W**, Sundquist J, Sundquist K, Ji J. Use of Phosphodiesterase 5 Inhibitors Is Associated With Lower Risk of Colorectal Cancer in Men With Benign Colorectal Neoplasms. Gastroenterology 2019;157:672-681.e4.

2. **Huang W**, Sundquist J, Sundquist K, Ji J. Phosphodiesterase-5 inhibitors use and risk for mortality and metastases among male patients with colorectal cancer. Nat Commun 2020;11:3191.

3. **Huang W**, Sundquist J, Sundquist K, Ji J. Mortality patterns in long-term survivors of childhood or adolescent central nervous system tumour in Sweden. J Neurooncol 2019;145:541-549.

4. **Huang W**, Sundquist K, Sundquist J, Ji J. Risk of Being Born Preterm in Offspring of Cancer Survivors: A National Cohort Study. Front Oncol 2020;10:1352.

5. Hemminki K*, **Huang W*,** Sundquist J, Sundquist K, Ji J. Autoimmune diseases and hematological malignancies: Exploring the underlying mechanisms from epidemiological evidence. Semin Cancer Biol 2020;64:114-121.

6. Ji J*, **Huang W*,** Sundquist J, Sundquist K. Hospitalization rate in offspring of cancer survivors: a national cohort study. J Cancer Surviv 2019;13:187-196.

7. Zöller B, Svensson PJ, **Huang W**, Ji J. Reactome Pathway Analysis of Venous Thromboembolism, Peripheral Artery Disease, Stroke, and Coronary Artery Disease. Thromb Haemost 2020. doi: 10.1055/a-1315-2307.

List of abbreviations

AER	Absolute excess risk
BMI	Body mass index
CI	Confidence interval
CNS	Central nervous system
HR	Hazard ratio
ICD	International classification of disease
OR	Odds ratio
RR	Relative risk

Introduction

Central nervous system tumor

Central nervous system (CNS) tumors are a group of highly heterogeneous neoplasms, caused by abnormal growth of various types of cells in brain or spinal cord [1].

Epidemiology

CNS tumor is the second most frequently-diagnosed tumor and the most common solid tumor in population under the age of 20 [2,3]. Tumors in CNS account for 11% of new cancer cases and 16% cancer-caused deaths in the younger population worldwide, with an estimated age-standardized incidence and mortality rates of 1.20 and 0.66 per 100 000 person-years in 2018, respectively [3,4]. The incidence varies by sex with a slightly higher rate in boys than in girls, as well as differs by areas with the highest rates in Europe, North America, and Australia [3,4]. Prevalence is largely different across subtypes of tumor. The most common subtypes in children and adolescents consist of pilocytic astrocytomas, malignant gliomas and medulloblastomas [5]. Multiple factors have been involved in mortality, mainly including histology, age at diagnosis, treatments, etc [6]. For instance, the five-year survival rate is more than 90% for pilocytic astrocytoma while the rate is less than 10% for glioblastoma [5]. Generally, the survival rate for most histological types decreases with age at tumor diagnosis [5].

As one of the countries with the highest incidence rate of CNS tumor, the rate in Sweden is continuously rising for decades while the mortality rate has slightly decreased (**Figure 1**) [7]. Thanks to the remarkable progress in treatments, the overall five-year age-standardized survival rate of CNS tumor in Sweden has been improved from 31% in the 1960s to 61% in the 2010s in male patients and from 40% to 75% in female patients [7]. For children and adolescent CNS tumors, the survival rate is even over 80% in 2010s [7].

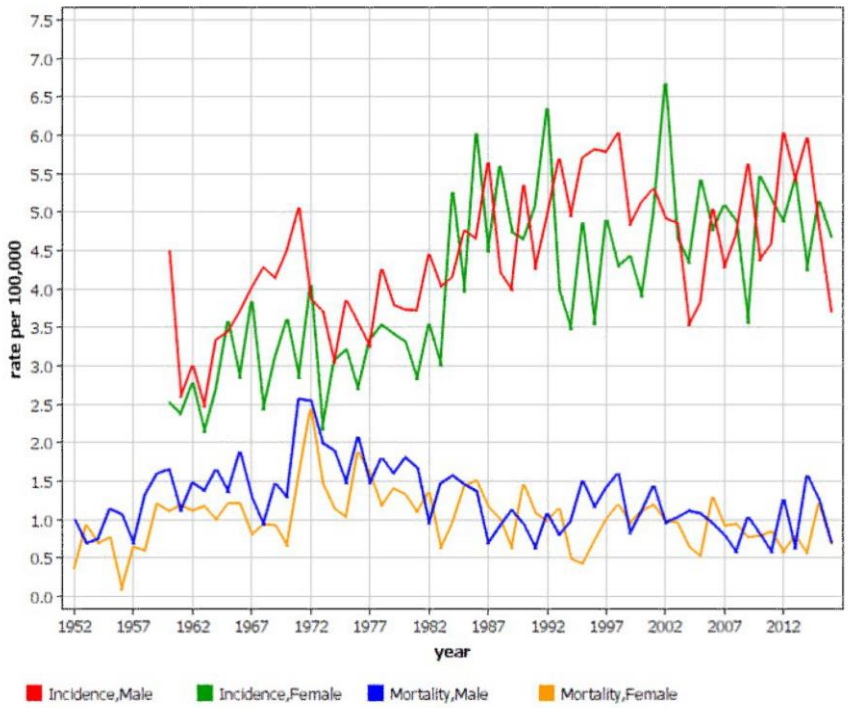

Figure 1:
Trend of incidence and mortality age-standardized rates of central nervous system tumor among Swedish population below age of 20 years. Data source: NORDCAN © 2019 Association of the Nordic Cancer Registries.

Risk factors

It is still largely unclear in terms of the causes of developing CNS tumor while a variety of factors have been linked to the pathogenesis.

Genetic factors

Genetic causes have been extensively studied but generating mixed results [6,8-10]. Predisposition syndrome is a well-known genetic risk factor [10]. However, genetic predispositions (i.e. neurofibromatosis type 1 or 2) just contribute to around 5% of cases with CNS tumor [10,11]. Familial aggregation has been observed in multiple types of malignancies, including nervous system tumor [12,13]. Family history of CNS tumor is suggested to be a potential risk factor [12,14,15]. While a review including 16 studies (10 cohorts and six case-control designs) found limited evidence for the positive association between family history and CNS tumor risk [15].

Parental factors

Evidence is emerging regarding the role of parental factors on tumor susceptibility, which may be connected via oocyte/sperm-mediated transgenerational inheritance or uterine environment [16-22]. For example, parental age at childbirth might be related to CNS tumor risk as a result of heritable variations in aging germlines [8,21,23,24]. Parental exposures to some medications, such as antihypertensive drugs, antibiotics, nitrosatable drugs and so on, were reported to have the potential to increase the risk of several tumors, including CNS tumor [8,25-28]. Furthermore, studies on some other parental-related factors are ongoing, such as parental exposures to some specific compounds (e.g. pesticide, petrochemicals, polycyclic aromatic hydrocarbons, and N-nitroso compounds), smoking, alcohol, and maternal nutrition [8,29-35].

Self-exposures

Radiation exposure has been recognized for decades as a risk factor for tumor in CNS, in which ionizing radiation is an established risk factor with dose-dependent pattern [8,36-41]. Current research has also linked infectious exposure in early life to CNS tumor risk, the strength of which differed by age of tumor diagnosis and type of tumor [8,42-46].

Physical conditions

Individual physical conditions were suggested to associate with the risk of CNS tumor. Similar with most neoplasms, the risk of CNS tumor also increases with age [5]. Some illness may be related to a higher risk of CNS tumor, such as congenital anomalies, birth defects, and autoimmune diseases (e.g. allergies, asthma, and eczema) [8,47-52].

Diagnosis and treatments

With the growth of tumor in CNS, some general symptoms appear due to the increased intracranial pressure, such as headache, seizures, nausea, vomiting, et al [6,53]. Besides, there are different symptoms corresponding to tumors in different sites, such as speech problems caused by tumor in cerebrum, trouble walking caused by cerebellum tumor, hearing loss caused by cranial nerve tumor, weakness or numbness caused by spinal cord tumor, and so on [6,53]. Imaging is usually used for the diagnosis of CNS tumor, which can be obtained through computed tomography or magnetic resonance imaging [54]. Computed tomography is always adopted as the first choice because of its availability and speediness [54]. Surgery is sometimes used to get a biopsy sample in order to confirm the histologic type of tumor [54]. Treatment for CNS tumor is highly dependent on the histology and location. Neurosurgery is always considered as the first step to remove the tumor; radiation therapy would be used for further treatment if there are remaining parts of tumor after surgical removal or surgery is not allowed in some cases; chemotherapy is often used

together with neurosurgery and/or radiation therapy for patients with faster-growing tumors (e.g. medulloblastomas) [6,53].

Prognosis and late effects

The prognosis of survivors with CNS tumor depends largely on tumor location, histology, treatment, and age at diagnosis [5]. In general, substantial improvement in tumor treatments has led to a significantly increase in overall survival time [3,4]. Thus more concerns are rising over long-term adverse effects from tumor or its treatments as the number of survivors with a history of CNS tumor is growing. In particular, majority of patients who were diagnosed at childhood or adolescence would become long-term survivors. Treatments for tumor always come with a series of acute side effects, such as nausea, vomiting, weight and hair loss, while most of which only last for months or several years after treatments [55]. However, late effects, which are common in these survivors as well, could happen insidiously and then last for decades, even for a lifetime [55]. At least one late effect is reported in three out of five survivors with childhood cancer, and about one-third of late effects are severe or even life-threatening [55]. In Childhood Cancer Survivor Study, survivors with CNS tumor were at 12.4 times higher risk of experiencing more than one chronic medical condition as compared to their siblings [56]. Multiple functions might be impaired by late effects in CNS tumor survivors, including reproductive, physical, mental, and neurocognitive functions [55].

Reproductive functions

With more and more survivors surviving to reproductive age, more attentions have been paid to the potential influence on reproductive system from tumor treatments [55,57,58]. Reproductive function in survivors of CNS tumor may be affected directly via gonadal damage caused by radiotherapy or chemotherapy [55,57-62]. Impairments of the hypothalamic/pituitary axis or the endocrine organs due to the tumor itself and its treatments could indirectly result in adverse reproductive outcomes through endocrine complications [55,57,58]. For female survivors, neurosurgery may cause sexual dysfunction; cranial or spinal radiation and chemotherapy have been linked to damage in a series of reproductive functions with a dose-response toxicity, such as hypogonadism, acute ovarian failure, uterine vascular insufficiency, et al [57,60]. For males, neurosurgery might be involved in damage of hypothalamic-pituitary axis; radiation in the cranial-neuroendocrine axis and some chemotherapeutic agents may lead to hypoandrogenism, oligospermia or azoospermia, and reduced fertility [58,59,62].

Physical functions

Increased survival rates of CNS tumor have also expanded the focus of research to evaluate the chronic physical health of these survivors in later life. As reported in the Childhood Cancer Survivor Study, there were over 80% of five-year survivors

with childhood CNS tumor suffering one or more chronic illness condition [63]. Any kind of therapy for tumor was significantly associated with an increased likelihood of chronic health conditions, with relative risks ranging from 3 to 14 when compared with their siblings [56]. These survivors have a higher incidence of various late morbidities, including endocrine diseases, sensory disorders, neurological diseases, cerebrovascular and cardiovascular diseases [55,63,64]. Furthermore, secondary malignancy is a devastating late effect, which remains the leading cause of death in survivors within 10 years following diagnosis [65]. The top three common occurring secondary malignancies in these survivors are CNS tumor, thyroid carcinoma, and soft tissue sarcomas [66].

Mental functions

Numerous studies have assessed the mental health of survivors with cancer in early life, but the results were inconsistent and varied by types of cancer [63,67,68]. A Danish cohort with 3710 childhood or adolescent cancer survivors found that survivors with CNS tumor experienced an excess risk of hospitalization due to psychiatric diseases [67]. Besides, survivors with CNS tumor may have few social networks and lower life satisfaction [68-70].

Neurocognitive functions

Neurocognitive damage occurs more frequently in CNS tumor survivors than survivors with other types of cancer [55]. A younger age at diagnosis of tumor in CNS may result in a higher risk to experience neurocognitive late effects as the brain and neuro-axis are developing and being vulnerable for tumor treatments [55]. The side effects of radiotherapy on neurocognitive functioning have been extensively studied; younger age at radiation, increased dose, increased field, and increased time from treatment are all related to an elevated likelihood of neurocognitive damage [55,71]. Neurosurgery and chemotherapy also play a role in neurocognitive decline but with less clear evidence. The impairments vary from mild impact in academic performance to severe intellectual disability [55,71]. It is widely observed that survivors with CNS tumor at a younger age have poor school performance, decreased academic attainment, and higher probability of unemployment [63,72-76]. A meta-analysis with 22 studies reported that survivors with paediatric brain tumour got the score on full-scale IQ below average, and cranial radiation/chemotherapy resulted in worse neurocognitive consequences [77].

Offspring of survivors with central nervous system tumor

Epidemiology

Improved prognosis for childhood or adolescent cancer has led to an increased number of cancer survivors who are able to have their own children. In Sweden, the number of children born from a mother or father who was ever previously diagnosed with cancer has continuously increased since the 1970s (**Figure 2**). The trend is similar for children born from survivors diagnosed with CNS tumor younger than 20 years old (**Figure 2**). Thus, in recent decades, emerging studies have been performed to investigate the impact of cancer and its treatments on their offspring, which could be summarized into the following categories of the outcomes in offspring: birth outcomes, physical and mental health, and academic performance. Despite substantial heterogeneity across different types of cancer, few studies have explored the details on the specific type of cancer due to the limited number of cases, such as CNS tumor.

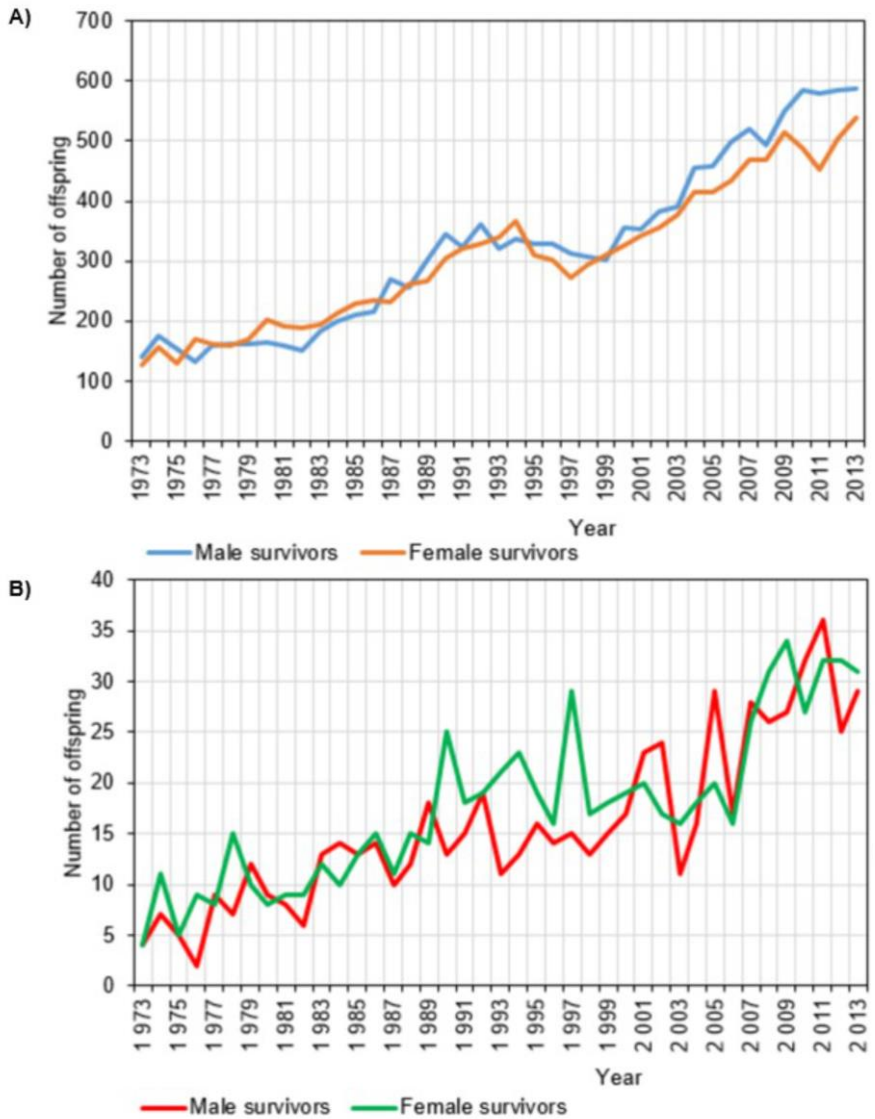

Figure 2:
Trend of numbers of offspring of cancer survivors in Sweden. A) Overall cancer survivors; B) Childhood or adolescent survivors with central nervous system tumor.

Birth outcomes

The potential adverse birth outcomes in the offspring of cancer survivors have been investigated for years, which varied by sex of survivors and type of cancer [78]. Available studies observed a higher risk of various adverse birth outcomes in offspring of female cancer survivors (e.g. stillbirth, low birth weight, and preterm birth), while studies for offspring of male survivors were relatively limited [79,80]. Data from the Swedish population showed a significantly lower probability to have a first live birth in both female and male survivors with childhood or adolescent cancer [81]. Further stratified analyses by cancer subtypes observed the inverse association in survivors with leukemia or CNS tumor [81]. In Nordic countries, the increased incidence of preterm birth and low birth weight was found in children of female cancer survivors, especially in the offspring of female survivors with CNS or genital tumor, but not in children of male survivors [82].

Preterm birth is a leading global public health issue, which is strongly related to neonatal death and premature death in children younger than five years old [83]. There are many factors associated with preterm birth, such as maternal age, parental physical and mental conditions, parities, and so on [83-85]. The role of parental physical conditions has been widely explored in the risk of having a preterm-born infant, including the parental history of cancer [83,86]. For female cancer survivors, damage in the ovary or uterus can potentially lead to preterm birth directly or indirectly, while for male survivors, treatment-caused genetic or epigenetic alterations in sperm may result in preterm birth of their spouses indirectly [85,87]. In addition, late effects in cancer survivors concerning physical and mental disorders might subsequently cause preterm birth [85,87,88]. Although numerous studies have investigated the influence of cancer and its treatments on birth outcomes, few studies have focused on CNS tumor.

Physical health

Disease susceptibility in offspring has been recently linked to not only parental genetic variants but also epigenetic inheritance, which are possible to be altered when parents were exposed to chemicals, radiation, or some other environmental factors [17-19,21,22]. Furthermore, as mentioned above, cancer and its treatments might lead to adverse birth outcomes, which were probably related to increased risk of multiple long-term morbidities in offspring [84,89-91]. Most survivors with CNS tumor in early life had undergone radiation or chemotherapy, but it is still unclear whether it will affect the physical health of their offspring. A Danish register-based cohort study has explored the relationship between a history of childhood or adolescent cancer and risk of hospitalization in their offspring but lack details for the specific type of cancer [92]. Substantial heterogeneity across cancer types calls for further studies for the offspring of survivors with specific cancer.

Mental health

The mental health of children with one parent diagnosed with cancer has been extensively assessed during the period when their parents were receiving treatment [93,94]. An increased incidence of psychiatric disorders was reported in these children for different reasons, including decreasing physical and emotional access from their parents, household roles shifting, daily routines changing, etc [93,94]. Nevertheless, few studies were conducted to assess the psychiatric health in offspring born after parental diagnosis with cancer, such as children of survivors with childhood or adolescence cancer. These children may experience less emotional disturbance mentioned above because their parents had been cured and survived for years when they were born. However, as mentioned before, survivors with CNS tumor in early life are more likely to experience psychiatric and neurologic problems, which may persist into adulthood [63,66,71,95-98]. Parental mental condition is known to be one of the strongest predictors of the mental health of their children [99-102]. Furthermore, existing data indicated that stress exposure in parents might cause a predisposition to mental disorders in offspring via epigenetic alterations in gametes and changes in gestational uterine environment [20,103-105]. Besides, adverse birth outcomes may also be mediators between parental tumor and psychiatric disorders [106,107]. It is thus imperative to assess the mental health of children of survivors with CNS tumor.

Academic performance

Academic performance depends on complex factors, such as cognitive function, physical and mental health, socio-economic status, etc [108-110]. Parents have also been reported to play an important role in the academic performance of their children [111-119]. Parental physical and mental conditions exert a significance on the level of parental education, parental monitoring on children, parent-children communication, even physical and psychological functioning of their children, all of which are likely related to children's school performance [111-119]. In particular, CNS tumor diagnosis in early life was independently associated with a higher incidence of late-on adverse neurologic sequelae, which potentially affect children's academic achievements subsequently [63,66,95-97,120]. Thus children's academic achievement might be affected by parental diagnosis of CNS tumor, which unfortunately has still not been studied.

Aims

The overall aim of this thesis was to explore the health status and academic performance in offspring of survivors who were diagnosed with CNS tumor below the age of 20.

The specific aims of each study were as follows:

Paper I: To explore the likelihood of being born preterm among the offspring of survivors with CNS tumor diagnosed below the age of 20.

Paper II: To assess the physical health among offspring of survivors with CNS tumor diagnosed below the age of 20.

1) To investigate the cumulative incidence rate of overall somatic diseases among offspring of these survivors
2) To investigate the risk of a specific type of somatic diseases among offspring of these survivors

Paper III: To assess the mental health among offspring of survivors with CNS tumor diagnosed below the age of 20.

1) To investigate the risk of any psychiatric disorder among offspring of these survivors
2) To investigate the risk of a specific type of psychiatric disorders among offspring of these survivors

Paper IV: To evaluate the academic performance among offspring of survivors with CNS tumor diagnosed below the age of 20.

Methods

Study population

Projects in this thesis were based on data from several Swedish nationwide registers, details of which were described in **Table 1**. By retrieving from Swedish Medical Birth Register, all singleton live births were identified (1973-2014). Parents of each child were further identified by linking these children to Swedish Multi-generation Register. History of parental CNS tumor was obtained by further linking to Swedish Cancer Registry. Matched cohort study design was used across four projects in the thesis. We selected all children with one parent who was previously diagnosed with tumor in CNS under the age of 20 and had survived for at least five years after the tumor diagnosis, as the study group. We excluded those children born within one year after the date when their parents had a diagnosis of CNS tumor. Five children, whose parents were not ever diagnosed with CNS tumor, were randomly selected as the reference group by matching with each child in the study group, conditional on year of childbirth (continuous), sex of child, maternal and paternal age at childbirth (continuous), plus region at birth in Paper I, or maternal and paternal highest education in Paper IV.

Table 1: Summary of the Swedish registers used in the proposed project**.**

Register	Period	Brief description
Swedish Cancer Register	1958-2015	Data with approximately 100% histological verification of cancers in Sweden, including site of tumor, histological type, stage, and date of diagnosis.
Medical Birth Register	1973-2014	Data on practically all deliveries in Sweden, including information from prenatal care, delivery care and neonatal care.
Multi-Generation Register	1932-2014	Data on index persons and their first-degree relatives (e.g. parents and siblings), including all individuals who had a residence permit in Sweden from 1961 and onwards and who were born from 1932 onwards (index persons).
National Patient Register	1964-2015	Data on somatic and psychiatric diseases diagnoses, created in 1964, including completed data of inpatient hospitalizations since 1987 and completed data of specialized outpatient care since 2001.
Cause of Death Register	1961-2015	Data on all deaths that have occurred in Sweden, including date and causes of death.
Swedish Ninth Grade Register	1989-2015	Data on the final grade achieved after completing the compulsory years of education at age of 16 in Sweden, including data from all regular schools receiving the uniform school curriculum and evaluation criteria for academic performance.
Total Population Register	1968-2015	Data on socioeconomic information of the Swedish population and its changes, including birth year, sex, marital status, mobility, income, education, employment, occupation, country of birth, urban/rural status, et al.

In Paper I, a total of 1369 children were identified with one parent with a history of CNS tumor under the age of 20, and 6845 children were selected as matched comparisons. After excluding children who died within three months after birth, there were 1364 children and 6820 comparison children included in Paper II and Paper III. Children, who were born after 1999, did not get the final grade by the end of 2015, thus 655 children who were born from 1973 to 1999 had the record of the final grade, and 3275 matched comparisons included in Paper IV. Flowchart is shown in **Figure 3**.

A unique individual national identification number (ID number) was assigned to each resident upon birth in Sweden. We replaced these numbers with serial numbers to provide anonymity, which were used to link several registers for projects included in this thesis.

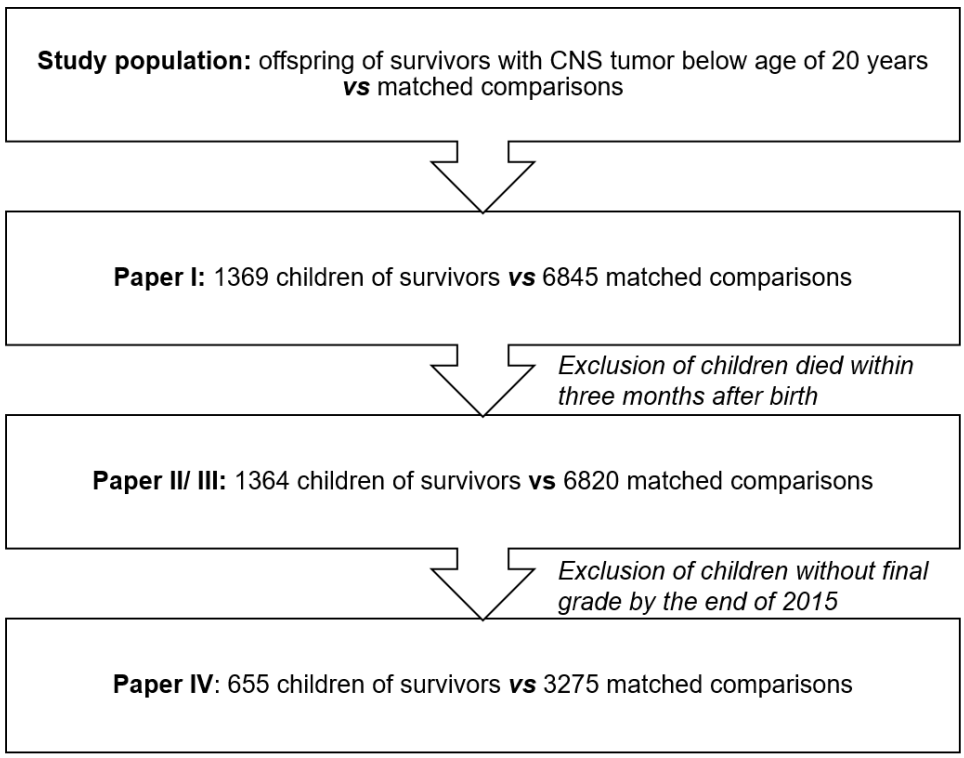

Figure 3:
Flowchart of study population.

Ethical statements

The Ethics Committee at Lund University approved (February 6, 2013) all projects included in this thesis (Dnr 2012/795). Written informed consent was not needed in register-based studies because all individual identification information had been removed to preserve anonymity.

Assessment of exposure

Information concerning maternal or paternal diagnosis of CNS tumor was obtained from Swedish Cancer Registry using the International Classification of Disease code (ICD-7 code: 193). The date of diagnosis and histologic type of tumor could be retrieved from this register. Children of CNS tumor survivors were classified by parental age at tumor diagnosis, in which survivors who were diagnosed below the age of 15 were defined as childhood survivors (0-14 years old), and those diagnosed between 15 and 19 were defined as adolescent survivors (15-19 years old). Children of survivors were also divided by the calendar year at parental tumor diagnosis (<1990 or ≥1990). Parental CNS tumor were classified into the following types based on histology: astrocytoma, ependymoma, hemangioma, meningioma, medulloblastoma, neurinoma, and others (including other less common types and unknown types).

Assessment of outcomes

Being born preterm

In Paper I, the outcome was being born preterm, defined as a live birth with less than 37 weeks of gestation. We collected gestational age at birth from Swedish Medical Birth Registry, in which maternal report of last menstrual period was used to calculate the pregnancy term in the 1970s while ultrasound estimation was used to measure it in the 1980s and later.

Somatic disease

In Paper II, diagnosis of somatic diseases was obtained from National Patient Register. ICD was used for coding in National Patient Register, in which ICD-7 code was used from the beginning of the register, ICD-8 available from 1969, ICD-9 available from 1987, and ICD-10 available since 1997. Each record in the register

contains date at admission, a primary diagnosis, and other secondary diagnoses. We kept the primary diagnosis in the analyses, which was the main reason for a patient to visit a doctor. The diagnoses of somatic diseases were classified into 12 main types as follows: (1) infectious and parasitic disease; (2) malignant neoplasms; (3) benign neoplasms; (4) disease of the blood or blood-forming organs; (5) endocrine, nutritional or metabolic diseases; (6) diseases of the nervous system or sense organ; (7) diseases of the circulatory system; (8) diseases of the respiratory system; (9) diseases of the digestive system; (10) diseases of the skin or subcutaneous tissue; (11) diseases of the musculoskeletal system or connective tissue; (12) diseases of the genitourinary system. Only the first record was kept if there was more than one record for one specific type for each individual.

The primary outcome was number of somatic diseases diagnosed during the study period, which was calculated across the 12 main types. The secondary outcome was a specific type of somatic diseases.

Psychiatric disorder

In Paper III, the outcome was psychiatric disorder, which was also collected from National Patient Register using ICD codes. The diagnoses of psychiatric disorder were categorized into 10 main subtypes as follows: (1) Organic, including symptomatic, mental disorders; (2) mental or behavioral disorders due to psychoactive substance use; (3) schizophrenia, schizotypal or delusional disorders; (4) mood disorders; (5) neurotic, stress-related or somatoform disorders; (6) behavioral syndromes associated with psychological disturbances and physical factors; (7) disorders of adult personality and behavior; (8) mental retardation; (9) disorders of psychological development; (10) behavioral or emotional disorders with onset occurring in childhood and adolescence. Mental retardation was further classified into mild type and others (including moderate, severe, profound and other types).

Academic performance

In Paper IV, the outcome was academic performance, which was recorded in Swedish Ninth Grade Register. It was measured by the final grade, obtained after completing compulsory education at the age of 16 in regular schools. Students in Swedish regular schools would receive a uniform school curriculum and uniform evaluation criteria for school performance. There were two grading systems used for academic performance measurement during the study period. The former one was used for children who had achieved their final grade before 1998 (i.e. children who were born from 1973 to 1982) with the mean score ranging from 1 to 5; the latter one was available since 1998 (i.e. children who were born from 1982 to 1999) with the mean score ranging from 80 to 320. To ensure the comparability between

the two grading systems, the year-standardized z-scores were thus calculated according to the original grades and then used for further analyses. In logistic regression model, "poor academic performance" was defined as below the 10th percentile of z-scores among the study population. The Z-score was also modeled as a continuous variable in quantile regressions by using each decile from the first decile to the ninth decile.

Assessment of covariates

Birth year and sex of offspring were obtained from Swedish Medical Birth Register. Region at birth was also collected from Swedish Medical Birth Register and categorized as big cities, south Sweden and north Sweden. Parental age at childbirth was retrieved by linking Swedish Medical Birth Register, Swedish Multi-generation Register, and Total Population Register. Parental highest education was modeled as 1-9 years (i.e. compulsory high school or less), 10-11 years (i.e. practical high school/some theoretical high school), and ≥12 years (i.e. some theoretical high school/college/post-graduate study). In Paper I, data on maternal body mass index (BMI), history of smoking, parity, and gestational complications were obtained from Swedish Medical Birth Register. Maternal BMI was assessed at the beginning of prenatal care, modelled as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obesity (≥30.0 kg/m^2). Maternal smoking was assessed at the beginning of prenatal care as well, modelled as non-smokers, smokers with 1-9 cigarettes per day, and smokers with ≥10 cigarettes per day. Parity was modelled as 1, 2, or ≥3. Pre-eclampsia, eclampsia, or other hypertensive disorders diagnosed during pregnancy was defined as gestational hypertensive disorders. In Paper III, information of maternal and paternal diagnosis with psychiatric disorders was obtained from National Patient Register.

Statistical analyses

Chi-squared test was used to compare the balance of general characteristics between children of CNS tumor survivors and their matched comparisons. In Paper I, conditional logistic regression was used to assess the odds ratio (OR) with 95% confidence interval (CI) to investigate the association of parental diagnosis of CNS tumor at childhood or adolescence with the risk of being born preterm in their children. Besides, a co-sibling design was conducted in families which had at least two children after parental tumor diagnosis by comparing the incidence of being born preterm between first-born children and their siblings born later.

In Paper II, we calculated relative risk (RR) and absolute excess risk (AER) to evaluate the association of parental CNS tumor and the risk of overall somatic diseases, in which the follow-up started at the date of childbirth and ended at the date of death, the date of emigration or the end of the study (i.e. December 31, 2015), whichever came first. The cumulative incidence rate of overall somatic diseases was defined as the number of overall somatic diseases divided by the sum of person-years of follow-up. The RR was calculated as the ratio of the cumulative incidence rate between children of survivors with CNS tumor and the matched comparisons. The AER was assessed as the difference in the cumulative incidence rate between children of survivors and the matched children. The 95% CIs of RR and AER were calculated by using the method created by Armitage and Berry [121]. Furthermore, Cox proportional hazard model was used to investigate the association of parental tumor with risk of a specific type of somatic diseases, in which the follow-up for the specific disease of interest started at the date of childbirth and ended at the date of the first diagnosis for the disease of interest, date of death, date of emigration or the end of the study (i.e. December 31, 2015), whichever came first.

In Paper III, Cox proportional hazard model was used to evaluate the hazard ratio (HR) with 95%CI, in which the follow-up began at the date of birth and ended at the date of first diagnosis of any psychiatric disease, the date of emigration, the date of death or the end of study (i.e. December 31, 2015), whichever came first. Further analyses were performed regarding the specific psychiatric disorders, in which follow-up started at the date of childbirth and ended at the date of first diagnosis of the specific psychiatric disorder, the date of emigration, the date of death or the end of study (i.e. 31 December 2015), whichever came first.

In Paper IV, conditional logistic regression was applied to explore the association of parental CNS tumor with the risk of poor academic performance in their children, in which academic performance was modelled as a binary variable (poor academic performance or not). Taking into account the skewness of z-scores for academic performance, it was also modelled as a continuous variable by using quantile regression. Quantile regression is a distribution-free method, which allowed us to investigate whether the association of parental tumor and academic performance remained stable across the whole distribution of z-scores (i.e. to evaluate whether the effects of parental tumor on the risk of getting good or poor academic performance was different).

Stratified analyses were further performed in all projects based on several important factors, such as paternal or maternal tumor, the sex of offspring, parental age at diagnosis (0-14 or 15-19 years old), the time interval between parental tumor diagnosis and childbirth (short, medium, long), and histologic types of tumor, etc.

All analyses were performed by using SAS software (SAS Institute, Cary, NC).

Results

Paper I

As shown in **Table 2**, a total of 95 children (6.9%) were born preterm among 1369 children who had one parent diagnosed with CNS tumor below the age of 20, while there were 356 preterm-born children among the matched group (5.2%). Children of survivors with CNS tumor were thus associated with a 29% increased risk of being born preterm (95%CI: 1.01, 1.65) after adjustment for several potential confounders. The observed association varied between sub-populations, with a significant positive association in girls, offspring of female survivors and childhood survivors, but without association in boys, offspring of male survivors and adolescent survivors.

Besides, the ORs were negatively related to the increased time interval between parental diagnosis with CNS tumor and childbirth, ranging from 1.37 in children born within 15 years since parental tumor, 1.27 in those born after 16-25 years, to 1.00 in those born after more than 25 years (**Figure 4**). Furthermore, in **Table 3**, a co-sibling analysis found that the risk of being born preterm was lower in children born later as compared to first-born children after parental diagnosis (adjusted OR = 0.49; 95% CI: 0.23, 1.04). The decreased risk appeared slightly greater among the offspring of female survivors than those of male survivors.

Table 2: Odds ratios and 95% confidence intervals of preterm birth among offspring of survivors with central nervous system tumor compared with matched comparisons.

Variables	Offspring of survivors		Matched comparisons		Crude	Adjusted [a]
	No. of individuals	No. of outcome, N(%)	No. of individuals	No. of outcome, N(%)	OR(95%CI)	OR(95%CI)
Overall	1369	95(6.9)	6845	356(5.2)	1.36(1.07,1.71)	1.29(1.01,1.65)
Maternal or paternal tumor						
Maternal	722	53(7.3)	3610	185(5.1)	1.47(1.07,2.02)	1.40(1.01,1.98)
Paternal	647	42(6.5)	3235	171(5.3)	1.23(0.88,1.75)	1.20(0.82,1.74)
Sex of offspring						
Female	636	44(6.9)	3180	139(4.4)	1.63(1.15,2.32)	1.57(1.08,2.28)
Male	733	51(7.0)	3665	217(5.9)	1.19(0.87,1.62)	1.13(0.81,1.58)
Parental age at diagnosis with CNS tumor						
Childhood	886	71(8.0)	4430	226(5.1)	1.62(1.23,2.13)	1.53(1.14,2.06)
Adolescence	483	24(5.0)	2415	130(5.4)	0.92(0.59,1.43)	0.89(0.56,1.41)

[a] Adjusted for year of childbirth, sex, maternal and paternal age at birth, region at birth, parity, maternal birth country, maternal highest education, maternal pre-pregnancy body mass index, maternal smoking, gestational hypertensive disorders and gestational diabetes mellitus.

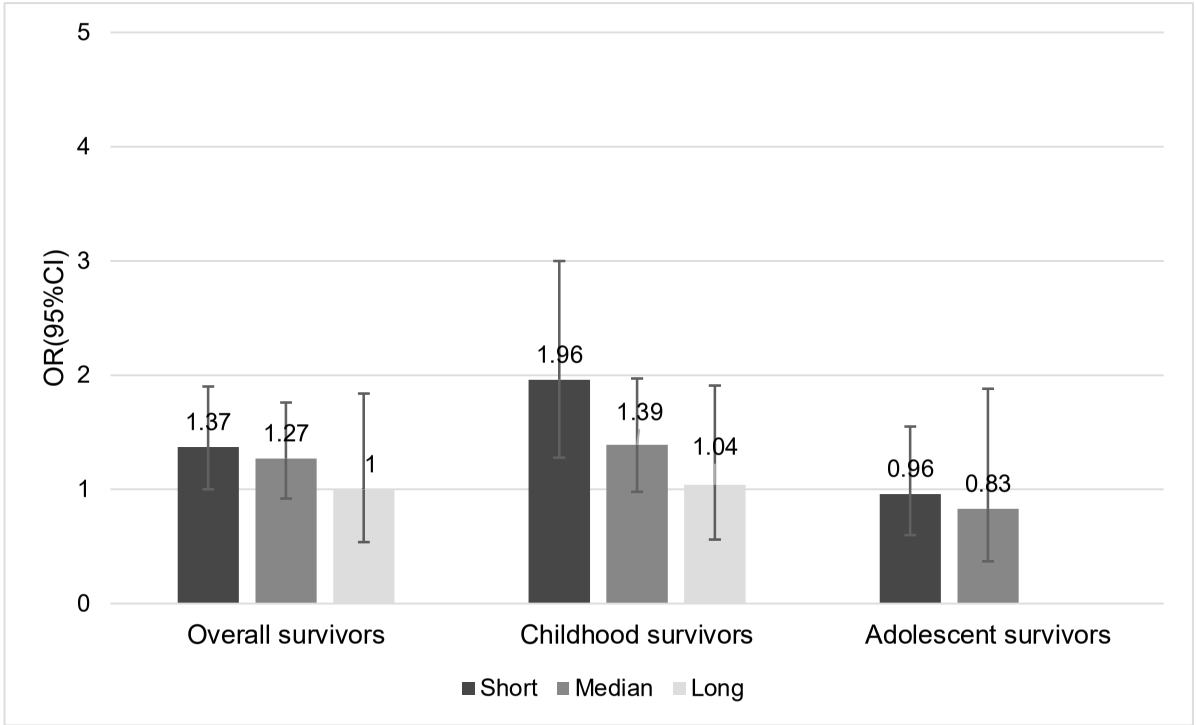

Figure 4:
Trends of odds ratios for risk of preterm birth among children of survivors with central nervous system tumor with the increase of time interval between parental diagnosis and childbirth. *Adjusted for year of childbirth, gender, maternal and paternal age at birth, and region at birth, parity, maternal birth country, maternal highest education, maternal pre-pregnancy body mass index, maternal smoking, gestational hypertensive disorders and gestational diabetes mellitus.

Table 3: Odds ratios and 95% confidence intervals of preterm birth among survivors with multiple pregnancies after diagnosis with central nervous system tumor using co-sibling design.

Variables	No. of offspring of survivors	No. of outcome, N(%)	Crude OR (95%CI)	Adjusted OR (95%CI) [a]
Overall				
First child	479	35(7.3)	1.00	1.00
Second or more	596	27(4.5)	0.54(0.29,1.01)	0.49(0.23,1.04)
Maternal tumor				
First child	236	19(8.1)	1.00	1.00
Second or more	324	15(4.6)	0.44(0.17,1.11)	0.33(0.09,1.17)
Paternal tumor				
First child	243	16(6.6)	1.00	1.00
Second or more	272	12(4.4)	0.65(0.27,1.55)	0.64(0.24,1.72)

[a] Adjusted for maternal age at birth and paternal age at birth.

Figure 5 presents the results regarding the association of specific types of parental tumor and risk of being born preterm. The increased risk varied by histologic type of parental tumor with the highest risk in children of survivors with medulloblastoma (adjusted OR = 3.44) and ependymoma (adjusted OR = 2.76).

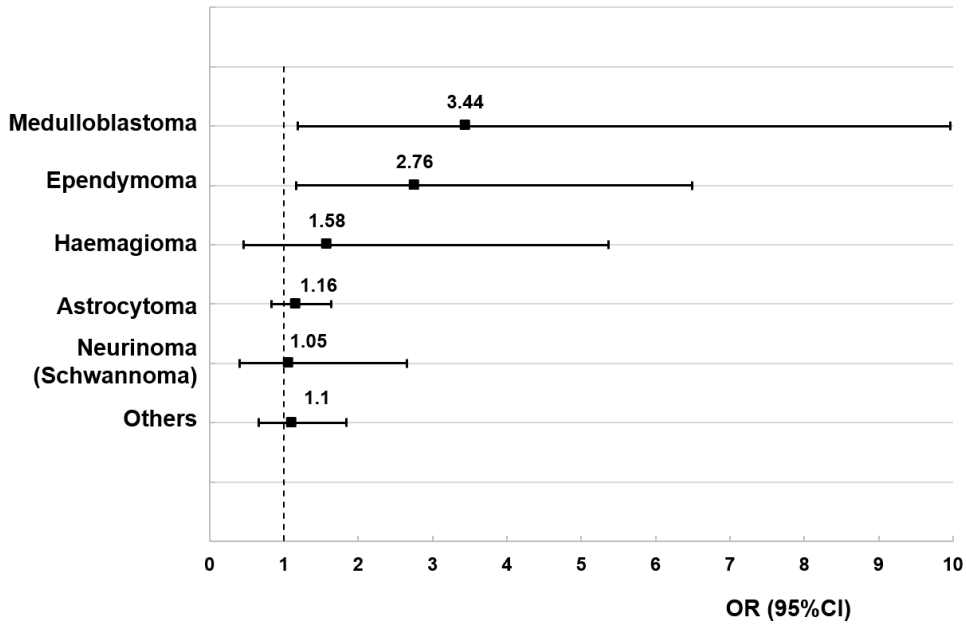

Figure 5:

Odds ratios and 95% confidence intervals of preterm birth among offspring of survivors with different types of central nervous system tumor compared with matched comparisons. *Adjusted for year of childbirth, sex, maternal and paternal age at birth, region at birth, parity, maternal birth country, maternal highest education, maternal pregnancy body mass index, maternal smoking, gestational hypertensive disorders and gestational diabetes mellitus.

Paper II

Five children, who died within three months after birth, were excluded from the study group, and there were 1364 children whose mother or father had a diagnosis with CNS tumor under the age of 20 and 6820 matched children included in Paper II. In **Table 4**, offspring of survivors with CNS tumor had a sum of 2231 diagnoses of somatic diseases, with an incidence rate being 94.77 per 1000 person-years. While the rate was 92.79 in the matched comparisons. However, the increased risk of overall somatic diseases was not statistically significant with the RR of 1.02 (95%CI: 0.98, 1.07) and the AER of 1.98 (95%CI: -2.06, 6.13). Stratified analyses found that preterm-born children of survivors were associated with a 19% increased risk of overall somatic diseases (95%CI: 1.01, 1.41), which was stronger in preterm-born children of female survivors (RR=1.26) or those of childhood survivors (RR=1.24) (data shown in Paper II). In addition, the association differed by the histologic type of parental CNS tumor but without statistical significance (**Figure 6).**

Table 4: Relative risk and absolute excess risk of overall somatic diseases among offspring of survivors with central nervous system tumor compared with matched comparisons.

Variables	Offspring of survivors		Matched comparisons		RR(95%CI)	AER (95%CI)
	No. of individuals	No. of outcome (IR/per 1000 person-year)	No. of individuals	No. of outcome (IR/per 1000 person-year)		
Overall	1364	2231(94.77)	6820	10770(92.79)	1.02(0.98,1.07)	1.98(-2.06,6.13)
Maternal or paternal tumor						
Maternal	720	1181(92.40)	3600	5811(92.96)	0.99(0.93,1.06)	-0.57(-5.98,5.05)
Paternal	644	1050(97.58)	3220	4959(92.59)	1.05(0.99,1.13)	5.58(-0.29,11.69)
Sex of offspring						
Female	633	1038(97.08)	3165	5155(97.42)	1.00(0.93,1.07)	-0.34(-6.37,5.94)
Male	731	1193(92.84)	3655	5615(88.91)	1.04(0.98,1.11)	3.93(-1.46,9.52)
Parental age at diagnosis						
Childhood	883	1398(90.98)	4415	7010(93.20)	0.98(0.92,1.03)	-2.22(-7.14,2.86)
Adolescence	481	833(101.90)	2405	3760(92.30)	1.11(1.03,1.19)	9.86(2.89,17.15)
Preterm birth						
Yes	93	186(123.78)	305	563(103.73)	1.19(1.01,1.41)	21.58(4.08,40.56)
No	1271	2045(92.79)	6515	10207(92.25)	1.01(0.96,1.05)	1.82(-2.25,6.00)

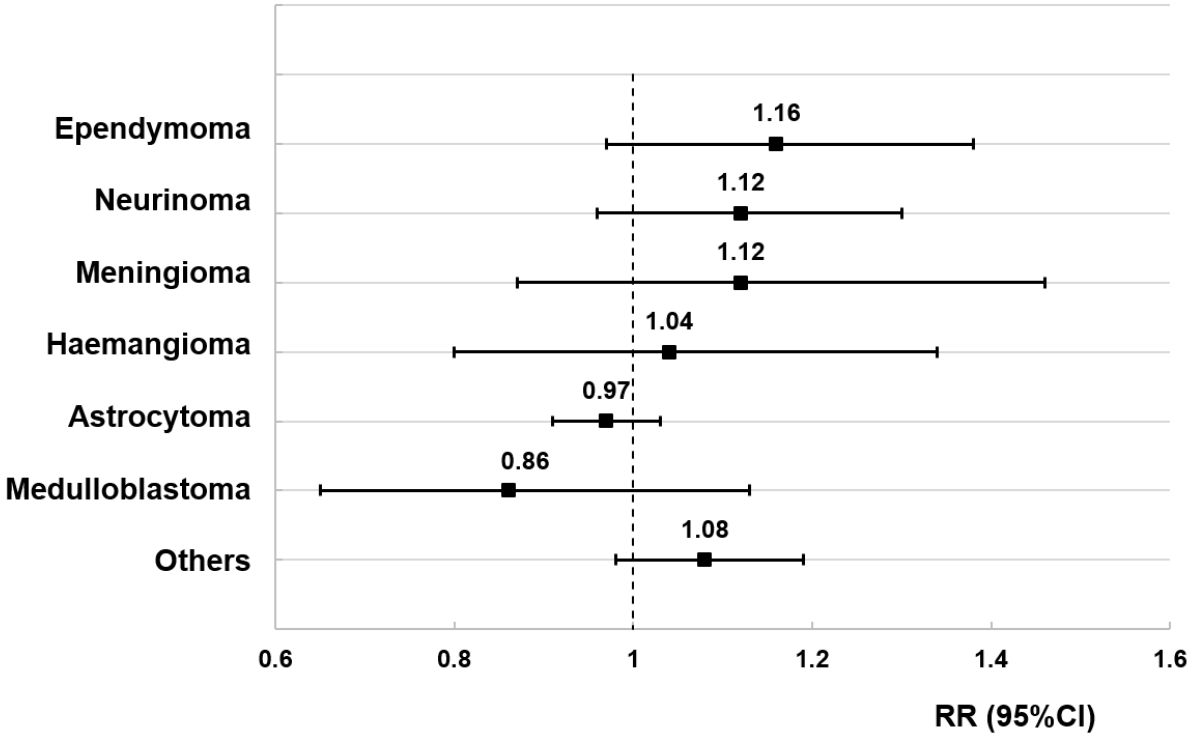

Figure 6:

Relative risks of overall somatic diseases among offspring of survivors with different types of central nervous system tumor compared with matched comparisons.

In **Figures 7 and 8**, offspring of survivors were at an elevated risk of infectious and parasitic diseases, which was more pronounced in offspring of male survivors with HR of 1.23 (95%CI: 1.03, 1.47). While a higher risk of CNS tumor was found in children of overall survivors (HR=4.91; 95%CI: 1.42, 16.96) (data shown in Paper II). In **Figure 8**, children of male survivors were associated with 5.01 times higher risk of overall malignancies (95%CI: 1.45, 17.3). The risk of other somatic diseases was comparable between the offspring of survivors and matched comparisons.

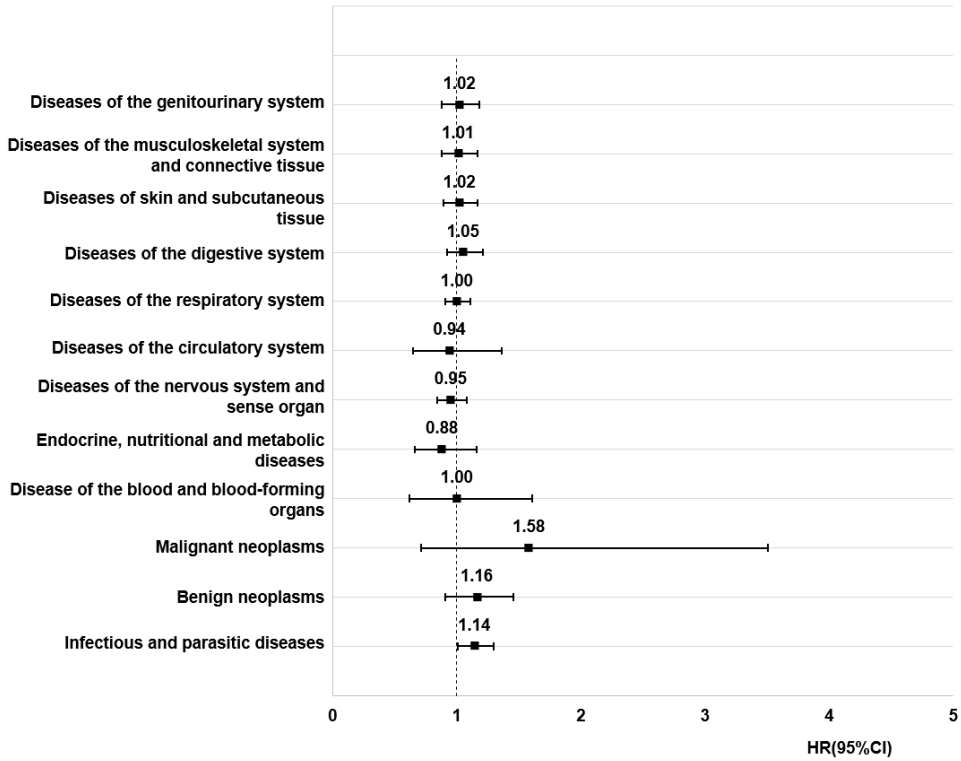

Figure 7:

Hazard ratio of specific types of somatic diseases among offspring of survivors with central nervous system tumor compared with matched comparisons.

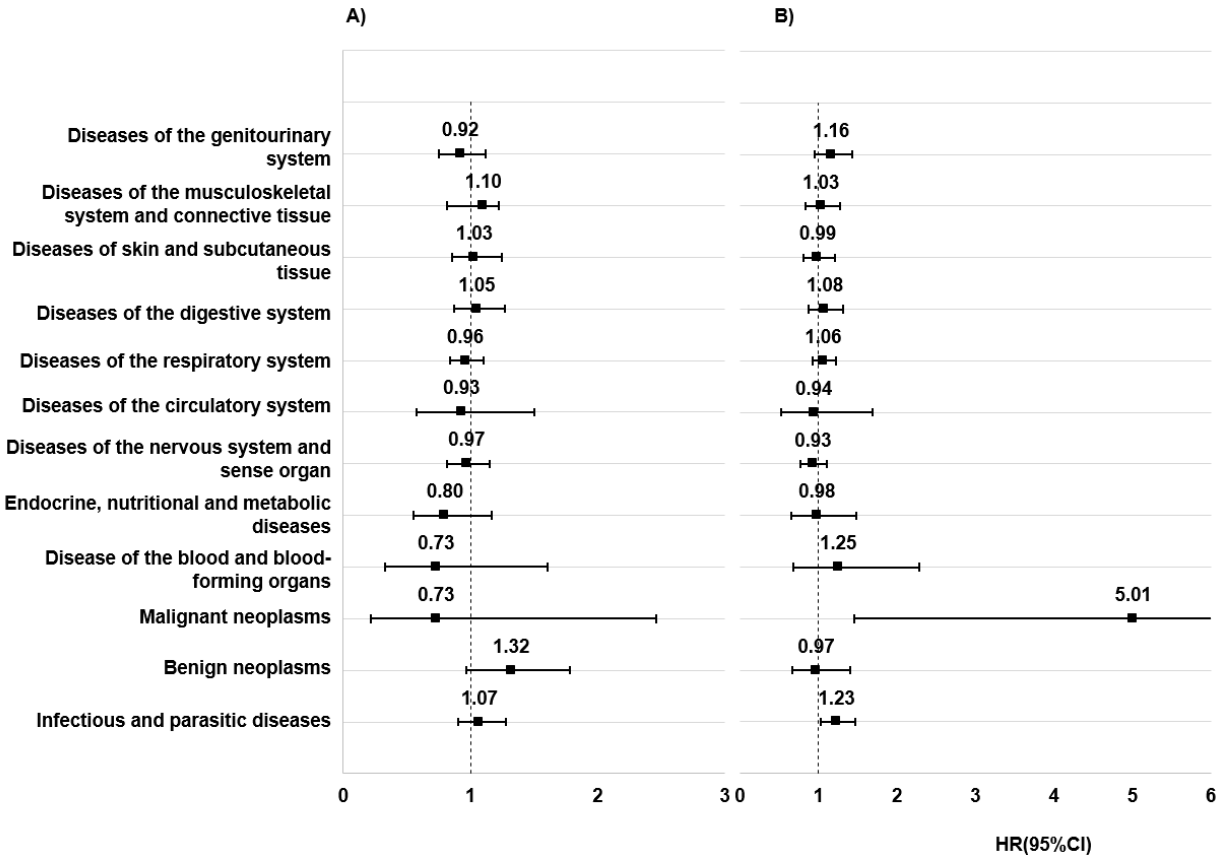

Figure 8:

Hazard ratio of specific types of somatic diseases stratified by maternal or paternal diagnosis with central nervous system tumor. A): Maternal tumor; B): Paternal tumor.

Paper III

We further investigated the risk of psychiatric disease in the study population used in Paper II. As shown in **Table 5**, a total of 189 in 1364 children of survivors with CNS tumor and 827 in 6820 matched children experienced psychiatric disease, generating the incidence rate of 8.46 and 7.47 per 1000 person-years respectively. The difference was not significant with an adjusted HR of 1.10 (95%CI: 0.94,1.28). However, boys had a 29% higher risk of mental disorder if they had one parent diagnosed with CNS tumor (95%CI: 1.04, 1.59). The HRs associated with a specific histologic type of parental tumor were different but none were significant (**Figure 9**).

In **Figure 10**, the incidence rate of most types of psychiatric disorders was comparable between children of survivors and their matched comparisons, except for mental retardation. Offspring of survivors with a CNS tumor had a significantly elevated risk of mental retardation (adjusted HR: 2.36, 95%CI: 1.21,4.58), which was more pronounced for mild mental retardation (data shown in Paper III).

Table 5: Hazard ratio of psychiatric disorders among offspring of survivors with central nervous system tumor compared with matched comparisons.

Variables	Offspring of survivors		Matched comparisons		Crude HR	Adjusted HR[a]
	No. of individuals	No. of outcome (IR/per 1000 person-year)	No. of individuals	No. of outcome (IR/per 1000 person-year)		
Overall	1364	189(8.46)	6820	827(7.47)	1.13(0.96,1.32)	1.10(0.94,1.28)
Maternal or paternal tumor						
Maternal	720	104(8.53)	3600	442(7.40)	1.15(0.93,1.42)	1.11(0.89,1.37)
Paternal	644	85(8.35)	3220	385(7.55)	1.11(0.87,1.40)	1.08(0.85,1.37)
Sex of offspring						
Female	633	78(7.66)	3165	399(7.91)	0.97(0.76,1.23)	0.90(0.71,1.15)
Male	731	111(9.14)	3655	428(7.10)	1.28(1.04,1.58)	1.29(1.04,1.59)
Parental age at diagnosis						
Childhood	883	130(8.95)	4415	553(7.71)	1.16(0.95,1.40)	1.11(0.92,1.35)
Adolescence	481	59(7.55)	2405	274(7.03)	1.07(0.81,1.42)	1.05(0.79,1.39)
Preterm birth						
Yes	93	19(13.53)	305	42(8.14)	1.72(1.00,2.97)	1.44(0.81,2.56)
No	1271	170(8.12)	6515	785(7.44)	1.09(0.92,1.28)	1.06(0.90,1.25)

[a] Adjusted for year of childbirth, sex of offspring, maternal and paternal age at birth, maternal and paternal highest education, maternal and paternal diagnosis with psychiatric disorders.

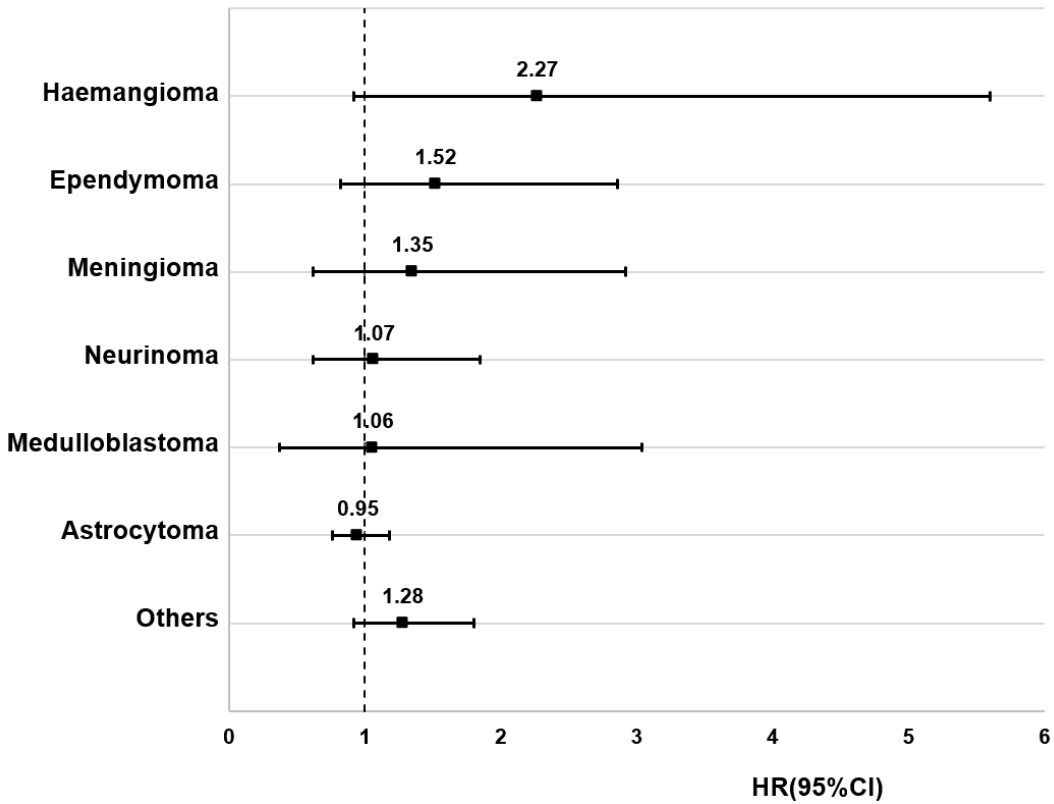

Figure 9:

Hazard ratio of psychiatric disorders among offspring of survivors with different types of central nervous system tumor compared with matched comparisons. *Adjusted for year of childbirth, sex of offspring, maternal and paternal age at birth, maternal and paternal highest education, maternal and paternal diagnosis with psychiatric disorders.

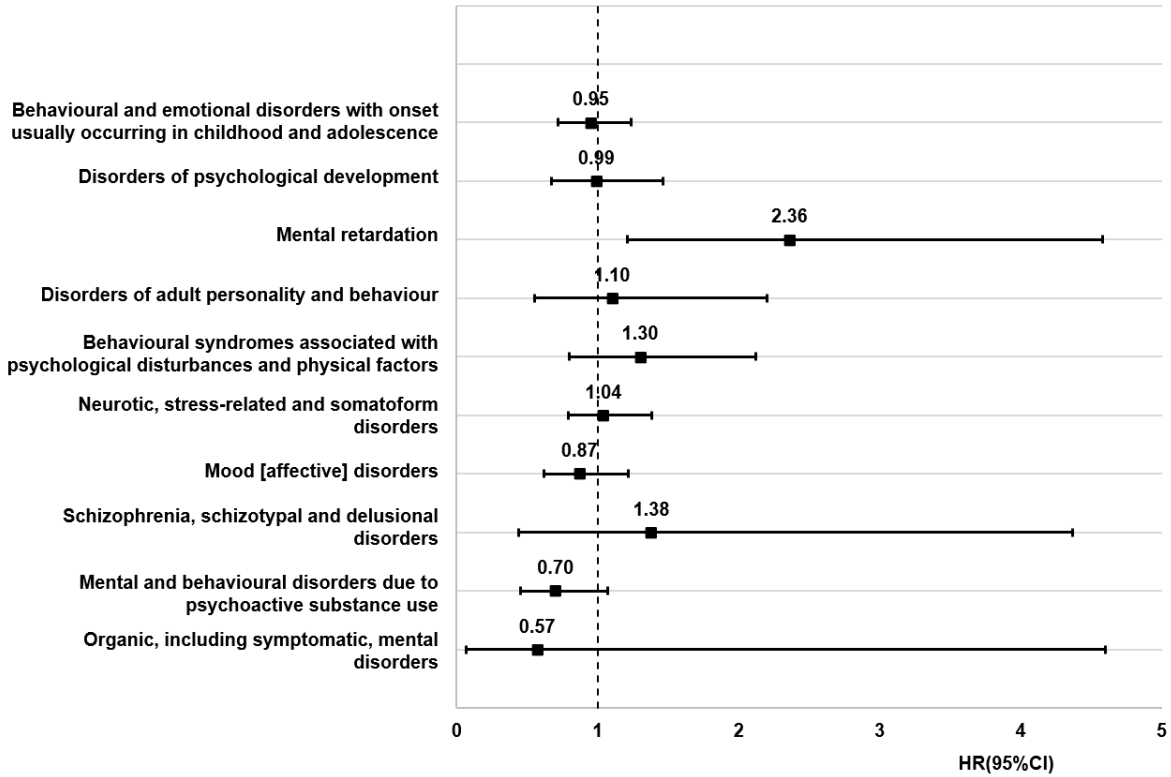

Figure 10:

Hazard ratio of each specific type of psychiatric disorder among offspring of survivors with central nervous system tumor compared with matched comparisons. *Adjusted for year of childbirth, sex of offspring, maternal and paternal age at birth, maternal and paternal highest education, maternal and paternal diagnosis with psychiatric disorders.

Paper IV

A total of 655 children with one parent diagnosed with CNS tumor completed the compulsory education and got the final grade in Sweden by the end of 2015. Thus 655 children of survivors and 3275 matched children were included in Paper IV. As shown in **Table 6**, 13.9% of children of survivors got a poor academic performance, while the proportion in the matched group was 10.0%, yielding an OR of 1.39 (95%CI:1.10,1.76). The observed association was significant in boys or offspring of male survivors, rather than girls or offspring of female survivors. Preterm birth strengthened the association with an OR of 2.22 in preterm-born children and 1.31 in full term-born children. Furthermore, as shown in **Figure 11**, children born within 10 years after parental diagnosis were at the highest risk to get a poor school performance (OR =1.50), followed by those born within 11-20 years (OR =1.44) and offspring born more than 20 years since parental tumor (OR =0.80). In addition, parental education was found to be inversely related to the strength of the association, the risk to get poor academic performance was comparable between groups in children born from mother or father with more than 12 years of education. In **Figure 12**, children of survivors with ependymoma showed a significant association with poor school performance with OR of 2.92 (95%CI: 1.15, 7.41).

In **Figure 13**, quantile regression found that the strength of the association between parental CNS tumor and academic performance was decreased with the increasing quantile of z-score for academic performance. The tendency remained similar in children of female survivors and those of male survivors, but the association with the paternal diagnosis was stronger than that with maternal diagnosis across the board.

Table 6: Odds ratios for poor academic performance among offspring of survivors with central nervous system tumor compared with their matched comparisons [a]

Variables	Offspring of survivors		Matched comparisons		OR(95%CI)
	No. of individuals	No. of outcome, N(%)	No. of individuals	No. of outcome, N(%)	
Overall	655	91(13.9)	3275	327(10.0)	1.39(1.10,1.76)
Maternal or paternal tumor					
Maternal	362	46(12.7)	1810	187(10.3)	1.23(0.89,1.70)
Paternal	293	45(15.4)	1465	140(9.6)	1.61(1.15,2.25)
Sex of offspring					
Female	304	23(7.6)	1520	123(8.1)	0.94(0.60,1.46)
Male	351	68(19.4)	1755	204(11.6)	1.67(1.27,2.19)
Parental age at diagnosis					
Childhood	433	58(13.4)	2165	216(10.0)	1.34(1.01,1.79)
Adolescence	222	33(14.9)	1110	111(10.0)	1.49(1.01,2.19)
Preterm birth					
Yes	44	12(27.3)	157	16(10.2)	2.22(2.02,4.86)
No	611	79(12.9)	3118	311(10.0)	1.31(1.02,1.67)
Maternal highest education					
1-9 years	66	27(40.9)	330	79(23.9)	1.71(1.10,2.65)
10-11 years	372	56(15.1)	1860	193(10.4)	1.45(1.08,1.96)
12+ years	217	8(3.7)	1085	55(5.1)	0.73(0.35,1.53)
Paternal highest education					
1-9 years	113	25(22.1)	565	95(16.8)	1.32(0.85,2.05)
10-11 years	325	54(16.2)	1625	168(10.3)	1.61(1.18,2.18)
12+ years	217	12(5.5)	1085	64(5.9)	0.94(0.51,1.74)

[a] "Poor academic performance" was defined as Z-score of academic performance below the 10th percentile in matched group.

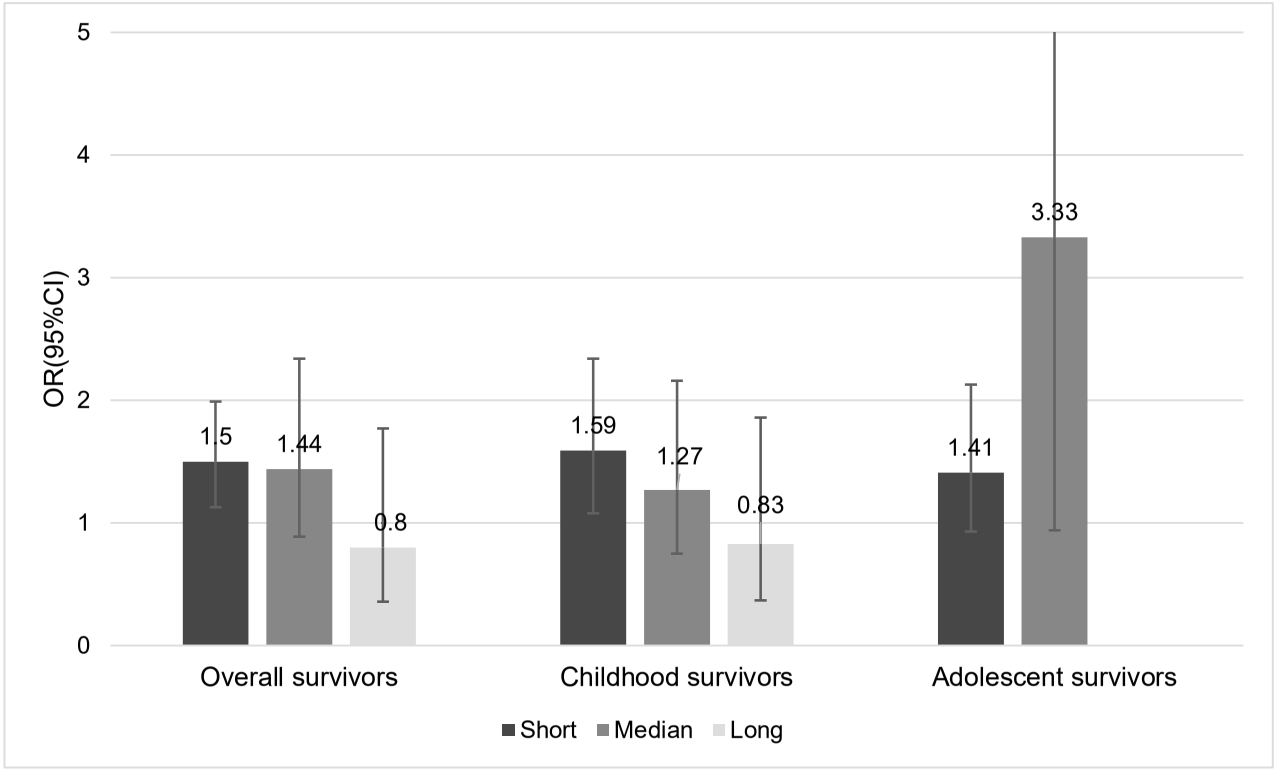

Figure 11:

Trends of odds ratios for risk of poor academic performance among children of survivors with central nervous system tumor with the increase of time interval between parental diagnosis and childbirth.

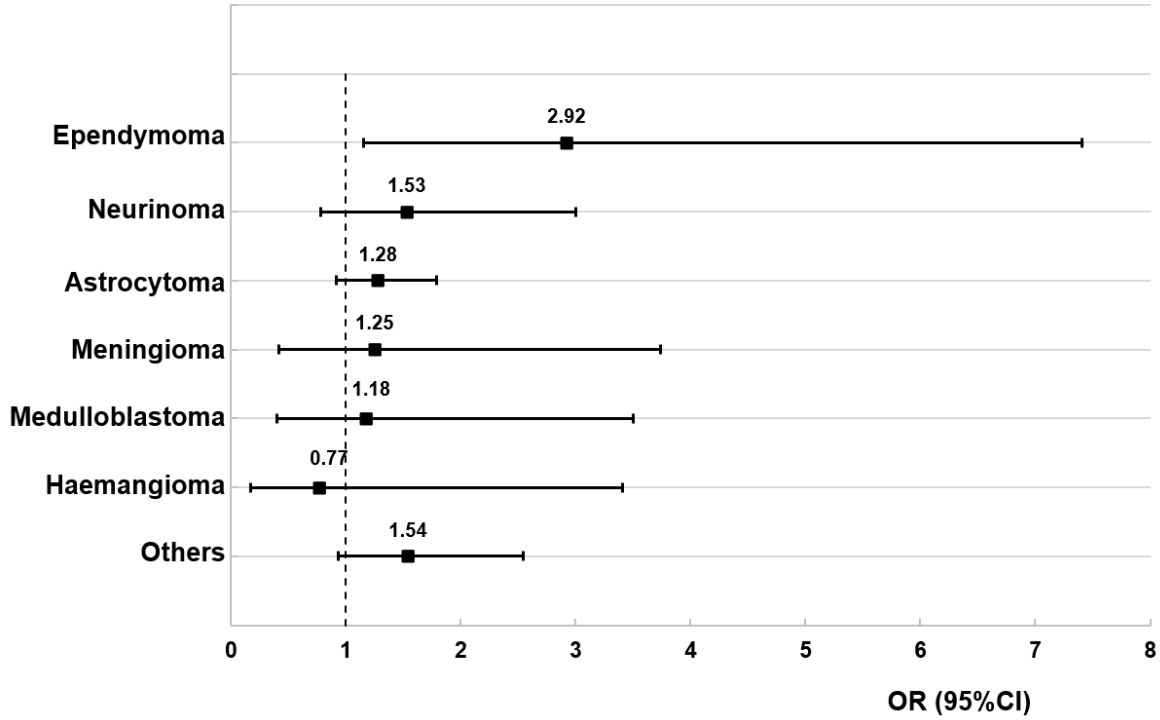

Figure 12:

Odds ratios of poor academic performance among offspring of survivors with different types of central nervous system tumor compared with matched comparisons.

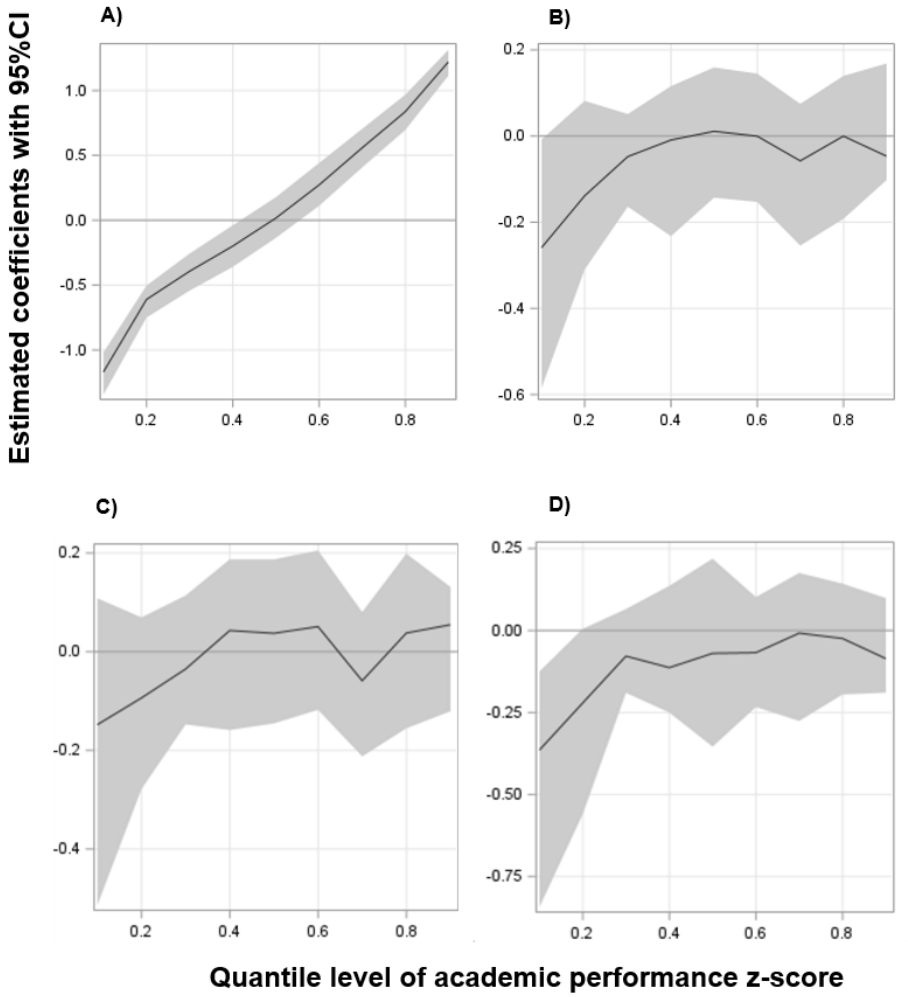

Figure 13:
Coefficients at each decile for academic performance using quantile regression. *Grey area indicates 95% confidence intervals. A) Matched comparisons (Intercept); B) Offspring of overall survivors; C) Offspring of female survivors; D) Offspring of male survivors.

Discussion

Main findings

This thesis provided a comprehensive assessment of potential adverse outcomes for offspring of survivors who were ever previously diagnosed with CNS tumor under the age of 20, ranging from birth outcome, health status to academic performance. In this thesis, these children were found to have a higher risk of being born preterm and getting a poor academic performance. Although the general health status (physical and mental health) in children of survivors was comparable with that in the general population, these children were found to have an increased risk of CNS tumor, infectious diseases, and mental retardation. Furthermore, the observed associations varied by sex of survivors, sex of offspring, age at parental diagnosis, histology of parental tumor as well as the time interval between parental tumor diagnosis and childbirth, which are discussed in detail below.

Offspring of female or male survivors

In this thesis, the increased risk of being born preterm was observed in offspring of female survivors rather than those of male survivors, but children of male survivors were more likely to have poor academic achievement. General physical and mental health were similar between children of survivors and general children, but there were differences in the risk of some specific diseases between the two groups.

Female cancer survivors have been linked to a higher risk of preterm birth while the risk among partners of male survivors has rarely been investigated [78,80,82,122-126]. Some of the prior researches further evaluated the risk associated with a specific type of tumor [80,82,122]. In line with our study in Paper I, two prior studies reported one to three times higher incidence of preterm birth in female survivors of CNS tumor, and another study in male cancer survivors found no association for survivors with CNS tumor [80,82,122]. It is reasonable as the impact of treatments in female survivors could be directly related to birth outcomes via female reproductive system damage, while treatments in males may only influence birth outcomes in their partners indirectly through genetic or epigenetic mutation in sperm.

A Danish register-based cohort study showed no increased risk of overall hospitalization in offspring of childhood or adolescent cancer survivors, while a

significantly higher risk of neoplasms [92]. Information regarding specific cancer was not available in this study. In Paper II, we did not find an elevated cumulative incidence rate of overall somatic diseases in children of all CNS tumor survivors but in preterm-born children of these survivors, in particular those of female survivors. It may indicate a mediated role of preterm birth between maternal tumor and children's physical health. It is noteworthy that children of male but not female survivors were associated with a significantly higher risk of a malignant neoplasm. Cancer susceptibility is recognized to be heritable, and familial aggregation has been observed in several malignant neoplasms, including brain tumor [12,13,127-132]. Apart from malignancies, infectious diseases were also more frequently observed in offspring of male survivors. The difference in malignancy risk between maternal and paternal tumor deserves further study. The higher risk of infectious diseases might indicate that paternal CNS tumor and its treatment could affect the immune function of their children, which might be one of the underlying pathways behind the elevated incidence of malignancies in these children.

No difference regarding hospitalization due to mental disorders was found between children of childhood or adolescent cancer survivors and the general population in a Danish cohort [92]. Consistently, in Paper III, the incidence rate of psychiatric disorders was comparable between children of survivors with childhood or adolescent CNS tumor and their matched children, regardless of female or male survivors. However, children of these survivors were at an increased risk of mental retardation (i.e. intelligent disability), predominately mild mental retardation. The causes behind mental retardation have not been completely elucidated. It is well-proven that genetic factors are closely related to the occurrence of severe or profound types of mental retardation, which are usually characterized as a part of syndromes (e.g. Down syndrome) [133]. Epigenetic alterations and psychological factors may be the main causes for mild type [133-138]. Previous studies found that inheritable epigenetic programming was involved in brain development, which might be changed if their parents were ever exposed to radiation, stress or some chemical agents [20,104,105,139]. Therefore, the increased risk of mild mental retardation in offspring may be partly explained by the potential epigenetic changes in gametes caused by radiation or chemotherapy tumor in early life. It requires experiments to examine it in the future.

In Paper IV, we assessed the academic performance achieved at age of 16 in regular schools in offspring of these survivors, in which children with mental retardation were not included as the majority of them received education in special schools in Sweden. A poor academic performance was found in offspring of male survivors but not children of female survivors in this study. Prior study with all survivors with childhood cancer reported the highest risk of suffering chronic medical conditions in survivors with CNS tumor, thus children of these survivors were most likely to receive less caregiving and support from their parents [55]. This probably subsequently affected their academic attainments. A previous study found that fathers' involvement played a more important role in the association between

parents' monitoring and academic performance [115], which may partly explain our results regarding the difference in academic performance between children of male and female survivors. Furthermore, a higher risk of certain somatic diseases was found in offspring of male survivors in Paper II, which may subsequently influence their school activity as well.

To sum up, there were considerable differences between the impact of maternal and paternal CNS tumor on their children, in which complex factors may be involved, calling for further studies.

Female or male offspring

Findings from this thesis showed that female infants, but not males, were associated with an elevated likelihood to be born preterm, while boys tended to experience psychiatric disorders and have poor school performance. General physical health seemed not to be influenced both in boys and girls of survivors. Although available studies have explored the potential adverse pregnancy outcomes in cancer survivors, few of these studies further investigated the difference between female and male infants [92]. The different risk of being born preterm for female and male infants in Paper I may be explained by the difference in sensitivity of sperm and oocyte for chemotherapy or radiation. Previous studies reported that nuclear radiation leads to few girls born as radiation may perform a greater impact on sperm with X chromosome or female fetus [140,141]. Nevertheless, boys of survivors were more likely to experience psychiatric disorders and get poor academic performance. Mental health and academic performance were always correlated to each other [108]. Parents with late effects caused by CNS tumor may provide less support for their children, which may influence children's mental status and academic performance. A prior study found a significant association between parents' monitoring and school performance in children, especially in boys [115]. These results indicated that parental involvement might play a more important role in the mental health and school performance of boys than that of girls.

Offspring of childhood or adolescent survivors

Parental age at tumor diagnosis may modify the association between parental tumor and adverse outcomes in their children, because the vulnerability of reproductive system to cancer therapy is probably different between children and adolescents [55]. In Paper I, an increased risk of being born preterm was found in children of survivors diagnosed during childhood but not adolescence thus indicating that children's reproductive system may be more sensitive to tumor treatments than adolescents'.

A previous study found pre-pubertal radiation had a greater impact on the reproductive system than post-pubertal radiation, which may partly explain the underlying mechanisms [78]. Moreover, in Paper II, the highest incidence of overall somatic diseases was found in preterm-born children of childhood survivors. In Paper III, an increased risk of intelligent disability was observed in children of childhood survivors although the general mental health was similar between offspring of childhood survivors and those of adolescent survivors. However, parental age at diagnosis played a smaller role in the association between parental tumor and academic performance among their offspring in Paper IV. In general, findings in this thesis indicated offspring of childhood survivors might be more likely to be affected by parental tumor and related treatments.

Offspring with different time intervals between parental tumor and birth

The side effect of cancer and its treatments was previously suggested to decline with time, which was supported by our findings [55,64,142,143]. In Paper I, the risk of being born preterm decreased gradually following parental diagnosis with CNS tumor. Furthermore, the co-sibling analyses in families with multiple children after parental diagnosis found that when compared with first-born children, the risk was lower among their siblings born later. In Paper IV, the strength of association between parental tumor and poor academic performance was also negatively related to the time interval from parental tumor and childbirth. Thus, CNS tumor survivors are recommended to care about the timing to have a child, and more concerns could be given to first-born children after diagnosis.

Offspring of survivors with different histological types of tumor

Both benign or malignant tumors in CNS can cause symptoms and need treatments due to the location [10,144]. Histology of tumor in CNS is highly related to treatment choices and prognosis in survivors. In the Swedish Cancer Registry, tumors originally from glial cells in the brain or spine are included in the astrocytoma subtype. Astrocytoma is the most common subtype of tumor in CNS among younger population [145]. The low-grade types are more common-occurring in children or adolescents, while the high-grade types are more often found in adults [5]. Parental diagnosis with astrocytoma in early life seems to exert little influence on their offspring except for an increased risk of mental retardation. Neurinoma (i.e. Schwannoma) is a nerve sheath neoplasm originally from Schwann cells, most of

which are benign [6]. Hemangioma is a benign tumor of blood vessels [6]. Meningioma is more likely to be slowly-growing [6]. Surgery is always the first option for these subtypes, radiation was sometimes added for remained tumor with incompletely surgical resection or tumors attached to the brain stem [6]. The incidence rate of adverse outcomes studied in this thesis was not significantly increased among children of survivors with neurinomas, hemangiomas or meningiomas as compared to the reference. Majority of ependymomas, approximately 90%, are malignant [6]. All medulloblastomas are malignant, invasive and rapidly-growing neoplasms [6]. Patients with malignant ependymoma or medulloblastoma always received a combined treatment of surgery, radiation, and chemotherapy [6]. Although these two subtypes are common in younger population, there are not many offspring of survivors with ependymoma or medulloblastoma, which may be due to its poor prognosis, thus fewer patients could survive to reproductive age and then have their own children. Offspring of survivors with ependymomas had a significantly increased risk of being born preterm and getting poor school performance, but not a higher risk of somatic or mental diseases. Children of survivors with medulloblastoma suffered the highest risk of being born preterm, however, there was no difference in the physical and mental health as well as academic performance between children of these survivors and general population. Overall, more attention should be paid to children of survivors with ependymoma or medulloblastoma. However, findings for offspring with specific subtype of parental tumor in this thesis may be interpreted cautiously because of the limited sample size, and more researches are needed.

Strengths and limitations

There are several strengths across four projects in this thesis. Firstly, the nationwide coverage of registers allowed us to focus on offspring of survivors with CNS tumor, as well as warranted the external validity. Secondly, the high quality of register-based data and the verified disease diagnoses eliminated recall bias and minimized misclassifications. Thirdly, the matched cohort design used across four projects helped to control the confounding effects from important factors.

We have to acknowledge some general limitations in all projects included in this thesis. Firstly, detailed information on tumor treatments is lacking in our datasets, thus it was unable for us to explore treatment-associated adverse outcomes in offspring of survivors. We call for further studies to examine it in order to provide tailored recommendations for survivors with different therapies. Secondly, a limited sample size may lead to insufficient statistical power when exploring associations between specific subtypes of parental tumor and outcomes in offspring. These results should thus be cautiously interpreted. Besides, the relatively small number

of subjects did not allow us to investigate the associations in terms of more narrowly-defined time intervals or gestational age groups, which may provide more detailed information. Thirdly, residual bias cannot be fully excluded because of some unknown or unmeasured factors, such as environmental exposures.

Some specific limitations should also be noted for each paper. In Paper I, in-vitro fertilization is a recognized risk factor for preterm birth, the information of which is however lacking in our datasets. To take it into account, we did stratified analyses by calendar year at parental tumor diagnosis (before or after 1990) as in-vitro fertilization was put into use since 1982 in Sweden and then became common from 1990 [146]. In Paper II and III, information on somatic or mental diseases from outpatient care was not completed until 2001. However, we selected comparisons matched by calendar year at childbirth that ensured the comparability between the study group and the matched group. Another limitation is that the median age of the study population at the end of follow-up was 16 years old. Therefore, follow-up was not long enough to explore the risk of common chronic diseases in offspring, which always occurred at older ages. In Paper IV, academic performance for children who received education in special schools is not available in Swedish Ninth Grade Register. However, among children born in Sweden during the period from 1973 to 1999, only 5.6% did not have the information of academic performance. And the probability of individuals with missing scores was comparable between children of survivors and comparison children (p value=0.146), suggesting a small role of that on the observed relationship.

Conclusions

In conclusion, the aim of this thesis is to identify the potential adverse outcomes in offspring of CNS tumor survivors who were diagnosed below the age of 20. Below is the specific conclusion for each project.

Paper I

Offspring of these survivors were associated with a significantly higher likelihood of being born preterm. The observed association varied in subgroups and declined with the time interval between parental tumor and childbirth.

Paper II

Offspring of these survivors did not experience an increased cumulative incidence rate of overall somatic diseases, but an elevated risk of malignancy and infectious diseases was found in the offspring of male survivors.

Paper III

Offspring of these survivors did not have a higher risk of psychiatric disorders but had a significantly increased incidence rate of mental retardation.

Paper IV

Offspring of these survivors were related to poor academic performance. The observed association varied in subgroups and declined with the time interval between parental tumor and childbirth.

Future perspectives

Continuing advances in cancer diagnosis and treatments contribute to a considerable increase in survival rates, especially for cancer patients diagnosed at younger ages. Thus a growing number of survivors who have the potential to grow up into adulthood and subsequently have their own children, which highlighted the importance of researches regarding the possible impact on their children from tumor and its treatments. However, current scientific evidence are not enough to allow oncologists to provide tailored recommendations for cancer survivors, who are greatly concerned about their children. Therefore, it calls for more detailed investigations for children of survivors with different types of cancer and survivors with different cancer therapies. In this thesis, we have explored multiple outcomes in children of survivors who were ever diagnosed with CNS tumor in childhood or adolescence, from birth outcomes, physical and mental health to academic performance. Although it is relatively comprehensive research for offspring of these survivors, some complementary studies are needed for these children in the future. Firstly, studies with larger sample sizes and sufficient statistical power are necessary to confirm our findings, in particular findings for subgroups, such as different subtypes of parental CNS tumor and different time intervals. Secondly, available studies suggested that late effects in cancer survivors depended highly on treatments, including the type of treatment, age at treatment, dose and duration of radiation or chemotherapy, etc. Therefore, it is imperative to explore treatment-specific side effects in children of these survivors in the future. Thirdly, although multiple outcomes have been investigated in this thesis, some other important outcomes are called for in further studies, such as other adverse birth outcomes (e.g. low birth weight, small for gestational age), long-term morbidities (the median age at the end of follow-up was just 16 years old in this study population), more specific types of diseases, highest education level and socioeconomic status. Last but not least, it is worth exploring the underlying mechanisms behind the impact of parental tumor and its treatments on their children, which remains largely unclear. Hopefully, findings from our studies could provide some clues for future preclinical and clinical studies concerning the potential impact of parental diagnosis with CNS tumor in early life on their children.

Popular Science Summary

More and more patients who were diagnosed with central nervous system tumor in childhood or adolescence were able to grow up into adulthood and have their own children. It results in increasing concerns among these survivors for their children. For example, whether their children will be affected by parental tumor and treatments, how long will be safe to have a child after treatment, whether their children will be born with problems, what kinds of diseases their children may have a higher risk of when they are growing up, and so forth. In recent years, some researchers explored the potential adverse outcomes in children of cancer survivors, which were however limited to children of overall cancer survivors. It is known that prognosis is highly different across different types of cancer. Thus, it is urgent to examine the influence of specific cancer types on their children to provide tailored recommendations for survivors with different types of cancer. In this thesis, we aimed to investigate the health status and school performance in children of survivors who were diagnosed with central nervous system tumor under age of 20.

In Paper I, we found that these survivors were more likely to have preterm-born infants, especially female survivors and childhood survivors. However, the risk declined with time, so these survivors were recommended to be concerned about the timing to have a child and to care more about the first pregnancy after tumor diagnosis. Findings from Paper II suggested that the overall physical health was similar between children of these survivors and the general population. But children, whose father had a diagnosis with CNS tumor, may be concerned over the risk of malignancy and infectious diseases. In Paper III, children of these survivors were not related to an increased incidence of general mental disorders but linked to a higher risk of mild intelligent disability. Furthermore, in Paper IV, these children tended to get poor academic performance. These findings recommend more attention should be paid to the neurodevelopment and cognitive function for children of survivors with CNS tumor.

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