Incidence of and survival from childhood cancer

The role of social and family factors in childhood cancer

Dissertation

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Submitted by

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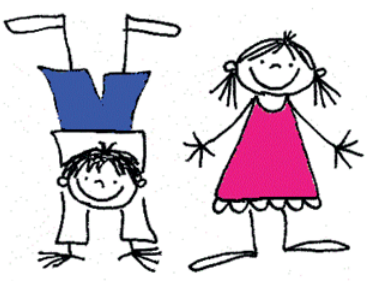

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English abstract

Introduction: Social inequalities, both within countries and between countries, influence the occurrence of and survival from cancer, including childhood cancer. This dissertation aimed to gain further insight into social inequalities in childhood cancer – on the national level within a country and also between countries with different levels of socioeconomic development. The first objective was to obtain a better understanding of the reported geographical differences in childhood cancer worldwide by studying incidence patterns in a Sub-Saharan African country (with a diverse racial/ethnic population) and comparing the findings to the incidence patterns of a representative high-income country (Germany). The second objective was to investigate survival from childhood cancers in relation to social and family factors within high-income countries.

Methods: The two objectives were addressed by seven conceptually independent but topic-wise interrelated studies. Four studies provided the core manuscripts for this thesis: i) childhood cancer incidence patterns by race in South Africa, and in comparison to Germany; ii) survival from acute lymphoblastic leukaemia (ALL) in relation to socio-demographic background in Germany; iii) survival from ALL in relation to family factors in Germany; iv) survival from childhood haematological malignancies in relation to family factors in Denmark. Data from the South African National Cancer Registry, the German Childhood Cancer Registry, a former German case-control study, as well as from the Danish registries served as the basis for these studies. The incidence data were analysed by applying descriptive epidemiological methods. Kaplan-Meier curves and Cox proportional hazard models were used for the survival analyses.

Results: Substantial differences in the reported incidence rates were observed within South African racial groups, with lowest rates among Black children and highest among White children. There were also considerable differences between White children in South Africa and in Germany, but the differences varied markedly by cancer type and by age at diagnosis. Social and family characteristics were found to be associated with survival from childhood cancers, although not consistently between Germany and Denmark and not across cancer types. An impact of socioeconomic factors on survival from ALL was not observed for either Germany or Denmark, however a beneficial effect of higher maternal education among children with non-CNS solid tumours in Denmark was observed. Higher birth order and having siblings was associated with poorer survival among childhood haematological cancer patients in Denmark, with associations being suggestive for ALL and non-Hodgkin lymphoma but stronger and statistically significant for acute myeloid leukaemia. Similarly, most associations with family factors were suggestive for survival from ALL in German children. Highest survival in Germany was seen for second-born children. Patterns of associations between parental age and survival from childhood cancers were diverse across studies.

Discussion: Findings of this dissertation highlight social inequalities in childhood cancer with respect to reported incidence differences between racial groups in South Africa and compared to Germany. Furthermore, survival differences between social groups in Germany and Denmark were observed, although not consistently across cancer types. To reduce those observed social inequalities in childhood cancer, a thorough understanding of the underlying mechanisms and pathways is needed. Observed incidence differences in South Africa might be, at least to some extent, due to socio-cultural factors related to access and utilization of health care services rather than reflecting actual differences in cancer risks. Under-ascertainment of cases may not only drive the findings for South Africa but the global reported geographical patterns of childhood cancer incidence. Despite highly specialized and standardised treatment and free health services for all children in Germany and Denmark, not all children benefit equally from improvements in childhood cancer survival. Further studies are warranted to gain knowledge on the impact of social and family factors on childhood cancer survival in other populations and to identify underlying pathways.

German abstract

Hintergrund: Soziale Unterschiede stehen im Zusammenhang mit der Inzidenz von Krebserkrankungen sowie mit dem Überleben nach Krebserkrankungen, einschließlich Kinderkrebs. In Rahmen dieser Dissertation sollten vertiefende Erkenntnisse über sozial bedingte Ungleichheiten bei Kinderkrebs gewonnen werden – sowohl auf nationaler Ebene als auch zwischen Ländern mit unterschiedlichem sozioökonomischem Entwicklungsstand. Die erste Zielsetzung dieser Arbeit war, ein besseres Verständnis über die berichteten geographischen Unterschiede im Auftreten von Kinderkrebs zu gewinnen und hierzu die Kinderkrebsinzidenz eines Landes in Sub-Sahara-Afrika (mit einer ethnisch vielfältigen Bevölkerung) zu untersuchen und die Ergebnisse mit der Inzidenz Deutschlands (als Repräsentant der Inzidenz von Industrieländern) zu vergleichen. Die zweite Fragestellung bezog sich auf das Überleben von Kinderkrebs in Bezug auf soziale und familiäre Merkmale innerhalb Bevölkerungen.

Methoden: Die beiden Fragestellungen wurden anhand von sieben konzeptionell unabhängigen, jedoch thematisch verknüpften Studien adressiert. Vier dieser Studien bilden die Kernmanuskripte dieser Dissertation: i) Die Inzidenz von Kinderkrebs in Südafrika verglichen zwischen ethnischen Gruppen und im Vergleich zu Deutschland; ii) Das Überleben von Kindern mit akuter lymphoblastischer Leukämie (ALL) in Bezug auf soziodemographische Merkmale in Deutschland; iii) Das Überleben von ALL im Zusammenhang mit familiären Merkmalen in Deutschland; iv) Das Überleben von Kindern mit malignen hämatologischen Erkrankungen im Zusammenhang mit familiären Merkmalen in Dänemark. Als Datenquellen dienten das südafrikanische Krebsregister, das deutsche Kinderkrebsregister, eine deutsche Fall-Kontroll-Studie sowie die dänischen Bevölkerungsregister. Die südafrikanischen Inzidenzdaten wurden mittels deskriptiv-epidemiologischer Methoden ausgewertet. Für die Studien zum Überleben nach Krebs wurden Überlebenskurven nach Kaplan-Meier und Cox poportinal hazard Modelle berechnet.

Ergebnisse: Die beobachteten Inzidenzraten von Kinderkrebs in Südafrika unterschieden sich erheblich zwischen ethnischen Gruppen innerhalb Südafrikas. Die niedrigsten Inzidenzraten wurden bei Kindern der schwarzen Bevölkerung und die höchsten bei weißen Kindern verzeichnet. Auch im Vergleich zwischen weißen südafrikanischen Kindern und deutschen Kindern zeigten sich große Inzidenzunterschiede, wobei sich die Abweichungen deutlich zwischen Krebsformen und Altersgruppen unterschieden. In den Studien zum Überleben nach Kinderkrebs wurden Zusammenhänge mit sozialen und familiären Merkmalen und dem Überleben von Kinderkrebs beobachtet. Allerdings bestanden diese Zusammenhänge nicht einheitlich für Deutschland und Dänemark und unterschieden sich auch zwischen den untersuchten Krebsformen. Weder für Deutschland noch für Dänemark zeigte sich ein Zusammenhang zwischen sozioökonomischen Faktoren und dem Überleben nach ALL, wobei hingegen in Dänemark ein positiver Effekt von höherer mütterlicher Bildung für Kinder mit solidem Tumor (andere als Tumore des zentralen Nervensystems) beobachtet wurde. Zunehmende Geburtenreihenfolge sowie die Anzahl an Geschwistern war mit niedrigerem Überleben bei Kindern mit malignen hämatologischen Erkrankungen in Dänemark assoziiert, obwohl sich die Zusammenhänge für ALL und Non-Hodgkin-Lymphomen überwiegend als nicht statistisch signifikant erwiesen. Statistisch signifikant und stärker ausgeprägt zeigten sich diese Zusammenhänge jedoch bei Kindern mit akuter myeloischer Leukämie. Auch in Deutschland erreichte die Mehrheit der beobachteten Zusammenhänge zwischen dem Überleben nach ALL und familiären Merkmalen keine statistische Signifikanz. Das beste Überleben nach ALL wurde in Deutschland für Zweitgeborene beobachtet. Bezüglich des Alters der Eltern und dem Überleben von Kinderkrebs zeigte sich kein einheitliches Bild.

Diskussion: Im Rahmen dieser Dissertation wurden weitere Erkenntnisse zu sozial bedingter Ungleichheit bei Kinderkrebs gewonnen. Diese Erkenntnisse beinhalten Inzidenzunterscheide zwischen ethnischen Gruppen in Südafrika sowie im Vergleich zu Deutschland und Unterschiede im Überleben nach Kinderkrebs im Zusammenhang mit sozialen und familiären Merkmalen in

Deutschland und Dänemark. Um Maßnahmen zur Verringerung der beobachteten sozialen Unterschiede zu entwickeln, ist ein genaues Verständnis der zu Grunde liegenden Wirkmechanismen und Kausalzusammenhänge wichtig. Die beobachteten Unterschiede in der Inzidenz innerhalb Südafrikas könnten zumindest zu einem gewissen Teil eher auf soziokulturelle Unterschiede im Zugang und in der Inanspruchnahme von Gesundheitsleistungen zurückzuführen sein als auf Unterschiede im Krebsrisiko. Untererfassung von Kinderkrebsfällen könnte nicht nur in Südafrika eine Rolle spielen, sondern auch die weltweiten geographischen Unterschiede von Kinderkrebs beeinflusst haben. Trotz der hoch spezialisierten und standardisierten Behandlung und dem freien Zugang zu Gesundheitsleistungen für alle Kinder in Deutschland und Dänemark scheinen dennoch nicht alle Kinder gleichermassen von den Fortschritten bei der Diagnose und Therapie von Kinderkrebs profitiert zu haben. Weitere Studien sollten den Einfluss von sozialen und familiären Hintergründen im Überleben von Kinderkrebs in weiteren Bevölkerungen untersuchen sowie Erkenntnisse über deren Kausalzusammenhänge aufdecken.

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List of abbreviations

ACCIS: Automated Childhood Cancer Information System

ALL: acute lymphoblastic leukaemia

AML: acute myeloid leukaemia

ASR: age-standardised incidence rates

CI: confidence interval

CNS: central nervous system

CPR number: civil personal registration number in Denmark

GCCR: German Childhood Cancer Registry

HIV: human immunodeficiency virus

HL: Hodgkin lymphoma

HR: hazard ratio

IARC: International Agency for Research on Cancer

ICCC-3: International Classification of Childhood Cancers

ICD-O: International Classification of Diseases for Oncology

IRR: incidence rate ratio

NCR: National Cancer Registry (of South Africa)

NHL: non-Hodgkin lymphoma

NHLS: National Health Laboratory Service (of South Africa)

RR: rate ratio

SEP: socioeconomic position

WHO: World Health Organization

Preamble

Although the overall incidence is low, childhood cancer is the leading cause of disease-related mortality among children in high-income countries [1]. Specific types of childhood cancer are very uncommon [2-4], collectively, however, they present an important public health problem.

Childhood cancer is a heterogeneous group of malignancies, each representing different epidemiological characteristics, biological features, treatment approaches, and survival probabilities. Little is known about their aetiology, although it is likely that both genetic and environmental factors play a role [5-8]. The early age at diagnosis suggests that childhood cancer might originate *in utero*, and that factors prior to birth, i.e. preconception or foetal environmental exposures, as well as those in early childhood may be important determinants of the cancers [9, 10]. While survival from childhood cancer has improved considerably over the last decades in developed countries, with five-year survival rates exceeding now 77% in most of Europe [11], it is still lower for some diagnoses such as certain types of leukaemia, brain cancers or sarcomas [11] and is presumably much lower in developing countries, although systematic data are largely missing [1, 12, 13]. A better understanding of risk factors influencing incidence and/or survival is still required.

The vast majority of reported data in the literature suggests that social factors, in particular the level of socioeconomic development of a country, have an impact on childhood cancer incidence and survival rates [1, 11, 14]. This is reflected in the reported higher incidence and survival rates in high-income countries [3, 4, 11, 15, 16], particularly for leukaemia, compared to low- and middle-income countries, especially in Sub-Saharan Africa [2, 13, 17, 18]. However, the geographical incidence patterns are increasingly put into doubt by raising the issue that under-diagnosis and under-reporting may at least partially explain those differences [19, 20]. This may be due to differences in access and utilization of health care services, high prevalence of other competing diseases (e.g. malaria, HIV/AIDS, tuberculosis) with sometimes cancer-like symptoms, high proportions of deaths from unknown causes and lack of systematic disease registration [20].

Recent, albeit inconsistent findings suggest that social and family factors including socioeconomic position (SEP), family structure and family size as well as place of residence and accessibility of treatment facilities could be associated with survival from childhood cancer not only in developing countries but also in high-income countries [21-29].

The overall aim of this dissertation was to use the childhood cancer networks established at the International Agency for Research on Cancer (IARC) to gain further insight in social inequalities in childhood cancer – at the national level within a country, but also between countries with different socioeconomic development. The cancer registry of South Africa was used for the first time to systematically quantify the registered burden of childhood cancers at national level and study stratification by racial groups. Since race is highly correlated with socio-cultural factors including SEP and access to private health care services in South Africa [30], differences in the reported incidence by racial groups might be at least partly explained by case under-ascertainment. No systematic follow-up of patients is performed in the South African cancer registry, so that the quantification of childhood cancer as public health problem also aims at supporting improved monitoring of occurrence and survival in the future.

The role of social and family factors in survival from childhood cancer was investigated in two high-income countries, namely Germany and Denmark, countries with uniform access to health care and standardised treatment for childhood cancers [31-33]. From a public health perspective the goal was to potentially identify families that require a more targeted approach to benefit from recent survival improvements.

Family characteristics were also associated with risk of childhood cancer in previous studies, although they were used as proxy measures of specific exposures. For instance, birth order was used as a proxy for child's exposure to infectious agents [34, 35]. If these exposures are associated with the risk of developing cancer, they may also be related to risk of relapse and, consequently, survival [36]. Thus, it is important to have solid evidence for both risk and survival, but also for the former the literature is not entirely consistent [37-41] and large-scale systematic studies are still needed. For that reason, investigating the role of birth order concerning childhood cancer risk at a nationwide level in Denmark is also part of this thesis.

The overall and specific objectives of this dissertation are further defined in Chapter 5 of this thesis.

List of articles

The doctoral dissertation is based on seven conceptually independent but topic-wise interrelated studies focusing on different social and family aspects of childhood cancer incidence and survival (or certain types of childhood cancer) complementing one another. Four studies were conducted as the leading author and serve as the core manuscripts for this thesis; three studies were co-authored and their findings further contribute to the content of this thesis *(article II, V and VII)*.

The following articles are the basis for this thesis. They are referred to in the text by their Roman numerals (I-VII):

I. **Erdmann F**, Kielkowski D, Schonfeld SJ, Kellett P, Stanulla M, Dickens C, Kaatsch P, Singh E, Schüz J: Childhood cancer incidence patterns by race, sex and age for 2000-2006: A report from the South African National Cancer Registry. *International Journal of Cancer* 2015, 136(11):2628-2639. **(core manuscript)**

II. *Schonfeld SJ, **Erdmann F,** Wiggill T, Babb C, Kellett P, Singh E, Schüz J: Hematological malignancies in South Africa 2000-2006: Analysis of data reported to the National Cancer Registry. (in preparation) (co-authorship)*

III. **Erdmann F**, Kaatsch P, Zeeb H, Roman E, Lightfoot T, Schüz J: Survival from childhood acute lymphoblastic leukaemia in West Germany: does socio-demographic background matter? *European Journal of Cancer* 2014, 50(7):1345-1353. **(core manuscript)**

IV. **Erdmann F,** Kaatsch P, Schüz J: Family circumstances and survival from childhood acute lymphoblastic leukaemia in West Germany. *Cancer Epidemiology* 2015, 39(2):209- 215. **(core manuscript)**

V. *Simony KS, Lund LW, **Erdmann F**, Andersen KK, Winther JF, Schüz J, Johanson C, Schmiegelow K, Dalton SO: Effect of socioeconomic position on survival after childhood cancer in Denmark. Submitted to Lancet Oncology. (co-authorship)*

VI. **Erdmann F**, Winther JF, Dalton SO, Lightfoot T, Zeeb H, Simony KS, Deltour I, Ferro G, Bautz A, Schmiegelow K, Schüz J: Family characteristics and survival from childhood haematological malignancies in Denmark, 1973-2006. Submitted to Leukemia. **(core manuscript)**

VII. *Schüz J, Luta G, **Erdmann F**, Ferro G, Bautz A, Simony KS, Dalton SO, Lightfoot T, Winther JF: Birth order and the risk of childhood cancer in the Danish birth cohort of 1973-2010. Submitted to European Journal of Epidemiology. (co-authorship)*

1 Health in children

1.1 Morbidity and Mortality in children

The population age structure differs across the world. About 17% of the population of high-income countries are children younger than 15 years, with slightly more boys than girls (estimates from the United Nations Population Division's World Population Prospects for 2012) [42]. Because of high birth rates on one hand, but also fairly high death rates and low life expectancy on the other hand, the population age structure in developing countries differs considerably from the age structure in developed countries [1]: Almost 40% of the population in low-income countries are younger than 15 years, while it is 32% in lower-middle-income countries and 22% in upper-middle-income countries, respectively [42]. Nearly 90% of the world's children live in low- and middle-income countries.

As well as differences in age structure between developed and developing countries, there are similarly differences in the burden of disease, mortality rates and causes of deaths.
While the under-five mortality in 2012 in high-income countries was 6.6 per 1,000 live births, it was substantially higher in low-income countries, with a rate of almost 80 per 1,000 and as high as 95 per 1,000 in Sub-Saharan Africa [42]. The causes of under-five mortality are predominately neonatal conditions (including preterm birth complications), communicable diseases and nutritional deficiencies, but vary widely between regions (with substantial variation across regions with similar level of socioeconomic development) and for infants younger than 1 month versus children aged 1-59 months [43]. While the causes of neonatal mortality are similar across populations (neonatal disorders and preterm birth), the causes of post neonatal mortality vary by region. For instance, in Sub-Saharan Africa for children aged 1 – 59 months diarrhoeal diseases, lower respiratory infections, Malaria, HIV/ AIDS and nutritional deficiencies are the most important causes of deaths. By contrast, in high-income countries, main causes include injuries, the sudden infant death syndrome and other non-communicable disease [43].
According to WHO mortality data for 2008, in children aged 5-14 years the most common cause of disease-related death in children was cancer in high-income countries (32.4%), with more than 5-times as many deaths from cancer as from communicable diseases [1]. In low-

and middle-income countries deaths from communicable diseases dominate cancer deaths in all age groups, although due to improving economic development the ratio between communicable and non-communicable becomes smaller. In children aged 5-14 years in low-income countries, about 18-times more deaths result from infections and parasitic diseases than from cancer, compared to about 2-times as many in upper-middle-income countries [1]. The burden of communicable disease varies considerably between and within developing regions. In Sub-Saharan Africa, similar to the mortality in children aged 1-59 months, diarrhoeal diseases, lower respiratory infections, Malaria and also HIV/ AIDS are the major causes of deaths in children under 15 years [43].

Malnutrition in children is still a major public health issue in most low- and lower-middle-income countries, with a prevalence of about 23 – 26% in children under 5 [42]. On the contrary, with an estimated prevalence of 3.3% for children under 5 years in upper-middle-income countries and of 1% in high-income countries (in the WHO Global Database on Child Growth and Malnutrition) [42] malnutrition is of minor relevance for those countries. There, however, the prevalence of overweight and obesity has substantially increased over the past decades. According to the Global Burden of Disease Study, about 24% of boys and 23% of girls aged 2-19 years were overweight or obese in 2013 [44]. However, the prevalence of overweight and obesity is also rising in children and adolescents in developing countries. With a prevalence of approximately 13 % in 2013 [44] overweight and obesity has become a major global health challenge, as chronic diseases including diabetes, cardiovascular disease, cancer and osteoarthritis in later life may be a consequence of overweight and obesity in early life [44].

1.2 Cancer in children

The term childhood cancer is most commonly used to describe cancers that occur in patients younger than 15 years of age [2], although this is an arbitrary cut-off and in practice based on convenience as many childhood cancer registries collect case information of children up to the age of 15 (or are sufficiently complete in their collection of case information up to this age). An alternative definition for childhood cancer, frequently used in the US, is cancers that occur in patients younger than 20 years [4, 45].

The spectrum of cancers in children compared to adults is very different. Haematological malignancies represent 40 – 60% of all cancers in the first 15 years of life [2, 3, 15], while they make up less than 10% in adults in developed countries. Structure of childhood leukaemia by types also differs from a structure of adult leukaemia. Several histological types of solid tumours almost exclusively occur in childhood, especially Wilms tumour, neuroblastoma and rhabdomyosarcoma. Tumours of the central nervous system (CNS) are the most common solid tumours in children; pilocytic astrocytoma and medulloblastoma are the most frequent types of brain tumours that almost exclusively occur in childhood [46]. There are also differences between childhood and adulthood cancers in terms of cancer origin and various clinical characteristics. The biological nature of cancers in childhood is clinically, histopathologically, and biologically distinct from that of adult-onset malignancies.

Childhood cancers tend to have short latency periods, are often rapidly growing and aggressively invasive, are rarely associated with exposures to carcinogens which are associated with adult onset cancers, and are generally more responsive to standard modalities of treatment, in particular, chemotherapy [47]. Unlike cancer in adults, many childhood cancers develop as a result of abnormal cell maturation. The tissue of tumour origin, rather than tumour location in the body, is the best predictor of tumour behaviour, and following prognosis and treatment [47].

For this reason a separate classification system for childhood cancers has been developed, based on the morphology and topography axes of the International Classification of Diseases for Oncology (ICD-O) [48] which is the main coding system for adult cancers. However, while most cancers in adults are classified according to topography, the internationally recognised childhood cancer classification is based mainly on morphology [49, 50]. The current standard for childhood cancer is the third edition of the International Classification of Childhood Cancers (ICCC-3), which classifies tumours coded according to the ICD-O-3 nomenclature into the 12 major diagnostic groups [49] shown in Table 1. Although tumours of benign or uncertain behaviour are generally not reported in cancer statistics for adults, the ICCC includes non-malignant intracranial and intraspinal tumours in categories III and X [49] due to similarities with malignant tumours in their clinical symptoms and prognosis.

Table 1: The 12 major diagnostic groups as well as subgroups of leukaemia and lymphoma of the International Classification of Childhood Cancer, third edition [49].

	ICCC-3 diagnostic group	**Term/Abbreviation used in this report**
I	Leukaemias, myeloproliferative disease and myelodisplastic diseases	Leukaemias
I a	Lymphoid leukaemias	ALL
I b	Acute myeloid leukaemias	AML
I c	Chronic myeloproliferative diseases	
I d	Myelodysplastic syndrome and other myeloproliferative diseases	
I e	Unspecified and other specified leukaemias	
II	Lymphomas and reticuloendothelial neoplasms	Lymphomas
II a	Hodgkin lymphomas	HL
II b	Non-Hodgkin lymphomas (except Burkitt lymphoma)	NHL
II c	Burkitt lymphoma	
II d	Miscellaneous lymphoreticular neoplasms	
II e	Unspecified lymphomas	
III	CNS and miscellaneous intracranial and intraspinal neoplasms	CNS tumours
IV	Neuroblastoma and other peripheral nervous cell tumours	Sympathetic nervous system tumours
V	Retinoblastoma	Retinoblastomas
VI	Renal tumours	Renal tumours
VII	Hepatic tumours	Hepatic tumours
VIII	Malignant bone tumours	Malignant bone tumours
IX	Soft tissue and other extraosseous sarcomas	Soft tissue sarcomas
X	Germ cell tumours, trophoblastic tumours, and neoplasm of gonads	Germ cell tumours
XI	Other malignant epithelial neoplasm and melanomas	Malignant epithelial neoplasms
XII	Other and unspecified malignant neoplasm	Other & unspecified malignant tumours

Leukaemia

Leukaemias are cancers of the blood causing the bone marrow to produce abnormal white blood cells. Leukaemia is classified according to the type of white blood cells it affects as either lymphoblastic leukaemia or myeloid leukaemia and according to how quickly it develops as acute or chronic; acute lymphoblastic leukaemia (ALL) is the most common type in children. Symptoms especially of ALL are relatively unspecific and include fatigue, fever and infections, weight loss, pallor, bruises, a fine rash of dark red sports, breathlessness,

swelling of the abdomen and swollen lymph glands. Some children may experience pain in the bones as result of increased bone marrow activities. Blood tests, bone morrow aspiration and biopsy and lumbar puncture are the most important diagnostic tests for leukaemia [51].

Treatment and prognosis depend, among other factors, on the type of leukaemia. Treatment for ALL typically spans 2 – 2.5 years and includes three phases: induction of remission, intensification (or consolidation), and maintenance (or continuation) [51, 52].

Lymphoma

Lymphomas are cancers that originate in the body's lymphatic tissues. Lymphomas are divided into two broad types, depending on the appearance of their malignant cells, Hodgkin and non-Hodgkin lymphomas including the subgroup of Burkitt lymphoma. Each of these types also has several subtypes. Children with Hodgkin lymphoma (HL) typically have abnormal cells called Reed-Sternberg cells (a cancerous B-lymphocyte) in the cancer-affected lymph nodes. In non-Hodgkin lymphoma (NHL), there is a malignant growth of specific types of lymphocytes which is also seen in ALL. In general, people with lymphoma have no or only minimal bone marrow involvement, whereas those with leukaemia have extensive bone marrow involvement [53]. The commonest places for lymphoma to be found are lymph nodes in the neck, liver, or spleen. Most common symptoms of lymphoma include painless swellings in the neck, armpit or groin; and more general symptoms are fever, night sweats, difficulty in breathing and weight loss [53]. Hodgkin lymphomas tend to be relatively slowly growing, whereas the majority of non-Hodgkin lymphomas are highly aggressive and fast growing. The most important diagnostic test is a lymph node biopsy [53]. Type of lymphoma determines treatment and prognosis; Hodgkin lymphoma is one of the most curable forms of childhood cancer [54].

Central nervous system (CNS) tumours

Together, the brain and spinal cord make up the central nervous system. There are many types of CNS tumours in children with most of them occurring in the brain. CNS tumours are classified by the affected cell type and in children astrocytomas (originating from astrocytes), medulloblastomas (originating from cells left from the earliest development of the body in the womb) and ependymomas (ependymal cells) are the most common ones. CNS tumours

are formed by the abnormal growth of cells and may be begin or malignant. Both benign and malignant brain tumours can cause severe symptoms and need treatment. Presenting features are mainly dependent on the location within the brain or spinal cord, the size of the tumour and how fast the tumour grows. Tumours in any part of the brain may raise the pressure inside the skull, causing headache, nausea, vomiting, seizures, strabismus and loss of vision, coordination and balance [55]. Diagnostic imaging such as magnetic resonance imaging and computer tomography are used for diagnosis. Treatment is based among others on the type of tumour, position, tumour size and age of the child [55].

Sympathetic nervous system tumours/ Neuroblastoma

Neuroblastoma develops from nerve cells called neuroblasts and most commonly originates from the tissue of the adrenal glands, the triangular glands on top of the kidneys. Neuroblastoma has a diverse pattern of clinical presentation and prognosis that ranges from spontaneous regression to metastatic tumours. It is the most common cancer diagnosed in infancy [56]. In a few cases, the tendency to get this type of cancer can be passed down from a parent to a child (familial type), but most cases of neuroblastoma (98%) are not inherited (sporadic type) [56]. The first symptoms are often vague and may include irritability, fatigue, loss of appetite, and fever [56]. Symptoms depend on primary tumour locations and metastases if present. Treatment of neuroblastoma depends on the stage of the cancer, the age and other prognostic markers.

Retinoblastoma

Retinoblastoma is the most common neoplasm of the eye in children and grows in the retina, a layer of nerve tissue in the back of the eye. Retinoblastoma affect very young children [57]. Two clinical forms of retinoblastoma are identified: 75% of all cases present with unilateral retinoblastoma (only one eye affected) and 25% with the bilateral form. Children with bilateral retinoblastoma carry a specific germline mutation (of the RB1 gene). The mutation is in 25% of all cases inherited from an affected parent and in 75% of all cases results from a de novo mutation *in utero* [57]. Visible symptoms include odd-looking pupil (looking white and reflecting light) and swelling of the eye. Treatment is risk-adapted by intraocular and extraocular stage, laterality and potential for vision [57].

Renal tumours

The most common form of kidney tumours in children is Wilms tumour. Most Wilms tumours are unilateral, but about 5% of children with Wilms tumors have bilateral disease [53]. The most common signs are a lump often larger than the kidney itself in the child's abdomen and abdominal pain, blood in urine and, more general, hypertension, nausea, constipation and fever [53]. Common tests to diagnose kidney tumours include blood and urine tests as well as diagnostic imaging. The primary treatment of all renal tumours in children is surgical removal [53].

Hepatic tumours

There are two main types of malignant hepatic tumours in children: Hepatoblastoma usually occurs in children under the age of three years, and hepatocellular carcinoma in older children. The most common sign is a lump or swelling in the abdomen, which can be painful. Other possible symptoms include weight loss, a loss of appetite, nausea and vomiting [53]. Diagnostic procedures include diagnostic imaging, blood tests and biopsy. Treatment of malignant liver tumours depends on staging [53].

Malignant bone tumours

Malignant bone tumours occur most often in teenagers. The two most common types of bone cancer in children are osteosarcoma and Ewing sarcoma. About 80% of childhood osteosarcomas develop at the ends of the long bones that form the knee [53]. However, osteosarcoma can develop in any bone of the body. Ewing sarcomas are more likely occur in pelvis, ribs or spine [53]. The most common symptoms are localised bone pain. This can be accompanied by tenderness, swelling and fever. The grading largely determines prognosis and treatment strategy [53].

Soft tissue sarcomas

Soft tissue sarcomas are a diverse group of cancers that develop in soft tissue around muscles, fat, blood vessels, lymphatic vessels, nerves, ligaments and tendons, which connects, supports, or surrounds bones and organs [53]. Rhabdomyosarcoma is the most common type of soft tissue sarcoma in children which usually affects infants and young children. It tends to occur in the head and neck area, bladder, vagina, and, in or around the

prostate and testes. In comparison to other cancers, sarcomas tend to occur in extremities of the body [53]. Symptoms are specific to the affected area. Some children may present with lump on specific sites, nasal, vaginal or rectal bleeding, headache, sinusitis, persistent ear, nasal discharge or bulging eyes. The primary treatment is surgical removal.

Germ cell tumours

Germ cell tumours are made of varied group of cancers that originate from cells that normally develop into gonads (testes in boys, and ovaries in girls) usually then affecting the gonads, but they can also occur in other parts of the body such as pelvis, brain and chest [53]. Treatment usually includes either surgery or chemotherapy, or often a combination of the two.

Epithelial tumours and melanoma

Epithelial cells form outer layer of skin and line internal cavities in the body. Most glands are usually composed of epithelial cells. Melanoma, although very rare, is the most common skin cancer in children, followed by basal cell carcinomas and squamous cell carcinomas. Melanoma typically occurs as skin cancer. It originates from the cells which produce pigment defining colour of skin hair and eye (melanocytes). The cancer does not present symptoms [53]. Exposure to ultraviolet radiation and a light skin type have been shown to be the main causes of skin cancer [58]. Diagnosis usually follows discovery of suspicious lesion which changes size, colour, itching or bleeding [53]. Treatment depends on the stage of melanoma and includes typically surgery to remove the lesion which might be sufficient for children with localized melanoma or non-melanoma skin cancer.

2 Incidence, aetiology and risk factors of childhood cancer

2.1 Incidence and geographical patterns of childhood cancer

Population-based cancer registries around the world report overall incidence rates of childhood cancer in under 15 years olds that vary between 50 and 200 per million children per year [59].

The incidence is well described for economically developed countries [60-62]. For instance, recent age-standardised incidence rates of 164, 178, and 157 per million children have been reported in Germany [3], US Whites [4], and Australia [15], respectively. According to the Automated Childhood Cancer Information System (ACCIS) database the incidence of cancer in children under 15 years of age during 1988-1997 was 139 cases per million for Europe overall, ranging from 131.1 in the British Isles to 160.1 in Northern Europe. When looking at individual countries, the highest incidence was reported for Finland (173 per million children) [61]. The incidence rates vary between age groups and sex, with highest rates in infants (< 1 year) but just slightly lower at age 1 – 4 years; incidence rates at ages 5 – 9 years and 10 – 14 years are similar to each other but substantially lower in the first 5 years of life. Boys of any age have a higher risk of cancer than girls (sex ratio boys to girls: 1.2) [3, 61].

In contrast, high quality data in less economically developed countries and, in particular, in Sub-Saharan Africa are limited [1]. From Sub-Saharan Africa childhood cancer incidence rates of 35, 120, and 174 per million were reported from Gambia [17], Zimbabwe (Harare city) [18] and Kyadono (including the city of Kampala) in Uganda [17]. It is noteworthy that data for Zimbabwe and Uganda are from restricted geographical regions including major urban centres of their countries.

The spectrum of tumour types in children differs across populations [3, 4, 15, 17, 63, 64]. In high-income countries patterns are quite consistent across regions: leukaemias are the most frequent childhood cancer (with 32% of all childhood cancer for Europe and 34% for Germany) with ALL accounting for up to 25% of all childhood cancers, followed by CNS tumours (22 - 24%), lymphomas (11%) and, lastly, other solid tumours than CNS tumours [3, 15, 16, 65]. In contrast, in Sub-Saharan Africa, NHL (Burkitt's lymphomas) and Kaposi

sarcoma are more frequent cancer types due to the specific exposure to infectious diseases in that region (namely Epstein-Barr virus, malaria, HIV and human herpes virus 8) [1, 66, 67]. HL is more commonly recorded in developed countries and within those populations, it is more common in individuals with higher SEP [7, 68].

Incidence rates vary by cancer type, but all individual childhood cancer types are very rare: for instance, there are only about 50-55 leukaemia cases per million children and about 2-3 hepatic tumour cases per million children in populations of developed countries [3, 15, 16]. Young children (aged 0-4 years) have a somewhat different spectrum of cancers than older children, as most cases of retinoblastoma, neuroblastoma, Wilms' tumour, embryonal rhabdomyosarcoma, hepatoblastoma, and infantile embryonal carcinoma occur in younger children. In children aged 5 – 14 years, sarcomas are more common. Haematological malignancies and brain tumours occur in all age groups [1, 3], but there is a pronounced age peak among 2-5 year olds for ALL [3]. Figure 1 shows as an example the distribution of childhood cancer types in Germany in 2012. Figure 2 shows the distribution of cancer types globally, using data from countries with population-based cancer registries.

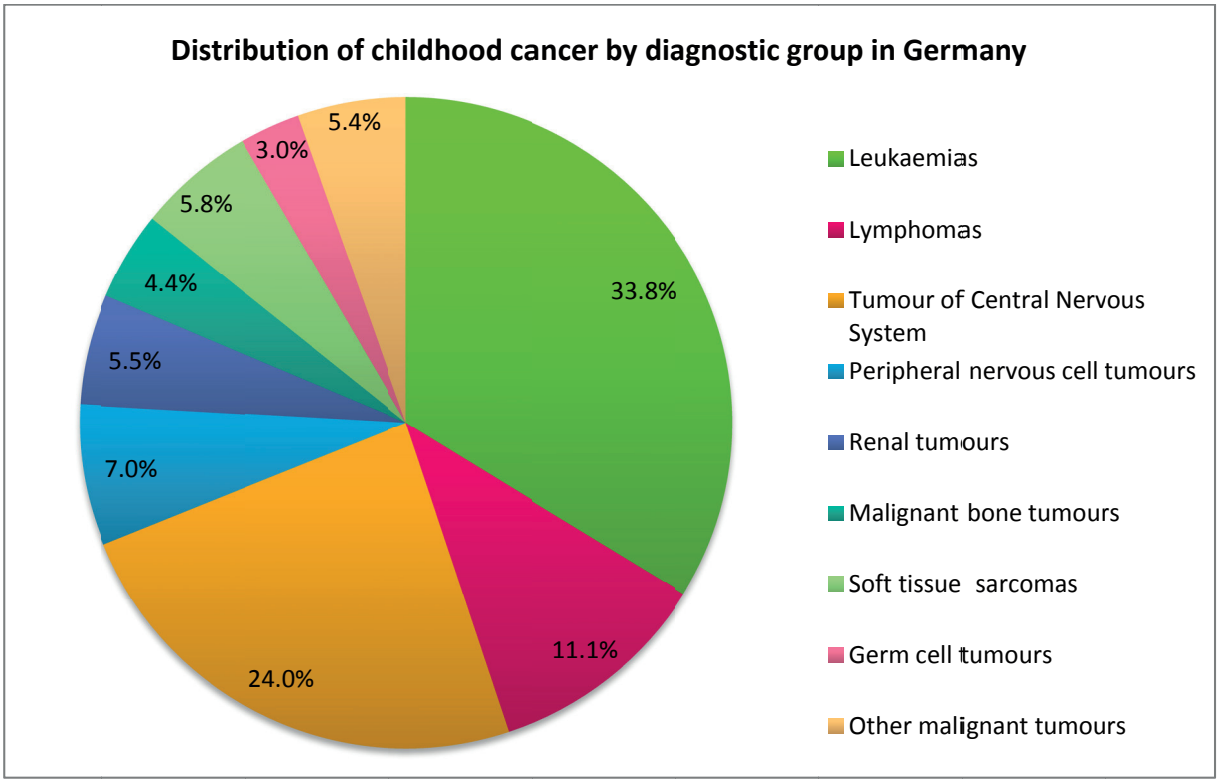

Figure 1: Reported cancers in children (under 15 years of age) in Germany for 2003 – 2012 by diagnostic group (defined by (ICCC-3), based on data from the German Childhood Cancer Registry [3].

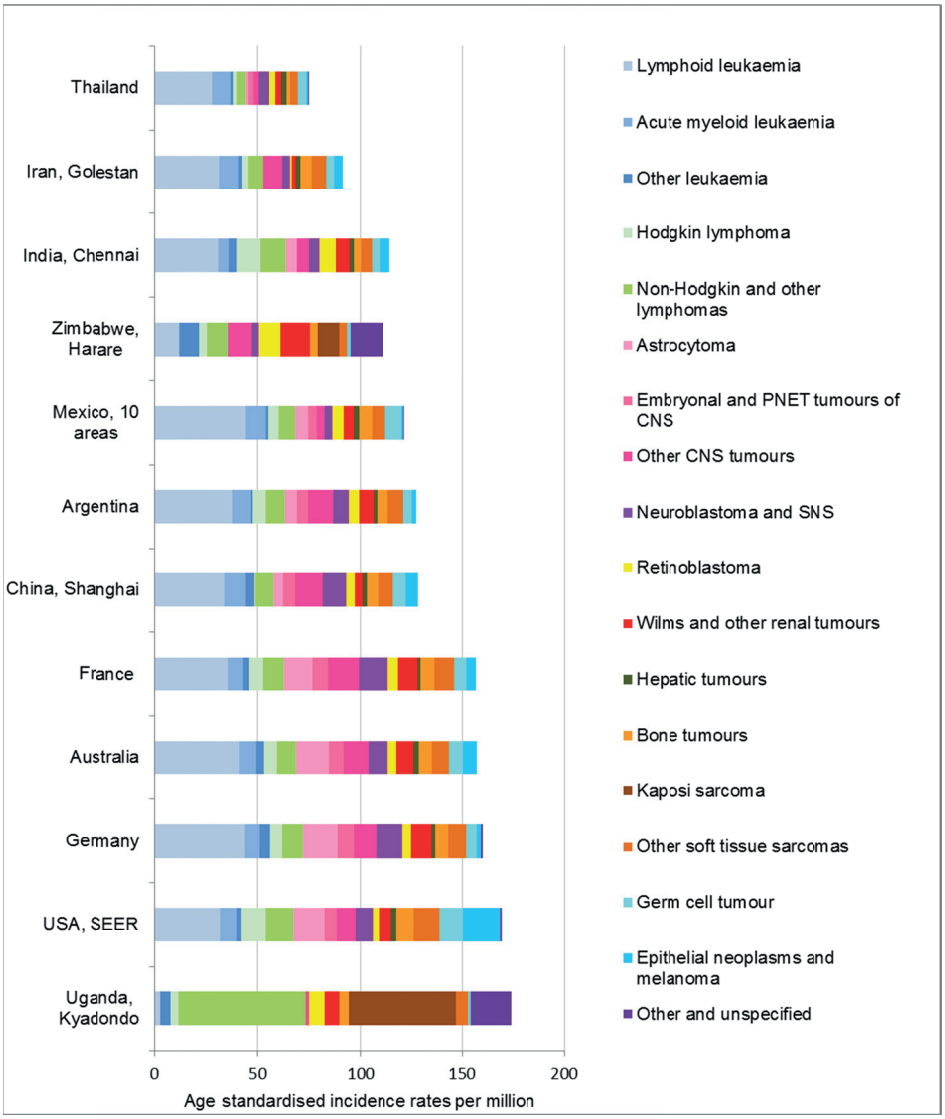

Figure 2: Incidence rates and distribution of cancers in children (under 15 years of age) in selected populations in the 1990s and 2000s. Reproduced from reference [2], by permission of the International Agency for Research on Cancer.

However, reported incidence rates do not only vary by between regions but also by ethnicity/ race within countries. Significant variations in incidence rates according to race are reported for the US [4]. With 173 per million aged 0-19 years in 2001-2003, White children had the highest cancer incidence of any race and an approximately 1.5-fold higher rate than Blacks. This difference was particular pronounced for leukaemia (1.8-fold higher) but smaller in lymphomas (1.3-fold higher) [45]. A large population-based case-control study of more than 13,000 cases confirmed that Black children have a decreased risk of childhood cancer compared to Whites in the US. Among both the Black population and children of mixed

White/Black ancestry, cancer rates were approximately 28% lower than that of Whites, whereas estimates for White/Asian as well as White/Hispanic children did not differ from those for Whites [69]. Authors speculated that different racial/ethnic groups may vary in terms of their environmental exposures and that there might be important interactions between selected exposures and underlying genetic susceptibility [69].

According to the data from population-based cancer registries, the overall incidence rate of childhood cancer has been increasing by about 1% per year over the last three decades in Europe, North America, Australia [3, 15]. The rate of increase is observed to have slowed down since the turn of the millennium. However, these temporal trends might be also related to improved diagnosis and more complete reporting of childhood cancer, although effects of changes in exposure and lifestyle cannot be excluded and remain a plausible explanation.

There is evidence that social factors, in particular level of socioeconomic development of a population, are related to the reported incidence of childhood cancer in the respective country [1, 14]. This is consistent with the higher reported incidence rates in high-income countries [3, 4, 15, 16] compared to low- and middle-income countries [1, 17, 63, 64, 70], especially Sub-Saharan Africa, and is particularly pronounced for leukaemia [17]. Observed geographical differences in incidence rates have been used to support several hypotheses of the association between exposures related to modern lifestyle and the risk of childhood cancer, particularly childhood leukaemia [34]. These include factors related to social contacts and patterns of infection or infectious contacts in early life [34], but also maternal diet during pregnancy [71], parental occupational exposures prior to conception or during pregnancy [6, 72], and exposures to electromagnetic fields [73] (see Chapter 2.2).
However, comparing international childhood cancer rates is challenging because of different diagnostic and reporting standards across countries. Recent studies from Brazil and India suggest that under-reporting of ALL may be sufficiently large to account for most, if not all, of the observed differences between these countries compared with Europe and North America [74, 75]. Less though is known on potential under-diagnosis and under-reporting in most of African or Asian countries [1], where registries are facing various challenges with respect to capturing information on cases. In these regions, many (young) cancer patients

may not even reach a physician/ a clinic, hence no treatment or misdiagnosis are major issues, and linkage between cancer registries (if they exist) and hospitals are not always in place [1, 14, 20, 76]. Geographical differences in incidence rates may also suggest unique genetic or environmental exposures that affect the risk of childhood cancer (or certain types of childhood cancer). However, for most of African or Asian countries the extent of under-diagnosis under-reporting remains unclear at present. The degree of incomplete ascertainment may vary by cancer type, race/ethnicity, sex or age [77], depending for instance on the fatality of the cancer, whether ethnicities/ racial groups have similar access to health care, gender-based differences in some cultures, or competing risks in certain ages (e.g., infant mortality due to infections [78]).

2.2 Risk factors of childhood cancer

As previously stated, childhood cancer is a heterogeneous group of malignancies with different aetiologies. Given the challenges related to childhood cancer epidemiology due to this great heterogeneity, coupled with low incidence rates, evidence regarding causal factors has accumulated slowly. Little is still known about the aetiology of these cancers, but it appears that genetic, intrinsic as well as environmental factors play a role [6-8]. The early age at diagnosis indicates that childhood cancer might originate *in utero*, and that factors prior to birth, including preconception and/or foetal environmental exposures, as well as those in early childhood may be important determinants [7, 10, 34]. For example for ALL, some genetic aberrations have been detected in neonatal blood spots of healthy children that later developed the disease [79], providing evidence of the initiation of at least some types of ALL prior to birth.

A few chromosomal and genetic conditions, exposure to high-dose ionizing radiation and prior chemotherapy, and birth weight are confirmed risk factors [7, 8] but explain only a small percentage (<10%) of all cases. Children with Down syndrome (trisomy 21) are at 10-20-fold higher risk to develop leukaemia in comparison to general children [80]. In nearly all patients with retinoblastoma germ line mutations in the RB gene cause the disease. These patients are also at increased risk of other cancers [57]. There are numerous other syndromes which are related to an extremely high cancer risk, such as Li-Fraumeni

syndrome, Gorlin syndrome and other [81, 82]. However, these syndromes are rare and explain only a small minority of all childhood cancers [7].

Exposure to infections has been one of the most extensively studied environmental exposures in relation to ALL risk, with two major hypotheses regarding the nature of this relationship. Kinlen [83] initially hypothesized that previously isolated, and thus immunologically naïve, rural populations are susceptible when exposed to unfamiliar infections because of population mixing. Later this was expanded to include in general children with more social contacts and thereby potential for exposure to infections. Meta-analyses give some support to the hypothesis, with most evidence coming from specific settings in the UK [84], for example around nuclear power plants or other major construction sites. Greaves' "delayed infection" hypothesis suggests that ALL (or, to be more precise, its most common subtype called common-ALL) results from an unregulated immune response from an immature and unchallenged immune system caused by delayed exposure to common infections in infancy [34, 85], i.e. lack of exposure to infections in infancy coupled with higher burden to infections later in life. Direct measurements of exposure to infections and the resulting immune response are not feasible. However, several proxies have been used including birth order, assuming lower potential of infections among firstborn children [10, 40], day-care attendance, assuming lower potential of infections among those not attending day-care [86], breast feeding, assuming better immunological training by those breast-fed [87], as well as directly assessing infectious illness history and vaccinations [88]. Protective effects were found for breastfeeding and day-care attendance [89, 90], although it is unclear whether exposure to infections or other factors drove these associations. For birth order, according to the "delayed infection hypothesis" it would be expected that firstborn children would have less contact with infectious agents than children with older siblings and, as such, have an increased risk of ALL. However, findings from epidemiological studies on ALL are inconclusive [37, 38, 40, 41, 91], as they are for other childhood cancers [10, 37, 39, 40, 92].

Recent pooled and meta-analyses provide some support of an increased leukaemia risk for both residential [72, 93] and maternal occupational [94, 95] exposure to pesticides. Many other promising hypotheses related to environmental factors have been studied including

history of maternal infections and medication use around the time of pregnancy [96], maternal [97] and paternal [10, 98] smoking, maternal alcohol consumption [10, 99], maternal coffee consumption [100] and vitamin use [101] and parental exposure to chemicals such as solvents and metals [7], but without conclusive evidence. Epidemiological studies have consistently shown a positive association of extremely low-frequency magnetic fields with an approximately two-fold higher childhood leukaemia risk at average 24-h exposure levels exceeding 0.3-0.4 μT [73]. A causal relationship, however, has not been established due to the potential for bias and confounding in those studies and the lack of supporting evidence from experimental studies and mechanistic data [102].
Few studies were published on gene-environment interactions, with inconsistent results to date, but this is a relatively recent approach and many more studies are in progress.

With respect to intrinsic factors of the children or their parents, birth weight was consistently found to be associated with several childhood cancers, albeit with differing patterns. Risk of ALL [103, 104], neuroblastoma [105] and Wilms tumour [106] is elevated with high birth weight with a linear rising risk with increasing birth weight, although to a varying degree. For acute myeloid leukaemia (AML) and CNS tumours [107, 108] the risk may be elevated at both high and low birth weight [103]. Very high risk in low birth weight children of hepatoblastoma was also observed [109]. The reasons behind the association of higher birth weight with childhood cancers are not fully understood but might include prenatal grow hormone exposure (insulin-like growth factor-1) [110], the underlying genetics of birth weight [111] or simply the higher number of cells at risk for carcinogenic transformation [8].
Advanced parental age has also been associated with most childhood cancers, but findings are not fully consistent across studies [10, 40, 112-115]. A large population-based cohort study from Sweden noticed no significant results for parental age in children 5 – 14 years age, but in children younger than 5 years, maternal age was associated with an elevated risk of retinoblastoma and leukaemia and paternal age with an increased leukaemia and CNS tumour risk [114]. In another Swedish investigation parental age was not found to be associated with ALL [115]. However, a recent large pooled analysis from the US observed significantly increasing risks of leukaemia, lymphoma, brain tumours, neuroblastoma, Wilms tumour, bone tumours and soft tissue sarcoma with 6% to 15% increase in risk per 5 years

advancing maternal age, while advancing paternal age was not independently associated with these cancers after adjustment for maternal age [113]. The reasons behind those observed associations are not clear, but may include genetic and epigenetic mutations related to advanced parental age.

Similar to most factors studied, findings for the association between SEP and childhood cancer risk are conflicting [40, 68, 115-119], with associations varying by study design, time period, cancer type and SEP indicator used and whether the indicator was at the individual or family level versus ecological grouping. The relationship with SEP has been most exhaustively studied for leukaemia risk, with heterogeneous results [40, 68, 115-119]. Little is known on SEP patterns of risk for other types of childhood cancer. A large pooled study from the US found an indication of a positive association with lower parental education for both Hodgkin and Burkitt lymphomas and for Wilms tumour and in contrast a possibly protective effect of lower parental education for astrocytoma (a common type of CNS tumour) and hepatoblastoma [68]. Finally, however, and irrespective of the SEP markers used, the observed associations between SEP and some childhood cancer types may reflect differences in exposure to certain risk factors of the respective cancer type that vary by socioeconomic groups.

3 Mortality, survival and prognostic factors of childhood cancer

3.1 Clinical trials and standardised treatment

Childhood cancer histologically embodies very diverse types of cancers, which are treated differently and with dissimilar survival [11]. Over the past decades, advances in tumour biology, risk grouping, and pharmacology have led to substantial improvements in treatment of childhood cancers which, alongside with advances in diagnostic procedures, have resulted in substantial survival improvements and declining mortality rates.

The longstanding integration of clinical research with front-line care in paediatric oncology is considered the most important reason for this substantial progress. First collaborative clinical research to identify effective treatment for children with cancer started in the US and dates back to the 1950s, when children with ALL were some of the earliest participants in clinical trials of new drugs for cancer treatment [12]. While the initial clinical trials primarily focused on new treatment protocols for leukaemia, the scientific agenda was soon expanded to common solid tumours, namely neuroblastoma and brain tumours. By the 1970s, every common childhood cancer was being studied as part of various collaborative clinical study groups from the US or Europe [12].

Diagnostic procedures and treatment protocols are nowadays largely standardised within developed countries [31-33, 120-122]. Almost all childhood cancer patients are treated according to the treatment schemes developed by collaborative study groups such as the Nordic Society of Paediatric Haematology and Oncology [31, 32, 120], the Berlin-Frankfurt-Münster study group (BFM) [33], the cooperative study group for childhood acute lymphoblastic leukaemia (COALL) [123], the United Kingdom Medical Research Council Childhood Leukaemia Working Party [122], the Children's Oncology Group (COG) [124] or the International Society of Paediatric Oncology (SIOP) [125], with specific treatment protocols depending on type, prognostic risk group and stage of cancer. For each cancer type several specific protocols exist for subtypes based on staging, histology, genetics and early response to treatment [12].The ongoing challenge is to maximise the chance of survival from childhood cancers while minimising the short-term and long-term side-effects of treatment [12]. Notably, however, survival remains poor for some childhood cancer types [11] and

developing countries have not benefitted from the progress made in developed countries (see Chapter 3.2). It is estimated that more than 90% of the 15,000 childhood cancer cases diagnosed annually in the EU [59] enter standardised treatment programmes. In developing countries, paediatric oncologists try to adapt the internationally established treatment protocols as best as possible but depending on the local circumstances they need to modify them. The main relevant factors include the availability of radiation facilities or chemotherapeutic agents and their related costs.

3.2 Mortality and survival from childhood cancer and geographical patterns

Nowadays, in high-income countries, survival from childhood cancer is generally good and better than for adult cancer. Survival rates for most childhood cancers, particularly leukaemia and lymphoma, improved substantially over the past decades [11, 62, 126, 127]. The 5-year survival rate from childhood cancer has increased from 30% in the 1960s to 80% nowadays in the developed world [11, 12, 62, 126-129].

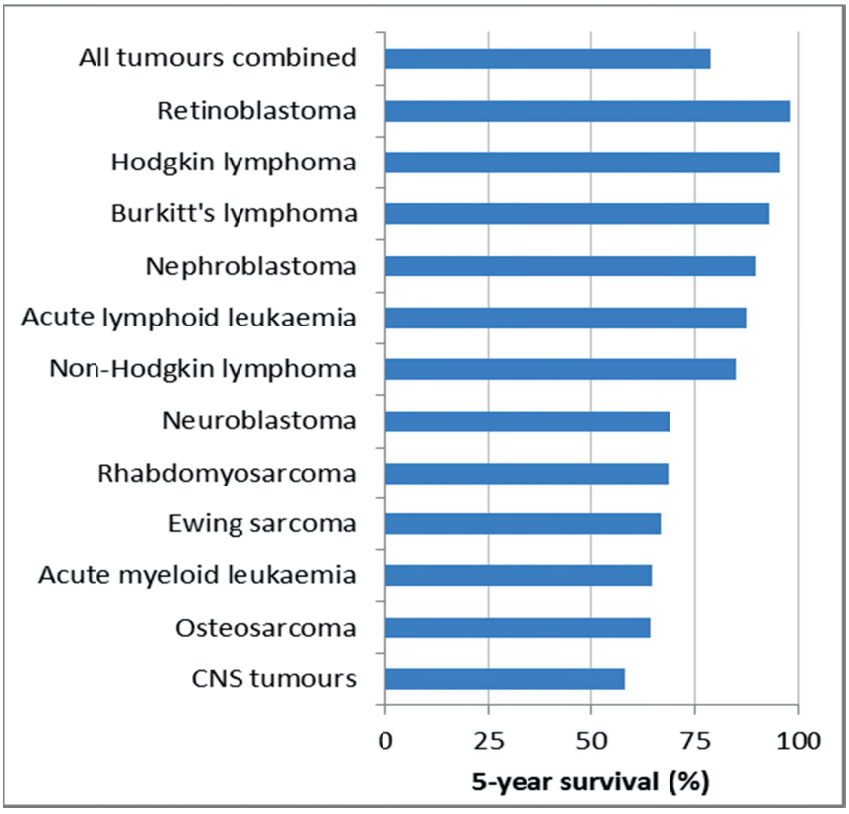

Figure 3: Country-weighted 5-year survival by ICCC-3 diagnostic groups for children (under 15 years of age) from 29 European countries diagnosed with cancer between 2000 and 2007 (EUROCARE-5 data). Figure is based on data from reference [11].

Figure 3 shows the 5-year survival for children from 29 European countries diagnosed with cancer between 2000 and 2007, presenting the most recent EUROCARE results (a European wide project on population-based cancer survival). For all childhood cancer combined survival after 5 years was 78%, however, there was considerable variation between cancer types [11]. Most haematological cancers carried favourable prognosis, with the 5-year survival ranging from 84% to 95% (86% for ALL), except for AML with less than 63% survival. The 5-year survival for CNS tumours was modest at 58% [11]. For most cancers, survival dropped considerably after the first year from diagnosis. Survival did not differ noticeably between boys and girls, but the 5-year survival of girls with ALL was slightly higher compared to boys. For all childhood cancer combined as well as just for ALL the 5-year survival was highest for children aged 1-4 years. Children aged younger than 1 year showed lowest survival for several cancers, including ALL, AML, non-Hodgkin lymphoma and most CNS tumours. In contrast, infants with neuroblastoma have good survival [11].

Despite these improvements in survival, disparities exist even between European regions. Table 2 presents the 5-year survival from childhood leukaemia diagnosed from 1999 to 2007 in Europe by regions. Survival differs obviously between European regions with lowest survival in Eastern Europe – a rather less privileged region compared to other European regions. Dissimilarities in survival persisted over the entire time period and were particular pronounced for AML [11]. Gatta and colleagues discussed that a lack of resources as well as differences in paediatric oncology services might explain these intra-European differences [11]. In recent decades, improvements in childhood cancer survival were most pronounced in Eastern Europe [11].

Table 2: 5-year age-standardised survival from leukaemia in European children (under 15 years of age) by region from 1999 to 2007. The table is based on data from reference [11].

	N (1995 – 2007)	% Survival		
		1999 – 2001	2002 – 2004	2005 – 2007
ICCC-3 Ia: Acute lymphoblastic leukaemia				
Northern Europe	2,305	84.8	87.9	86.7
UK and Ireland	5,022	81.5	87.0	89.4
Central Europe	8,565	86.1	90.0	90.1
Southern Europe	1,202	83.6	86.0	87.2
Eastern Europe	2,003	69.7	75.8	80.3
All Europe	19,097	82.2	86.3	87.6
ICCC-3 Ib: Acute myeloid leukaemia				
Northern Europe	445	66.9	71.4	67.3
UK and Ireland	1,005	65.6	61.1	66.5
Central Europe	1,525	60.8	62.8	67.3
Southern Europe	218	79.1	58.8	67.4
Eastern Europe	398	42.9	45.4	49.0
All Europe	3,591	63.3	59.5	64.4

The survival improvements are reflected in the decline in childhood cancer mortality rates. According to data from the US the childhood cancer mortality rate (in children under 20 years of age) has decreased by more than 50% between 1975 and 2006. The decrease was mainly due to the declining mortality for leukaemia (64% reduction), gonadal cancer (85%), Non-Hodgkin lymphoma and Hodgkin lymphoma (75%), and neuroblastoma and bone cancer (35-40%). The leading causes of cancer death in children are leukaemias and CNS tumours [62]. Similar decreases in mortality were also noticed in Europe [65]. The rate of decrease in mortality, however, has slowed down since the early 2000s [2] with an estimated mortality rate of 29 per million children in Europe in 2012 [59].

The substantial improvement in survival is mainly limited to high-income countries. Information on childhood cancers in middle- income countries is scarce and indicates that, despite of the different reporting periods, the proportion of 5-year survivors is much lower

in India [70], China [130] and Thailand [64] than those observed in high-income countries. Reliable population-based survival data for low-income countries do not exist, but survival is supposed to be much lower than in high- and also middle-income countries [1, 13, 14]. Mortality-to-incidence ratios give an indication of survival probabilities (Figure 4). Contrary to the reported incidence, cancer mortality is much higher in children in less-developed regions. For instance, for 2012, childhood cancer mortality in Africa was estimated as 50 per million children which represents about 60% of the estimated incidence, while in North America the mortality/incidence ratio is less than 15% (estimated mortality of 23 per million children) (Figure 4) [59]. Limited resources, organization of care, late presentation, co-morbid infections (e.g. HIV) and malnutrition are among the barriers preventing improvement in survival. Moreover, access to treatment is limited in low- and middle-income countries [1, 12]. An unknown proportion of children in less-developed countries with potentially curable cancer never receive treatment or, in fact, even be able to access basic medical services provided by a trained physician.

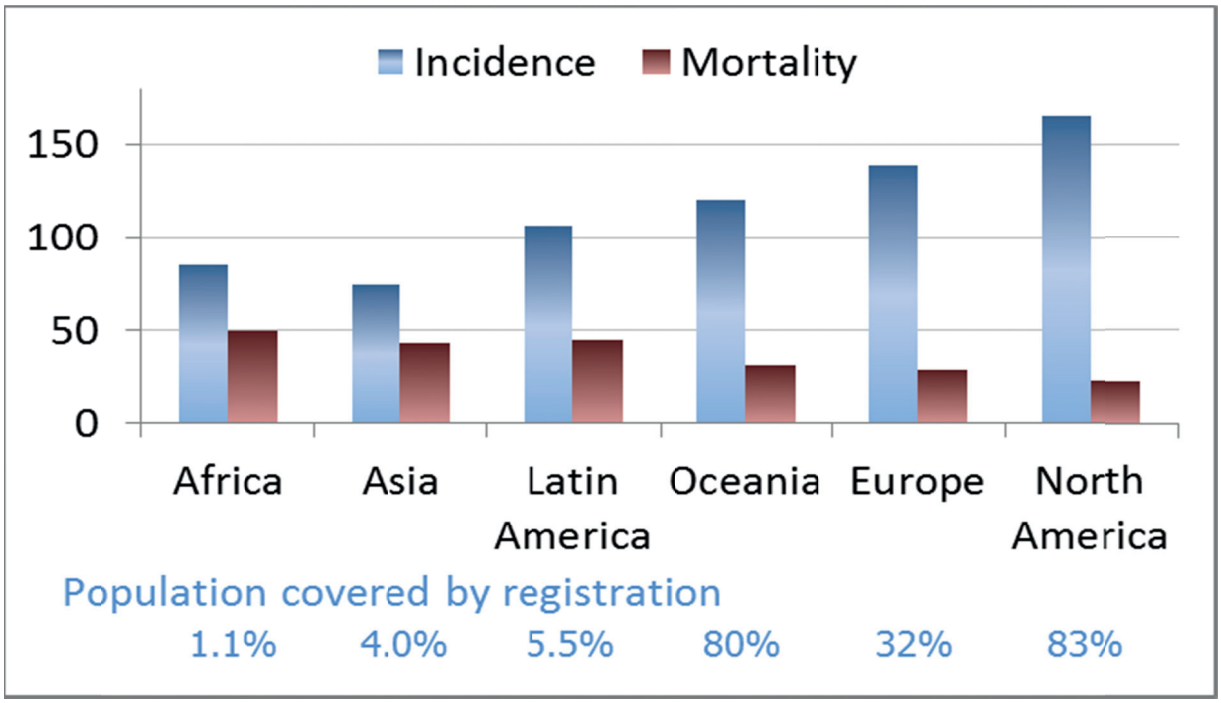

Figure 4: Estimates of incidence and mortality rates (per million) for cancer in children (under 15 years of age) in 2012 based on GLOBOCAN [59], and percentage of population coverage be cancer registration (all ages) [2].

3.3 Clinical prognostic factors

Important prognostic factors for childhood cancers are patient sex and age at diagnosis, as well as clinical parameter including disease subtype, histology, stage, grade, white blood cell count or site [51, 54, 55, 57, 62, 131]. However, patterns of prognostic factors vary considerably by type of cancer.

For ALL, clinical prognostic factors are age, sex, presenting leucocyte count, racial group, immunophenotype, recurrent chromosomal abnormalities, spread to certain organs (such as cerebrospinal fluid or testicles (boys)) and response to initial therapy [51, 52, 132]. Clinical prognostic factors for AML include age, cytogenetic and molecular markers, leukocyte count, and response to induction therapy [133]. For lymphoma age, sex, clinical stage, histology, site, chromosomal abnormalities, tumour burden and response to initial therapy are important clinical factors for prognosis [54, 134]. With respect to solid tumours, predominantly stage, histology, tumour site, tumour size and age are the most robust prognostic factors [55-57, 135]. Prognostic factors are used for the stratification of therapy as patients with high risk features receive more intensive or specific treatment [51, 54-57, 133].

3.4 Social and family factors and survival from childhood cancer

For adult cancers, it is well established that socioeconomic characteristics influence survival. More socially deprived patients have consistently inferior survival than those who are better off [136-138]. By contrast, little is known about the potential role of social and family factors in childhood cancer survival. Evidence from low- and middle-income countries is largely regional within individual countries and typically focused on leukaemia and socioeconomic factors [139-143]. Observed associations between inferior survival and low SEP [139-143] have been attributed to a range of factors including malnourishment [140, 144], and treatment abandonment [143, 145].

For developed countries, only few studies have investigated the relationship between social and family factors and survival from childhood cancer, mainly studying leukaemia survival and with diverse findings, even within Europe [21, 22, 24-26, 146-148]. The sparse evidence includes findings on SEP (with different markers used, varying considerably between studies), ethnicity/ race, number of siblings, maternal age at child's birth, parent's marital

status, attendance to day care and place of residence. An overview of the current state of evidence is given below:

Socioeconomic factors

Socioeconomic differences in childhood cancer survival have been observed in some developed populations including United Kingdom, Norway, Greece, and South Korea [21, 22, 26, 148, 149], but the evidence is inconsistent and sometimes conflicting.

Markedly higher ALL survival was observed among more affluent socioeconomic groups, measured by both area-based deprivation scores and father's occupational status, in England, Scotland and Wales [21, 148], while a similar study from Northern England [127] that used solely area measures of SEP did not find significant differences in survival for any type of childhood cancer. An exception was CNS tumours with survival being higher for children living in more deprived areas compared with those from more affluent areas [127]. For earlier time periods (before 1990) little evidence of a socioeconomic gradient in survival from ALL was reported for England and Wales [150], although small differences in survival between socioeconomic groups (3-6%) were noticed. Also a recent study from Ireland observed only weak trends in survival disparity from ALL in relation to SEP, but no clear evidence was found of a deprivation-related impact for other childhood cancers [25].

For Greece, findings from a recent nationwide study indicate an association between parental socio-professional level and ALL survival. Children diagnosed with ALL of lower SEP status experienced 40% worse survival than more privileged children [26]. The association between maternal education and ALL survival observed in previous Greek studies [146, 147] appeared to persist no longer [26]. On the contrary, a very comprehensive study from Norway on social inequalities in childhood cancer survival observed an about 15% reduced mortality rate for children with highly educated mothers [22]. Findings from the Netherlands on parental education have been less convincing and correspond to leukaemia cases diagnosed already in the 70ies [24].

Recent investigations from Ontario, Canada did not find evidence for a relationship between SEP, measured by neighbourhood income quintile and material deprivation quintile, and survival from childhood lymphoma [29] nor for an impact of SEP, defined by only neighbourhood income, on ALL survival [28]. Also in California, a US state with no universal access to health care, the SEP neighbourhood status appeared not be related to survival

from childhood leukaemia; however, lack of health insurance or an unknown status of insurance coverage was associated with inferior survival from leukaemia [27].

Race/ ethnicity

The impact of race/ ethnicity on disease outcome has been studied in several childhood cancers [151-158], although the evidence has been more extensively described for haematological malignancies than for solid tumours [159]. Poorer outcome was reported for Black children compared to White children by the majority of the studies.

For instance, large studies based on population-based data and cooperative group trials in the US noticed significant racial and ethnic differences in survival from ALL, with poor survival for Black children compared to White children but similarly inferior outcome for Hispanics [153, 160, 161]. Bhatia and colleagues reported superior outcome for Asians compared to White children [160], while a recent comprehensive investigation based on the SEER data did not confirm a generally better survival for Asians but dissimilarities in outcome by Asian subgroups [153]. However, the evidence is very limited.

These racial/ ethnic differences in childhood cancer survival may be attributable to disease biology and host pharmacogenetics but are probably also linked to socioeconomic and cultural factors, including differences in access to health care, inadequate education, advanced disease stage at presentation, adherence to therapy and disbelief in modern medicine [159]. However, some studies identified race/ ethnicity as an independent predicting factor [140, 152].

Family factors

Literature addressing a potential impact of family factors on childhood cancer survival is very rare. The large Norwegian survival study on children with cancer did not only point towards the relationship with maternal education but reported that having no siblings was associated with mortality reductions of almost 20% [22]. In contrast, a study from Greece on children diagnosed with ALL in the late 1990s-early 2000s observed better prognosis for children with increasing number of siblings [146]. However, this finding was not confirmed by the recent follow-up study. Likewise no relationship between survival from AML and number of siblings was observed [26].

No studies were identified that had addressed the possible importance of birth order on childhood cancer survival, neither of parental age at the child's cancer diagnosis. A study of mother's age at child's birth from Norway did not indicate a relationship with childhood cancer survival, whereas the most recent observations from Greece indicated better survival from AML with older maternal age [22, 26]. Findings from Greece, although not statistically significant, suggest a possible positive effect for child's attendance to day care (before diagnosis) for ALL survival [146]. Furthermore, marital status of the child's parents might be associated with survival from childhood cancer. Greek children of unmarried parents had a 2-fold increased risk of death from ALL and a 20% increased risk of AML death [26]. However, on the contrary, no effect of marital status of the parents was observed in Norwegian children [22].

Similarly, the evidence on place of residence, used as an indicator for the degree of urbanization or distance from the child's residence to the next treatment centre, is very limited. A study from Australia, a country with vast areas of very low density population, reported better survival rates for all childhood cancers and specifically leukaemia for children living in major cities compared to those living elsewhere. However, no evidence of geographical variation in survival was observed when solely looking at children with lymphoma [23]. Living in rural areas was also associated with less favourable prognosis in recent multi-national findings from Bulgaria, Turkey and Russia for survival from leukaemia as well as from lymphoma [162]. In contrast in Greece, where an earlier study found indications of a trend of poorer survival with increasing distance to treatment centre [146], this was not confirmed in more recent years, which was suggested to be linked to considerable improvements in the motorway infrastructures [26]. Likewise, no evidence of an association between living in a rural area or distance to the closest paediatric tertiary centre and ALL survival was found for children diagnosed in Ontario [28]. A study from the US investigating neuroblastoma survival based on the SEER database observed higher survival in children living in metropolitan areas versus children from nonmetropolitan areas [163].

4 Theoretical framework: Social inequality and cancer in children

Pervious chapters cite important evidence on social inequalities in cancer and specifically childhood cancer. This chapter gives an overview on the current empirical evidence around social inequalities in cancer and discuses theoretical explanatory frameworks of social inequalities in health and specifically in cancer.

4.1 Empirical evidence of social inequalities

Numerous studies have revealed strong evidence for social inequalities in health within and between countries. For instance, life expectancy at birth in 2012, ranged from 45 years in Sierra Leone to 83 years in several high-income countries including Switzerland, Japan, Iceland and France [42]. Likewise, large differences persist within countries – for example there is a 20 year gap in life expectancy between the most and the least advantaged social groups in the US [164]. Another striking example is the probability of death in men between age 15 and 60 years, with a probability of about 8% in Sweden, 80% in Zimbabwe and 90% in Lesotho. Clear socioeconomic gradients in adult mortality rates also exist within countries [164].

A large body of evidence has been published on inequalities in cancer, indicating that social inequalities similarly exist in cancer incidence, mortality and survival across countries [59, 165] as well as within countries, including high-income countries [136, 138, 166-168]. Not only do incidence, mortality and survival rates differ across populations by levels of socioeconomic development, with substantially lower survival rates in less-developed countries [169], but also the cancer spectrum differs. In high-income countries cancers of the lung, breast, prostate and colorectum are by far the most frequent cancer types. Although colorectal, breast, and lung cancers have also become more frequent in less-developed regions, poverty and infection-related cancer, such as cancers of the liver, cervix, stomach and oesophagus still contribute considerably to the cancer burden in low- and middle-income countries [165]. Irrespective of level of socioeconomic development, the major cause of cancer deaths is lung cancer. In high-income countries colorectal cancer ranks

clearly second, while, as a result of high incidence and very poor prognosis, liver, stomach and oesophagus cancer remain major causes of cancer deaths in low- and middle-income countries [165].

The evidence for social inequalities within countries derives predominately from high-income countries. Associations between socioeconomic factors and the incidence of different cancers are heterogeneous. Low socioeconomic position for instance has been associated with increased risks for cancers of the cervix, lung, head and neck, and stomach and reduced risks for cancers of the breast, colon, prostate and malignant melanoma [136, 168]. Social inequalities in adult cancer incidence can be partially explained by known risk factors related to lifestyle, occupational exposure, reproductive behaviours and biological agents [66, 136, 168, 170]. It appears that social circumstances at different times across the life course are associated with risks of different cancer types [170]. Moreover, different socioeconomic factors may point towards different mechanisms of social inequalities [170].
Evidence for social inequalities in survival has been consistently found in many populations, for many cancers and for various socioeconomic indicators [136, 138, 167, 168, 170]. More socially disadvantaged patients have poorer survival compared to more affluent patients. Underlying causes may be related to the time of diagnosis, to tumour characteristics including most importantly stage at diagnosis which has been widely recognised as differently distributed across socioeconomic groups, to the treatments received and to patient-specific factors such as life style and co-morbidities [138, 170, 171].

4.2 Theoretical frameworks of social inequalities

There are many frameworks dedicated to elucidate the social determinants of health and of health inequalities, how those determinants operate and how they can be improved to reduce social inequalities in health. Besides rather general frameworks such as those designed and used by the Word Health Organization (WHO) and their Commission for Social Determinants of Health [172] or others for example adopted for use in Germany [173, 174], some specifically focus on social determinants of cancer inequalities [175, 176].

The WHO model is a conceptual framework for action on the social determinants of health, taking note of the specific theories of the social construct of health and based on previous frameworks, including significantly the Diderichsen's model of "the mechanisms of health inequality" [172]. The WHO model intended to provide a comprehensive conceptual framework to i) identify the social determinants of health and the social determinants of health inequalities; ii) point out how major determinants relate to each other; iii) illustrate the mechanisms by which social determinants create health inequalities; iv) provide a framework for evaluating which are the most important determinants to address and v) to map specific levels of intervention and policy entry points for interventions on social determinants of health [172]. Figure 5 shows the comprehensive WHO model. It illustrates how social, economic and political mechanisms have an effect on socioeconomic position, whereby populations are stratified by income, education, occupation, ethnicity/race, gender and other factors ("structural determinants"). Socioeconomic positions in turn constitute specific determinants of health reflective of people's rank in social hierarchies. These "intermediary determinants" include material circumstances, behaviours and biological factors, psychosocial factors as well as the health system and impact directly on health and well-being. Poor health in turn, can also feed back on a given individual socioeconomic position [172] to negatively impact and lower a person's position.

The WHO model differentiates clearly between the social cause of health and well-being and the factors assigning the distribution of theses causes between different socioeconomic positions. Together, socioeconomic and political context, socioeconomic position of individuals and the structural mechanisms between these two are the "structural determinants". These are the determinants of health inequalities and they operate through a set of the intermediary determinants of health (social determinants of health) to ultimately impact health and well-being [172]. By understanding the health care system itself as a social determinant of health, the WHO model departs from many previous models [172].

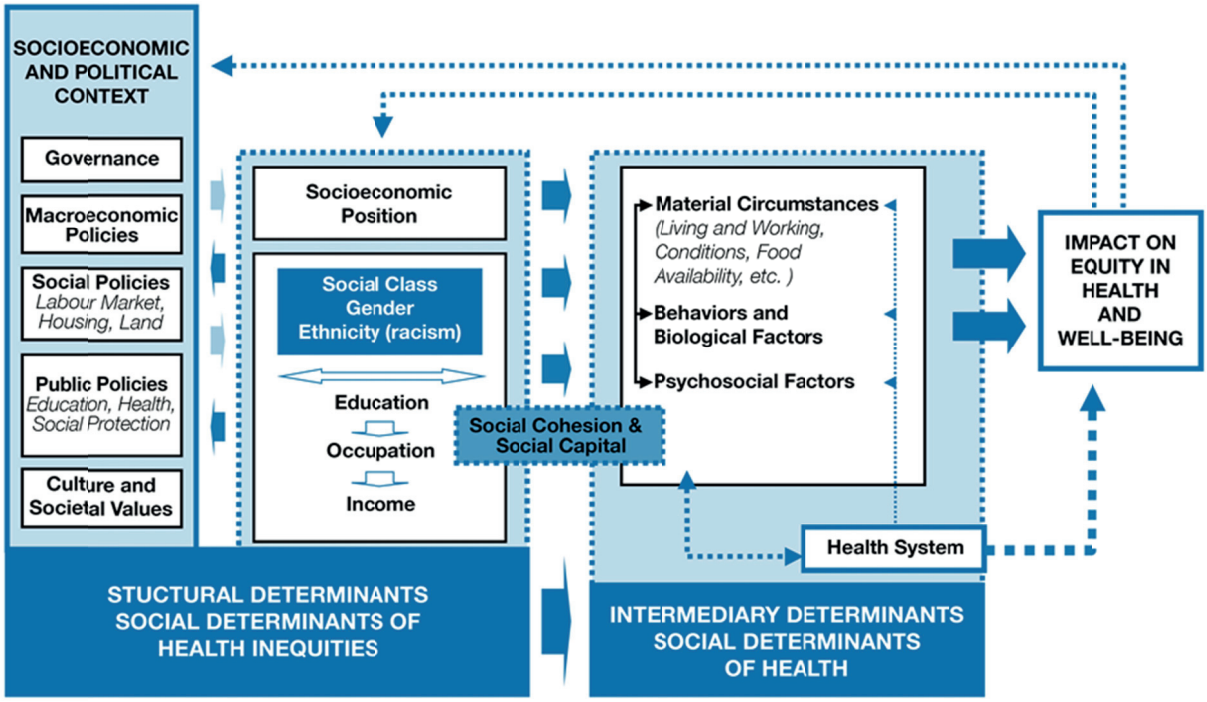

Figure 5: The WHO conceptual framework on social determinants of health and of health inequalities [172].

Figure 6 shows a conceptual framework proposed by Hiatt and Breen [175], in contrast to the WHO model specifically focusing on social determinants of cancer inequalities. The model conceptualises how social determinants interact with other factors in the aetiology and mortality of cancer and takes into account the impact of interventions along the cancer continuum [175]. The cancer continuum is the horizontal axis for this framework and depicts the course of cancer - from disease-free through pre-clinical phase to diagnosis, to morbidity and survivorship, and to the end of life. Levels of analysis are added to the cancer continuum. For simplicity, four levels have been selected but the authors state that multiple additional levels could be introduced into this framework as needed [175]. The model focuses on social determinants, on the impact of health care systems, on behavioural and psychological factors and the biological mechanisms of carcinogenesis. Highlighting the critical impact on cancer outcome, a health care level was introduced; however, health care systems are less likely to influence cancer incidence than mortality [175].

In the framework the relationships of different levels are visually simplified as a simple, linear process. However, complex, multidirectional interactions link different levels' influences into a net of relationships. Social determinants interact in a complex and

multidirectional way with other levels. Each "cancer phase" is influenced by different factors of the social environment, and together they compose a life course approach [175].

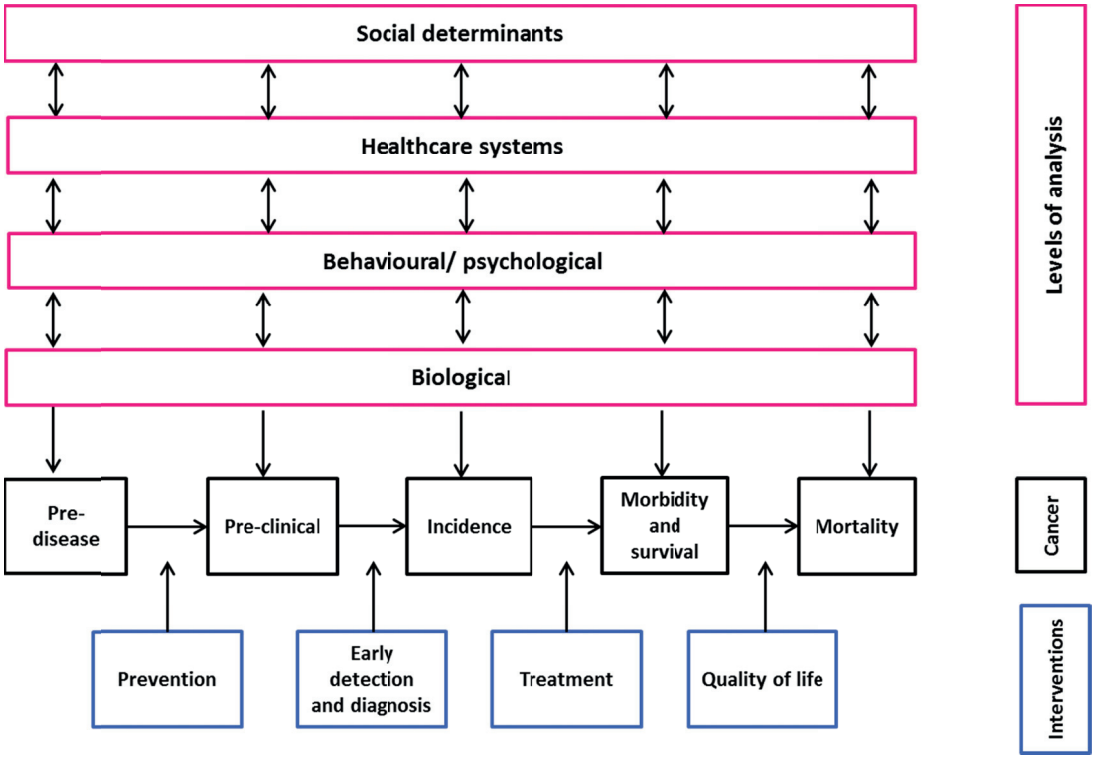

Figure 6: By Hiatt and Breen [175] proposed framework on social determinants of cancer. Framework illustrates how social determinants relate to other levels of analysis and types of interventions along the cancer continuum.

Comparing both presented frameworks, major distinctions include the specific focus on cancer inequalities in the model proposed by Hiatt and Breen [175] versus the focus on general inequalities in health and well-being in the WHO model [172]. Hiatt and Breen's framework takes the course of cancer into account and stresses that each phase of the cancer continuum is influenced by different interacting factors. Moreover, it considers the impact of interventions along the cancer continuum [175]. The WHO framework does not emphasize the course of health/disease over time or the impact of social determinants over time. However, importantly it emphasises the distinction between social determinants of health inequalities versus social determinants of health and thereby distinguishes between the mechanisms by which social inequalities are created and the conditions of life which then result and impact directly on health and well-being [172]. Both models have in common that they perceive the health care system itself as a key determinant of inequalities in cancer and health [172, 175].

Insertion: Definition of socioeconomic position (SEP)

SEP is an established concept in health research. According to Krieger et al. [177], the concept of "socioeconomic position" refers to both material and social resources and assets as well as individual's rank or status within a social hierarchy of a society. SEP is measured in numerous ways which indicates the complexity of the multidimensional construct [177, 178]. SEP can be measured on different levels: at the individual level (such as by education or occupation), at the household level (such as by the household/family income or savings) and the area or neighbourhood level (such as by area deprivation index or available facilities). There are strengths and limitations of all measures of SEP, which may vary by age, sex, race/ethnicity and country [177-179]. Different socioeconomic factors might impact health at different phases across the life course and through different causal pathways [178].

Besides SEP, various other terms, such as social or socioeconomic status or social class, are often interchangeably used in health research [177]. In line with the definition by Krieger et al. [177] for this report SEP rather than socioeconomic status is used.

4.3 Social inequalities in childhood cancer

The empirical evidence that social inequalities also exist in childhood cancer is comprehensively described in previous chapters. In brief, Chapter 2.1 describes geographical differences in the reported incidence of childhood cancers by level of socioeconomic development of a country [1, 14], with higher reported incidence rates in high-income countries [3, 4, 15, 16] compared to low- and middle-income countries [1, 17, 63, 64, 70], especially Sub-Saharan Africa, and particularly pronounced in leukaemia [17]. Recent evidence suggests that under-diagnosis and under-reporting might account for some of these observed geographical differences in incidence rates [19]. Similarly, substantial childhood cancer survival inequalities exist between countries. These inequalities are seen within both well-resourced regions such as Europe with roughly 10% poorer survival in Eastern Europe compared with the rest of Europe [11], and to a presumed much greater extent for less-developed regions [2, 12] (see Chapter 3.2). With respect to social inequalities within countries, Chapter 2.2 describes the conflicting and limited evidence of an association between SEP and childhood cancer risk. The current evidence on childhood cancer survival inequalities and social and family factors is extensively described in Chapter 3.4. Findings for

high-income countries including Europe are inconsistent. Different social and family factors are likely to have different impact and importance, varying noticeably by country. However, dissimilarities in welfare systems, including access to health care and public family support, geographic coverage and distance to treatment facilities, lifestyle and socio-cultural aspects, treatment protocols as well as methodological differences between studies make an international comparison difficult.

While social inequalities in cancer have been extensively studied in adults, there appears to be a gap in the childhood cancer epidemiologists' literature particularly with regard to empirical evidence on underlying mechanisms and pathways of social inequalities in childhood cancer, as well as the theoretical frameworks needed to direct investigations. Neither the WHO framework nor the framework proposed by Hiatt and Breen are suited to point out causal pathways for childhood cancer inequalities. The framework proposed by Hiatt and Breen might be more suited to investigate social determinants of cancer in adults than in children. The framework addresses interventions such as early detection or primary prevention which are of high importance for adult cancer but less relevant for childhood cancer. The model could be used as a basis to develop a tailored model specifically focusing on pathways of social inequalities in childhood cancer.

The concept of structural and intermediary determinants emphasised in the WHO model applies equally to cancer in adults and cancer in children. However, whereas the social determinants of health inequalities are universal, the social determinants of childhood cancer are likely to differ from those of adult cancer. For instance in contrast to cancer in adults, differences in survival from childhood cancer would be expected to be (at least in high-income countries) less related to co-morbidities and lifestyle [136, 138, 170], but more related to reasons such as adherence to treatment recommendations [180] and psycho-social aspects.

5 Objectives, material and methods

This chapter describes the specific objectives and hypotheses of the dissertation and gives an overview of the data sources utilized, the study populations and the statistical methods applied. Table 3 summarizes the objectives, material and methods of all seven articles.

5.1 Objectives and hypotheses

The overall aim of this dissertation was to gain a better understanding of the relationship between social and family factors and incidence of and survival from childhood cancer, using the international childhood cancer research networks established at IARC.

5.1.1 Objective I

Reported incidence rates for childhood cancer vary considerably by socioeconomic development of a country, with particularly low rates in Sub-Saharan Africa, particularly for leukaemia (see Chapter 2.1). As observed geographical differences in incidence rates have been used to put forward several hypotheses related to risk factors of childhood cancers (see Chapter 2.2), one of the two main objective of the dissertation was to study childhood cancer incidence data from a Sub-Saharan African country. South Africa was chosen due to availability of not yet analysed or published data, its large childhood population, and having a diverse racial/ethnic population [181] that would also allow insight into socio-cultural structures within the country. Among the 14.5 million children under the age of 15 years living in the country in 2006, 83.7% were Black African, 8.8% mixed ancestry, 1.9% Indian/Asian and 5.6% White [181].

The terms “race” or “racial group”, focusing on both biological and cultural differences, are frequently used in South Africa. Although different approaches and terminologies for issues around race and ethnicity are discussed in epidemiology [182], “race” or “racial group” rather than “ethnicity” are used from hereafter in this thesis.

Since race is correlated with socio-cultural circumstances including access to private health care services in South Africa [30], particular emphasis was given to investigation of differences between racial groups and to discussing potential under-diagnosis and under-reporting of childhood cancer in the country. Results were compared with data from

Germany, as a representative high-income country [183] that has a long-established population-based childhood cancer registry and a large childhood population. The German Childhood Cancer Registry (GCCR) was willing to provide me with incidence data tailored to the inclusion criteria of the available South African cancer registry data for direct comparison *(article I)*. An independent analysis on haematological malignancies among adults in South Africa adds to the knowledge on incidence patterns by race in South Africa *(article II)*.

Hypotheses I:

- The reported incidence of childhood cancer is higher in Germany in comparison to South Africa.
- The distribution of reported childhood cancer by diagnostic group and age group, differs between Germany and South Africa.
- The reported incidence of childhood cancer in South Africa differs between racial groups.

5.1.2 Objective II

Diagnostic procedures and treatment protocols are largely standardised within developed countries [31-33, 120-122] and, particularly in Europe, welfare systems ensure free health care services for children. Therefore it would be expected that survival from childhood cancer in populations with free health services should be fairly equal across social groups and independent of family circumstances. On the other hand treatment periods are often long with emphasis on compliance. Besides physician's compliance to the treatment protocols, parents' and child's adherence to the treatment and supportive care, the interaction between families and physicians may affect survival. Associations between social and family factors and survival have indeed been noticed in some studies. However, the evidence is sparse and conflicting, even within Europe [21, 22, 24-26, 146, 147] (see Chapter 3.4).

Therefore, the second objective of the dissertation was to investigate the role of social and family factors on survival from childhood cancer or certain types of childhood cancer. Hereby knowledge for further improvement of survival and reduction of social inequalities in cancer care should be gained. Data from Germany and Denmark were utilized, which had not been studied for this purpose before *(articles III-VI)*. In both countries, all children and adolescents are presumed to have equal and free access to health care services, irrespective of their social circumstances [184, 185].

Hypotheses II:

- Children with higher socioeconomic position have better survival from childhood cancer/ certain types of childhood cancer in comparison to children with lower socioeconomic position.
  - Children from families with higher parental education have better survival in comparison to children from families with lower parental education.
  - Children from families with higher monthly income have better survival in comparison to children from families with lower monthly income.
- Family circumstances affect survival from childhood cancer/ certain types of childhood cancer.
  - First born children have better survival in comparison to later born children.
  - Only children have better survival in comparison to children with siblings.
  - Children with cohabiting parents have better survival than children with single parents.
  - Children with young parents at date of diagnosis have worse survival than children with older parents.
  - Children living in more rural areas have worse survival than children living in urban areas.

Supplementary objective II

Some family characteristics have been shown to be related to the risk of childhood cancer; they are hypothesized to be proxies for specific exposures, for example birth order as proxy for the child's exposure to infectious agents. If these exposures are associated with the risk of developing cancer, they may also be related to the risk of relapse and, consequently, influence survival. Therefore it is important to have clear evidence, if there is an association for risk and/or survival. Thus studying the role of birth order with respect to childhood cancer risk at a nationwide level in Denmark was a supplementary objective of this thesis.

Supplementary hypothesis II:

- Children of higher birth order have a higher childhood cancer risk compared to children of lower birth order.

Table 3 provides a comprehensive overview of objectives and associated scientific articles.

Table 3: Overview of objectives, material and methodological features by article.

	Article I	Article II	Article III	Article IV	Article V	Article VI	Article VII
Objective addressed	Objective I	Objective I	Objective II	Objective II	Objective II	Objective II	Supplementary objective II
Contribution to the thesis	Core manuscript	Co-authorship	Core manuscript	Core manuscript	Co-authorship	Core manuscript	Co-authorship
Outcome	Incidence patterns	Incidence patterns	Survival predictors	Survival predictors	Survival predictors	Survival predictors	Cancer risk
Cancer type under study	All childhood cancer	Adult haematological malignancies	Acute lymphoblastic leukaemia	Acute lymphoblastic leukaemia	Haematological malignancies	All childhood cancer	All childhood cancer
Period of diagnosis	2000 - 2006	2000 - 2006	Oct. 1992 – Sept. 1994	Oct. 1992 – Sept. 1994	1990 - 2009	1973 – 2006	1973 – 2010
Data source	South African National Cancer Registry	South African National Cancer Registry	Former case-control study + GCCR	Former case-control study + GCCR	Danish registries	Danish registries	Danish registries
N study population	4,601	14,662	788 (647)	647	3,797	1,819	2,461,283
Statistical methods	Descriptive methods	Descriptive methods	Kaplan-Meier estimates, log-rank test, Cox regression models	Kaplan-Meier estimates, log-rank test, Cox regression models	Kaplan-Meier estimates, Cox regression models	Kaplan-Meier estimates, log-rank test, Cox regression models	Poisson regression models

5.2 Data sources

Different data sources served as a basis for conducting the seven independent studies; some studies were based on several data sources. The South African Cancer Registry provided data for *articles I* and *II*. Data from the German Childhood Cancer Registry (GCCR) were analysed for *articles I, III* and *IV*. Cases from a former German case-control study on childhood cancer aetiology served as another data source for *articles III* and *IV*. Danish registry data were the basis for *articles V, VI* and *VII*. The various data sources are described below.

5.2.1 The South African Cancer Registry

The South African National Cancer Registry (NCR) was established in 1986 as a pathology-based surveillance system of the National Health Laboratory Service (NHLS) (pathology services of the public sector) [186]. The NCR collects all malignant diseases including non-melanoma skin cancer but does not receive information about benign tumours (including benign CNS tumours). Copies of pathology reports confirming a cancer diagnosis are submitted to the NCR on a voluntary basis (until 2011), by laboratories in both public and private sector histology. Although reporting was on a voluntary basis, laboratories were actively followed up. Concerns regarding voluntary sharing of patient data led some private laboratories to withhold cancer pathology reports, beginning in 2005 [186]. New legislation introduced in April 2011 makes the reporting of diagnosed cancer cases to the NRC compulsory. The legislation requires health professionals and laboratories to report confirmed cancers within 3 months of diagnosis to the NCR [187].

The information provided by the pathology reports constitutes the basis of the cancer registry. Data reported for each patient include: patient's name and surname, sex, age at diagnosis, race group, diagnosis and tumour information (topography, morphology), date of diagnosis and whether the report was received from a private or public (NHLS) laboratory. Diagnosis is coded by trained NCR coders, by organ site and morphological type according to ICD-O-3 [48] [188]. Only primary incident cases with histology, cytology or haematology confirmation are recorded. Each multiple primary cancer is recorded as an additional case. Doubtful, in-situ or borderline cancers are excluded. For multiple notifications of the same cancer, only one record is kept. All cases not resident in South Africa (e.g. results of

specimens sent to South African laboratories by other countries) are excluded. No follow-up information for instance on vital status is collected.

Since the beginning of the 1990s an increasing number of reports are received without information on racial group, with 54% of childhood cancer cases having missing data on racial group between 2000 and 2006. An imputation method is used to allocate cases missing this information to a racial group [186]. The method makes use of a reference database of approximately 1.4 million surnames with known race (surname algorithm) [189]. Sensitivity analyses using data collected prior to the mid-1990s when race was routinely reported have shown that this method is highly accurate. Surnames which do not appear in the database are classified as unknown race. The database is continuously updated with the addition of each new patient whose racial group is known, and information from other sources is also used to improve quality and completeness.

The two studies analysing data from the South African Cancer Registry *(article I and II)* were restricted to cases diagnosed between 2000 and 2006, a time period under which the cancer registry worked under stable and defined conditions.

5.2.2 The German Childhood Cancer Registry

The GCCR at the University of Mainz was established in 1980 and is a nationwide population-based childhood cancer registry, collecting data on all malignancies and benign CNS tumours diagnosed before the age of 15 with annually about 1,800 new cases. Since 2009 the age range has been expanded to include all cases younger than 18 years. Physicians report patients' diagnosis on a voluntary basis and patients or their guardians are required to give their consent for registration. As most patients are enrolled in clinical trials, a network of paediatric oncology centres guarantees the coverage of all childhood cancer cases. Only about 1% of families do not give their consent and further 1% is missing for other reasons. The completeness of registration is higher than 95% since 1987 [3, 190, 191].

Active vital status follow-up is conducted routinely by the GCCR using information from clinical studies, treating hospitals, families and communities. A set of minimal information for each patient including date of birth, diagnosis, date of diagnosis, date of first recurrence or relapse, date and type of secondary neoplasm, vital status, date of death, date of last

contact and current address are stored and regularly updated. Information on racial group is not collected by the GCCR, but racial diversity is low in Germany. German children are usually Caucasian and larger migrant groups living in Germany originate from elsewhere in Europe or in Turkey [192] and are therefore also Caucasian.

In the first years after diagnosis the GCCR receives follow-up information from the respective clinical trial or hospital. At the end of the regular clinical follow-up the GCCR takes over surveillance and contacts the patients or parents directly, if the last follow-up information dates back 5 years or longer [190, 191].

5.2.3 The German case-control study

A population-based case-control study on potential risk factors of childhood cancer was conducted in the 1990s in West Germany. Particular emphasis was given to maternal factors and factors related to pregnancy and birth, factors related to the immune system, exposure to ionising radiation as well as parental occupations and environmental factors [193]. Cases were identified by using the nationwide GCCR. Besides children with leukaemia, cases with non-Hodgkin lymphomas, with tumours of the central nervous system, neuroblastomas, nephroblastomas, malignant bone tumours, and soft tissue sarcomas were included in the study. Cases were eligible, if diagnosed between October 1992 and September 1994, before the age of 15 years and if the child was living anywhere in former West Germany (excluding West Berlin). Controls were randomly selected via files of local offices for registration of residents. Controls were matched on age, sex and place of residence at diagnosis (community). The families of 2,286 children with cancer and 2,998 controls were asked for their consent to participate in the study. Information on potential risk factors as well as information on socio-demographic characteristics including parental education, parental occupational training and net monthly family income was collected by self-administered questionnaire and a subsequent telephone interview with both parents. Of the 2,286 contacted case families, 1,938 (84.8%) completed the questionnaire. An additional criterion was that cases and controls must have lived in their respective community for at least half a year before diagnosis (which could only be assessed after recruitment). 3.4% of recruited families did not meet this criterion and were excluded. This left a total of 1,867 eligible childhood cancer cases of which 1,772 participated in the telephone interview. Among families of healthy control children, 2,126 (70.9%) families returned the questionnaire, 2,057

fulfilled the additional eligibility criteria and 1,957 participated in the telephone interview [193, 194].

5.2.4 The Danish Registries

In Denmark information on many issues are stored in national population-based registries, ranging from information on birth, deaths, immigration and emigration over disease incidence to social and economic issues [195]. The Danish Civil Registration System registers all persons who have a permanent residence in Denmark including every live born baby and new inhabitant. It stores information on name, gender, date of birth, place of birth, citizenship, identity of parents and continuously updated information on vital status, place of residence and spouses [196]. Since 1968, all residents of Denmark are assigned a unique civil personal registration number (CPR number) by the Danish Civil Registration System, which is used in all national registries (including health and social registries), enabling accurate linkage of information between registries [196]. The CPR number includes date of birth and sex and allows, via the Danish Civil Registration System, linkage to first-degree relatives. This linkage is considered to be 100% correct. CPR was established for administrative purposes independently of health and social factors. Although no studies exist that explore the quality of the information recorded by the CRS, a very high quality is assumed [196].

The social registers of Denmark, such as The Population's Education Register (established in 1981) or The Income Statistics Register (established in 1970) are exclusively handled by Statistics Denmark. To guarantee confidentiality and fully preserve anonymity, individual data from Statistics Denmark is not delivered to any external institution or person. Instead, researchers from specific authorized environments can establish remote online access to data from Statistics Denmark or link datasets containing data from Statistics Denmark [195].

The Danish Medical Birth Register was established in 1973 and collects information on pregnancy and child's birth. The Danish Cancer Registry contains records of all incident malignancies and certain precancerous and benign lesions in the Danish population from 1943 onwards. Besides tumour characteristics some personal characteristics including date of diagnosis, date of birth, sex, the municipality and county/ region as well as the date of death or emigration. These variables, however, are derived from the Civil Registration System and updated once a year [196].

5.3 Social and family factors

A broad, but still limited range of social and family factors were considered for inclusion in this dissertation. The selection of characteristics was driven by the *a priori* defined hypotheses (see Chapter 5.1) but was restricted by the availability of certain characteristics in the data sources of the dissertation. Race, SEP, place of residence, birth order, number of siblings, parental age and cohabitation status of the parents were studied within the different articles. As a proxy for children's SEP several makers of parental SEP were used.

From the South African Cancer Registry data racial group was the only available social characteristic. Since racial group is highly correlated with socioeconomic circumstances including access to private health care services in South Africa [30], race in these analyses is primarily understood as a social characteristic rather than a genetic factor *(article I & II)*.
For the German survival studies information on socioeconomic factors (*article III*) and family factors (*article IV*) were derived from the former German case-control study collected via standardised telephone interview and were therefore predefined. The socioeconomic factors disposable family income, parental education and parental occupational training were available and the family characteristics birth order, number of siblings, parental age and degree of urbanization of the place of residence.
The Danish registries enabled the investigation of a broad variety of social and family factors including maternal income, parental education, number of full and half siblings, cohabitation status of the parents, parental age, birth order and degree of urbanization of place of residence *(article V & VI)*. However, as the analyses for *article VI* were conducted at IARC in France and the social registries of Denmark do not allow analyses of their data outside of Denmark socioeconomic factors could not be included in that study but were covered by the other Danish article *(article V)*.

More detailed information on the definition and data collection of the social and family factors used for the various investigations can be found in the respective articles (s. Appendix).

5.4 Study populations

An overview of the different study populations analysed in the context of this dissertation and their special features is given below. The term childhood cancer was defined in two ways depending on the data source. Childhood cancer was defined as any cancer diagnosed before the age of 15 for the *articles I, III* and *IV (German and South African data)*. *Articles V, VI* and *VII,* based on the Danish registry data*,* used the alternative definition of childhood cancer: any cancer occurring in patients below the age of 20.

Article I - Childhood cancer incidence patterns by race, sex and age for 2000 – 2006: A report from the South African National Cancer Registry:

4,601 newly diagnosed childhood cancer cases were reported to the South African National Cancer Registry during the period 2000 to 2006; with a greater number of cases among boys than girls (55% vs. 45%). 67.9% of the reported childhood cancer cases were Black Africans, 8.7% had a mixed ancestry, 3.2% were of Indian/Asian ancestry, 15% were Whites and for 5.2% information on racial group was missing. The percentage of cases reported by the public laboratories of the NHLS ranged from 92% among Black children to 66.5% among Whites. The most commonly reported childhood cancer was leukaemia (19%).

Article II - Haematological malignancies in South Africa: 2000-2006:

Between 2000 and 2006, there were a total of 14,662 haematological malignancies in adults (defined as over the age of 14 years at diagnosis) reported to the South African National Cancer Registry. Almost 50% of the cases were reported among the Black population, one-third among Whites, 10% among individuals of mixed ancestry, 4% among Indians/Asians and for just below 5% information on racial group was missing. The distribution of racial groups differed considerably on whether cases where notified by public or private laboratories. 84% of the cases reported among Blacks were reported by the public laboratories compared to 50% of the reported cases among Whites. Regardless of gender or race, NHL was the most commonly reported haematological malignancy, accounting for at least 50% of cases in most gender and racial groups. In all groups, this was followed by leukaemia, contributing 15-25% of cases in the various subgroups.

Article III - Survival from childhood acute lymphoblastic leukaemia in Germany – Does socio-demographic background matter? :

The study population consisted of all childhood ALL cases diagnosed between October 1992 and September 1994 in West Germany and identified by the GCCR in the context of the former German case-control study. Children were followed for 10 years after diagnosis, using survival data from the GCCR. Of the 788 cases identified, 58.4% were boys and more than 60% were 1 - 5 years of age at diagnosis. Information on socioeconomic characteristics was available for 647 cases. Information was missing for a further 6.5% on income, 5% on maternal education and 10% on paternal school education. Most commonly, families ranked in the second lowest categories – a monthly family income between 2,000 and 4,000 DM (53%) and education with "low degree" ("Hauptschulabschluss") (paternal: 43% and maternal: 38%). Over the follow-up period of 10 years 137 children had died. The 10-year overall survival of all cases was 82.5%.

Article IV - Family circumstances and survival from childhood acute lymphoblastic leukaemia in West Germany:

The article studied the same study population as analysed in *article III* but solely included cases for which family characteristics were available. Of the 647 cases, 334 (52%) were firstborns and 159 (25%) were the only child; almost half of the families had two children. With respect to place of residence, most families were living in urban areas, and most parents were aged ≤ 30 years at diagnosis. Numbers of missing values were very low for the key variables, ranging between 0.5% for maternal age and 1.6% for paternal age. Children were followed for 10 years with 10-year overall survival being 84.7%, based on 98 deaths.

Article V - Effect of socioeconomic position on survival after childhood cancer in Denmark:

The nationwide survival study was conducted by linking data from the Danish public administrative registries with the Cancer Registry. 3,797 children diagnosed with cancer below the age of 20 between 1 January 1990 and 31 December 2009 were identified. Most of the children were diagnosed in the age range of 0-4 years (29%) or 15-19 years (33%), with slightly more boys diagnosed with cancer than girls. The most common cancers were CNS tumours (26%) followed by leukaemia (24%). About half of the parents had a vocational education, and about 80% were cohabiting. 62% of the childhood cancer patients had one or

more full siblings. Follow-up time was not censored for this study. Median follow-up time was 9.0 years (range 0-22 years) with 841 deaths and an overall survival of 78%.

Article VI - Family characteristics and survival from childhood haematological malignancies in Denmark, 1973-2006:

Similar to article V this survival study analysed data from the Danish administrative registries. The study population comprised all children born and diagnosed with any haematological malignancy in Denmark between 1 January 1973 and 31 December 2006. Of the 1,819 children diagnosed with haematological malignancies in this time period, 59% were boys and 40% of the cases occurred in children ages 1 to 4. More than half of the cases were diagnosed with ALL (56%), followed by HL (compromising 13% of all cases), AML (12%) and NHL (9%). Among all cohort members, 834 (46%) were firstborns and 664 (37%) were second-born. 285 (16%) were the only child at date of diagnosis. Most families were living in provincial cities (53%). Mothers and fathers were most frequently aged 31-35 years at their child's diagnosis. Children were followed for 10 years. Overall 10-years survival was 72.1% based on 504 deaths.

Article VII - Birth order and the risk of childhood cancer in the Danish birth cohort of 1973-2010:

This cohort study was also based on data from the Danish registries. The birth cohort comprised 2,461,283 children born between 1973 and 2010 inclusively, of which 1,262,979 (51.3%) were boys. Among the total cohort, 1,099,058 children were firstborn (44.7%), 906,852 (36.8%) second-born, 336,017 (13.7%) third-born, and 119,356 (4.8%) had a birth order of four or higher. 227,913 (9.3% of total and 20.7% of firstborn) remained only children. In the study population accruing a total of 38.6 million person-years of follow-up; 5,699 childhood cancers were observed, with leukaemias and CNS tumours each representing approximately one quarter of cases. 45.6% of cancer cases were firstborn, similar to the proportion in the overall cohort.

More detailed information on the study populations can be found in the respective articles (s. Appendix).

5.5 Statistical methods

The statistical methods used for this dissertation depended on the respective article. *Articles I* and *II* analysed incidence data from the South African Cancer Registry applying descriptive epidemiological methods. *Article III* to *VI* analysed survival data from Germany and Denmark using Kaplan-Meier curves and Cox proportional hazard models. *Article VII* analysed the childhood cancer risk in a birth cohort using Poisson regression models. A more detailed description is given below and in the respective articles (s. Appendix).

Generally, childhood cancer cases were grouped according to the International Classification of Childhood Cancer, depending on the time period of the data either ICCC -1 or ICCC-3 (see Chapter 1.2).

Analyses of childhood cancer and adult haematological malignancies incidence data from the South African National Cancer Registry (articles I and II)

Descriptive epidemiological methods, in particular calculation of (relative) frequencies, sex ratios, age-specific and age-standardised incidence rates stratified by racial group and/or certain diagnostic subgroups were used to analyse the reported incidence of childhood cancer and adult haematological malignancies in South Africa (*article I* and *II*). The directly age-standardised incidence rates (ASR) were calculated using the weights of the Segi world standard population [197]. Consistent with the approach used in the annual reports of the South African National Cancer Registry, the Alternative South African mid-year population estimates from the Centre for Actuarial Research, University of Cape Town were used as the denominator [181, 198] for calculating incidence rates. These mid-year population estimates are similar in magnitude to the official mid-year estimates but maintain an age distribution that is consistent with that of the most recent Census in 2011 [181]. Therefore they were considered as the more appropriate population estimates for the purposes of studying differences by age group.

For *article I*, the incidence rate proportions in South Africa compared to the reference incidence rates of Germany were calculated to investigate differences for specific subgroups of childhood cancer. For this purpose, the ASRs in Germany in the respective sub-categories (by cancer type and by sex), as well as age-specific rates, were set to 100% and these were compared to the reported incidence rates among White and Black South Africans separately.

The German childhood cancer incidence rates were provided by the GCCR according to specifications defined by me to exactly match the eligibility criteria of the South African Cancer Registry in terms of included diagnoses and diagnostic time period.

For *article II*, Incidence rate ratios (IRRs) and 95% confidence intervals (CIs) were estimated using Poisson regression models with the number of cases for a given category of haematological malignancy as the outcome, the population size as the log offset and a log link function, overall and stratified by racial group, comparing rates of adult haematological malignancies among females to that of males. Similar models, stratified by gender, were used to compare incidence rates across the racial groups, using the Black population as the reference group.

Survival analyses (articles III – VI)

Two primary outcomes were defined for the two German survival studies (*articles III & IV)*: overall survival, with death from any cause as the endpoint, and event-free survival, with the first (if any) relapse (defined as >5% lymphoblasts in bone marrow), second malignant neoplasm or death as events. Since information on relapse is not recorded in the Danish Cancer Registry only overall survival was defined as outcome for the Danish studies *(article V & VI)*. Children were observed from the date of diagnosis until the date of event (previous defined event, e.g. death from any cause, relapse or secondary malignancy), emigration or lost to follow up, or date of 10 years of follow-up, whichever came first. Follow-up period was censored at 10 years as very few disease-related events occur afterwards, whereas the incidence of competing risks rises. An exception is the Danish survival study on SEP and survival from childhood cancer *(article V)* for which the follow-up period was not censored.

For graphical illustration (unadjusted) survival probabilities stratified by selected social and family characteristics were calculated, using Kaplan-Meier curves. Statistical significance (defined as $p \leq 0.05$) of differences in survival probabilities was assessed by the log-rank test [199]. Cox proportional hazards models were used to assess the impact of selected social and family characteristics on survival with time since diagnosis as the underlying time scale. It is the most commonly used multiple regression model for analysing survival data in health research and illustrates the relationship between the event incidence and a set of mutually

adjusted covariates using hazard ratios [200, 201]. Models were adjusted for the well–established prognostic factors child's age at diagnosis [31-33, 120] and sex [120, 132] as well as for the possible mediating effect of other social variables (*adjustment varied between articles and models*). Results were expressed as adjusted hazard ratios (HRs) with corresponding 95% confidence intervals.

Analyses of Danish birth cohort data and childhood cancer risk (article VII)

All children were followed up from date of birth until 20 years of age, date of death, date of first cancer diagnosis, or end of study period (October, 31, 2013), whichever occurred first. Poisson regression models were used to evaluate associations between birth order and different types of childhood cancer, estimating the rate ratios (RRs) and corresponding 95% confidence intervals, with and without controlling for maternal age, paternal age, and birth weight. The firstborn children served as the reference group for the comparisons.

6 Key results

This chapter provides a summary of the main results observed in the conducted studies, organised according to the two objectives of this dissertation. More detailed descriptions of the study results can be found in the respective articles (s. Appendix).

6.1 Objective I – Reported childhood cancer incidence patterns by race in South Africa

With a reported ASR of 45.7 childhood cancer cases per million in South Africa the ASR in Germany was more than 3-times higher (144.4 per million). Key results with respect to childhood cancer in South Africa *(article I)* include substantial differences in the reported incidence rates and the distribution of childhood cancer types both within South African racial groups as well as between South African and German children. Moreover, a particularly low incidence rate in South African infants compared to German infants was observed.

Overall, as well as for the major diagnostic groups including leukaemias and lymphomas, White South African children had approximately 3-fold higher ASRs than Black South Africans, with mixed ancestry and Indian/Asian children falling in between these two groups. ASRs were 4-5-times higher among Whites than Blacks for malignant CNS tumours and malignant bone tumours whereas rates were relatively similar for retinoblastomas and soft tissue sarcomas.

Comparing German children with White South African children, the overall childhood cancer ASR in Germany was 1.25-fold higher, but there were large variations across diagnostic groups. While the difference was striking for leukaemias (primarily driven by the low ALL rates among South African children), being more than 2-fold higher in Germany, and also markedly higher for sympathetic nervous system tumours, germ cell tumours and malignant CNS tumours, ASRs were similar for some other types such as soft tissue sarcomas, lymphomas and hepatic tumours. Notably, they were even somewhat higher in South African Whites for renal tumours and malignant bone tumours. An 8-fold higher incidence in South African Whites was seen in malignant epithelial neoplasms driven by high numbers of skin cancers.

German infants had a 2-fold higher incidence rate when compared to infant South African Whites and almost 10-fold higher compared to infant Blacks, whereas in 10-14 year olds the incidence rates of Germans and South African Whites were almost identical.
Patterns across the South African racial groups and in comparison with Germany were generally similar for boys and girls.

Similar to the pattern observed for the reported childhood cancer incidence, incidence rates of adult haematological malignancies in South Africa varied markedly by race *(article II)*, with generally higher rates among White, mixed ancestry and Indian/Asian populations compared to the Black population. Differences were most pronounced between White and Black populations, incidence rate ratios for males and females combined ranged from 1.56 (95% CI 1.38-1.76) for myeloma to 3.77 (95% CI 3.38-4.21) for HL. For all four major types of haematological malignancies investigated, incidence rates were consistently higher in the White population compared with the Blacks, irrespective of age, but these differences tended to increase with age.

6.2 Objective II - The role of social and family factors in survival from childhood cancer

Results of the analyses on ALL survival in German children confirm the well-known non-linear relationship between age at diagnosis and survival ($p < 0.001$) *(article III)*; infants had an approximate 6 to 7-fold (depending on the model) increased risk of dying and 4-fold increased risk of any event, compared to 1-5 year old children, while older children had an about 2.5-fold increased risk of death. Boys showed worse survival compared to girls (HR_{adj} 1.52; 95% CI 0.96; 2.40 for overall survival).
With respect to socioeconomic factors *(article III),* neither parental education nor family income showed a trend or significant impact on survival from childhood ALL in West Germany. For income, all HRs were close to 1. For maternal education, the HR was somewhat elevated, although not statistically significantly, in the small group of mothers having no school degree in the event-free analysis (HR_{adj} 1.80; CI 0.47; 2.56). The results for family characteristics *(article IV)* indicate that family factors may have an impact on survival from childhood ALL in Germany, although most associations were suggestive rather than statistically significant. The group of second-born children had a statistically significant

better survival compared to first- or later born children, with HRs ranging between 0.54 and 0.64 compared to firstborns, depending on the model. Poorer survival was observed for children having 3 or more siblings (HR_{adj} 1.58; 95% CI 0.73; 3.44 in the fully adjusted model for overall survival). Mutually adjusting for birth order and number of siblings resulted in even higher HRs for the relationship between number of siblings and ALL survival.

A non-linear relationship in the West German data was found for parental age at diagnosis, with poorer survival for children with younger fathers and mothers, and most distinct for children with older fathers (paternal age ≥ 41 years HR_{adj} 2.09; 95% CI 1.04; 4.20). A sensitivity analysis distinguishing between having either a young mother or a young father and having two young parents (both ≤ 25 years) indicated that particularly the latter was related to poorer survival; elevated HRs of up to 1.76 were found. Whether children lived in urban or rural areas of West Germany had no impact on survival.

The population-based and comprehensive Danish studies indicated that having parents with a higher SEP was associated with better survival of children with cancer *(article V).* The effects of the different indicators of SEP differed, however, by cancer type. A beneficial effect of maternal higher education compared to children of mothers with a basic education was only observed among children with non-CNS solid tumours (HR_{adj} 0.66; 95% CI 0.44; 0.99). A positive effect of cohabitating parents on survival found in the overall analysis of all childhood cancers combined, was mainly observed in children with CNS tumours (HR_{adj} 0.70; 95% CI 0.51; 0.97) and non-significantly so in children with non-CNS solid tumours. Number of full siblings was most strongly and statistically significantly associated with the survival of children with non-CNS solid tumours, who had a 45% increase in the risk for dying if they had one sibling (95% CI 1·11; 1·89) and a 29% increase if they had two or more full siblings (95% CI 0.93; 1·79). Associations with maternal age at child's birth were inconsistent across cancer types.

In separate analyses for ALL, the risk estimates were closer to null than those for all cancers. Similarly, in separate analyses of subgroups of non-CNS solid tumours that require early surgery or more complex treatment, no difference was found from the results for the combined group of non-CNS solid tumours.

The second Danish study *(article VI)*, solely focusing on survival from haematological malignancies, observed worse survival from ALL and AML with increasing birth order and among children with siblings compared to children without any siblings. The associations with AML were stronger and reached statistical significance in contrast to rather suggestive results for ALL. A HR_{adj} of 1.62 (95% CI 0.85; 3.09) was observed for 4th or later born children with ALL, while the HR_{adj} was 5.76 (95% CI 2.01; 16.51) for children with AML. Mutually adjusting for birth order and number of siblings in one model abolished the association between number of siblings and survival from ALL and AML, but did not substantially alter the HRs for the effect of birth order on ALL survival and showed even higher HRs for the association with birth order and AML survival. Children with older parents showed a tendency of inferior survival from ALL, while for survival from AML young maternal age was related to poorer prognosis. An effect of better AML survival among children with older mothers was attributed to the high survival of children having both an older mother and an older father. The HR_{adj} was 0.55 in the fully adjusted model (95% CI 0.17; 1.80). Sensitivity analysis distinguishing between having either an older mother or an older father and having two older parents (both ≥ 46 years) showed that particularly the latter was related to poorer survival from ALL. Restricting the analyses to children diagnosed from 1990 onwards showed similar results to those for the full period 1973-2006.

Wide confidence intervals reflected the small numbers available for the analyses of NHL survival. Poorer survival was observed for children with full and half siblings compared to only children. Although for most of the categories not statistically significant, the trend test reached statistical significance. No clear relationship was found for number of full siblings only. Young parental age might be related to poorer survival, but numbers were small.

Supplementary objective II – Birth order and the risk of childhood cancer

The results did not show associations between birth order and risk of any childhood cancer subtype, including ALL for which the *a priori* evidence was strongest. For the majority of cancer types, RRs were all around one. Considering stillbirths and/or controlling for birth weight or parental age in the analyses had no effect on the results, indicating that both number of subsequent siblings or pregnancy order did not matter.

7 Discussion

Findings from this thesis highlight the social inequalities in childhood cancer that have been observed with respect to reported differences in incidence between racial groups in South Africa and between South African and German children. In addition, differences in survival between social groups in Germany and Denmark have been found further highlighting the impact of social inequalities even within high-income countries. The present discussion is organised according to the two objectives of this dissertation, followed by more general considerations of potential underlying pathways of social inequalities in childhood cancer.

7.1 Reported childhood cancer incidence patterns by race in South Africa

The first objective was to study the incidence of childhood cancer in a Sub-Saharan African country, namely South Africa, focusing on differences between racial groups and discussing the potential for under-diagnosis and under-reporting of childhood cancer in this country.

Interpretation of key findings

Key findings include substantial differences in the reported incidence rates and the distribution of childhood cancers within South African racial groups and between South African and German children, who represent the incidence patterns of high-income countries. Furthermore, a particularly low incidence rate in South African infants compared to German infants was observed. Patterns across the South African racial groups and in comparison with Germany were generally similar for boys and girls.

The key results (see Chapter 6.1) provide support for all hypotheses defined *a priori* in Chapter 5.1.1:

- The reported incidence of childhood cancer was higher in Germany in comparison to South Africa.
- The distribution of reported childhood cancer by diagnostic group and age group differed between Germany and South Africa.
- The reported incidence of childhood cancer in South Africa differed between racial groups, being much higher in White children compared to Black children, with Indian/ Asian and children with mixed ancestry falling in-between.

Similar to childhood cancer, higher incidence rates of adult haematological malignancies among White and Indian/Asian populations compared to the Black population are also observed, which adds to the evidence of reported cancer incidence differences by racial group in South Africa. Although direct quantitative comparison is not useful as the types of haematological malignancies in adults are very different compared to children (with particular regard to leukaemias and the lack of chronic leukaemias in children), there is a general trend of lower reported incidence in Blacks that can be seen.

Racial differences in childhood cancer in South Africa and the potential for under-ascertainment

Incidence differences by racial group in South African children have also been observed previously in regional studies [202-204] as well as in the annual NCR reports [205]. In a study from 1974-1983 in Johannesburg, significant differences in the incidence of leukaemia between Black and White children were found, with much lower rates in Black children [203]. A more recent study from the Western Cape observed a lower incidence of ALL among children with mixed ancestry compared to White children [204].

Significant variations in incidence rates according to race have also been noted in the US (see Chapter 2.1). White children showed an overall 1.5-fold higher childhood cancer incidence than Black children, which was slightly higher for leukaemia (1.8-fold) and lower for lymphoma (1.3-fold) [45]. However, differences in incidence rates between racial groups in the US were much smaller than those observed in South Africa. Even assuming that the differences in incidence rates between racial groups in the US are entirely explained by differences in genetic susceptibility and variability in environmental exposures, for the South African setting it can implied that the further excess differences found are likely due to additional factors.

The observed incidence differences may instead be partly explained by socioeconomic and/or cultural factors related to access or utilization of health care services and health care seeking behaviour. In South Africa, race is strongly correlated with socio-cultural circumstances (such as education, income, medical aid and cultural beliefs), and having a low socioeconomic position is considerably more common among Blacks [30]. Higher unemployment in Blacks [30] may result in a lack of financial resources available for seeking

medical help. Only 7% of the Black population and 16% of the population with mixed ancestry in 2006 were covered by medical aid (which provides access to private health care services) compared to 29% of Indian/Asians and 63% of the White population. The post-apartheid bill of rights grants everyone the right to basic education, but as a consequence of the previous regime 21.5% of the Black population still had no schooling, compared to 7.4% of Whites [30]. A lack of parental education and low awareness of cancer, particularly in children [1], might delay or inhibit health care seeking behaviour. Furthermore, some parents might not know that cancer is treatable and therefore do not seek medical care.

The non-specific nature of many early symptoms (e.g. for leukaemia which often presents with symptoms similar to those of infections) (see Chapter 1.2) may result in delayed diagnosis or failure to detect the disease [20]. This may explain why differences in incidence for cancer types with clearly visible symptoms (such as retinoblastoma or hepatoblastoma with the tumour itself being large) are smaller than for cancer types with rather non-specific symptoms or less visible tumours. A greater proportion of Black South African families live in rural/remote areas [30], and may not access the medical centre due to inadequate public transportation infrastructure or the inability to pay for transport and accommodation when their child is ill [1]. Therefore, cancer diagnosis may be delayed or the child may possibly never get diagnosed. In addition, primary healthcare facilities and local/regional hospitals may lack awareness of and experience in diagnosing paediatric cancer [1, 14, 75]. For instance, the observation from the Western Cape that the lower incidence of ALL in children with mixed ancestry compared to White children was particularly pronounced in children from rural areas [204] would support this explanation.

Traditional medicine and cultural beliefs continue to play an important role in healthcare delivery in South Africa, particular among the Black population [206]. Some parents may rely on traditional healers using herbs or witchcraft rather than attending a medical centre for diagnosis and treatment. Some families might first seek advice from traditional healers before seeking Western medical treatment, which may cause a delay in diagnosis and clinical treatment [1].

Although the potential for under-diagnosis is much higher for the Black population, the lower incidence rates for some cancers in South African Whites compared to rates from Germany may be due in part to under-ascertainment rather than necessarily reflecting a

lower cancer risk. Under-diagnosis, due to parents not being aware of the warning signs of cancer or clinicians being less experienced at detecting childhood cancer (particular types with non-specific symptoms) may be a general issue [1], irrespective of racial groups. The pathology-based reporting process of the NCR itself may cause some under-ascertainment, as cancers without a pathology-based diagnosis are not recorded [186] (see Chapter 5.2.1). This might be of particular concern for some brain tumour cases diagnosed solely by medical imaging, but could also apply more generally to the situation of cancer patients who present at a late stage and for whom the cancer was too advanced to benefit from a more precise diagnosis. It is also possible that some leukaemia cases might have been diagnosed only from peripheral blood tests performed outside the tertiary laboratory structures. This would be expected to occur primarily among children who die before being referred to a tertiary hospital where bone marrow biopsies would have been analysed, and could explain why rates of leukaemia were particularly low. Therefore, even if malignancies are accurately diagnosed they may not be captured by the NCR, resulting in under-reporting of the actual diagnosed incidence of cancer.

Notably, however, there were also some cancers that were more common in South African Whites. While higher exposure to ultraviolet radiation may explain the excess of skin cancer in the White population [58], the higher rates of hepatic, renal and malignant bone tumours were unexpected and may suggest that the excess in South Africa is even higher than observed.

Incidence rates were particular low among infants, with the rates in Germans being 2-fold higher when compared to South African White infants and almost 10-fold higher compared to Blacks. However, among 10-14 year olds the incidence rates of Germans and South Africans were almost identical. This suggests that under-diagnosis may be a particular issue among both Black and White South African infants. Diagnosis during infancy is difficult in general. Moreover, in South Africa, with its overwhelming burden of infectious disease [78], cancer may not be among the first diagnoses suspected and thus even children cared for in the private sector may not be diagnosed before they die. In contrast to age, incidence rate proportions were similar for boys and girls and differences in diagnosis or reporting by sex appeared to not play a great role in South Africa. This finding was unexpected, as recent evidence points out that rates of cancer registrations in girls remain lower than expected in

low- and middle-income countries [77]. Nonetheless, my findings indicate this is not the case in South Africa.

International context

The observed distribution of childhood cancer types in South Africa is unique and differs from those observed in other Sub-Saharan African [2, 18] and middle-income countries [63, 64, 207], as well as high-income countries [4, 15, 16]. In high-income countries, leukaemias are the most frequent childhood cancer, followed by brain tumours, lymphomas and other solid tumours [3, 4, 15, 16] (see Chapter 2.1). Particularly in Sub-Saharan Africa, children are more prone to develop NHL (Burkitt's lymphomas) and Kaposi sarcoma due to higher exposure to infections (namely Epstein-Barr virus, HIV and human herpes virus 8) [1, 66, 67]. South Africa is an upper-middle-income country [183] with a relatively high level of wealth in some regions, and is therefore distinct from the Sub-Saharan region [14]. This study reveals that leukaemias in South Africa, as in high-income countries, are the most frequently reported cancer type, although rates are substantially lower, particularly for ALL. These differences might be again the result of the cumulative effect of genetic predisposition, the added burden of various infectious diseases, environmental exposures and chronic immune stimulation, but in addition due to incomplete diagnosis and registration.

Differences between the reported and *actual* incidence of childhood malignancies in low-income countries is generally assumed to be most striking for leukaemia due to the unspecific symptoms resembling those of infectious diseases, thereby resulting in death before cancer is suspected or diagnosed [17, 20]. Many Sub-Saharan African countries report fewer brain tumours, and substantial under-estimation is assumed [17]. In South Africa this seemed to be more pronounced in the Black population as the observed incidence rate in White children was more than 70% of that reported for Germany. For lymphomas and some solid tumours, visible symptoms (see Chapter 1.2) might encourage parents to seek medical help and early death is less common.

Strengths, limitations and methodological considerations

This study presents, for the first time, the incidence of childhood cancers in South Africa on a national level and is one of very few studies on childhood cancer from Sub-Saharan Africa. The strengths of conducting this analysis in South Africa include the availability of cancer registry data, the large population of children, and the racially diverse population. The latter strength allowed us to investigate differences by racial group, which is an important determinant of socioeconomic circumstances and access to high quality health care in South Africa (via the private health care sector).

The second major strength of this study was the availability of directly comparable data from Germany. Incidence rates of German children represent typical rates of childhood cancer occurrence in a high-income country. The GCCR has a very high estimated level of childhood cancer ascertainment (>95% since 1987 [3]) in a large population of children which has an assumedly high similarity in genetic make-up with White South African children. The registry was able to provide data in a structure comparable to that of the South African database with respect to the time period (2000 – 2006) and included diagnoses (e.g. exclusion of benign brain tumours not recorded in the National Cancer Registry of South Africa (NCR)), making the comparison very meaningful.

The South African cancer registry captures data from all public-sector pathologically confirmed cancers across the country as well as a large proportion of cancers diagnosed in the private sector. However, as some private laboratories discontinued reporting to the NCR in 2005 because of concerns about patient privacy [186] (see Chapter 5.2.1), marginal under-reporting of childhood cancer cases diagnosed in the private healthcare sector is likely for the years 2005 – 2006.

A major limitation of the study is the pathology-based reporting process of the NCR. Since cancers without a pathology-based diagnosis are not captured, the reporting process itself might result in under-reporting (see above & Chapter 5.2.1). Since the early 1990s an increasing number of pathology reports have been received without information on race. An imputation method (using a surname algorithm) was used to assign racial group to cases missing this information (see Chapter 5.2.1). Thus, misclassification of some cases with regard to race cannot be excluded, but previously-conducted validation analyses of the imputation method have shown this method to be reasonably accurate, so that this

limitation is considered to be of minor importance. Another limitation of this study was the lack of data on stage at diagnosis, which could provide further insight into differences in stage at diagnosis and diagnostic delay by race and age groups [202]. Moreover, no other socio-cultural characteristics such as socioeconomic factors (education, income), place of residence or cultural beliefs (e.g. belief in traditional healer) were available. Those characteristics are most likely related to access and utilization of health care service as well as certain environmental exposures, and would have been very interesting to study. Nevertheless, this is a limitation that can be considered to be a characteristic of all population-based cancer registry data.

Finally, the analysed data were from the time period 2000-2006, a period when the cancer registry operated under defined and stable conditions. However, these results might not reflect the current situation. Studies based on more recent data will be important once available for analysis, especially considering the introduction of new legislation in 2011 which made reporting of all confirmed cancers to the NCR mandatory (see Chapter 5.2.1).

Considering the overall objective of this dissertation, a major limitation is that childhood cancer incidence patterns were studied in only one Sub-Saharan country and not in one of the low-income countries in the region [183]. It is questionable to what extent the findings from South Africa are generalizable to other Sub-Sahara African countries. With regard to differences in the burden of infections [66], environmental exposures, genetic susceptibility and access to as well as utilization and quality of health care [1, 14], patterns might differ considerably in other populations. Analysing data from other developing countries, for instance from Central Africa, might provide further insight into geographical differences in childhood cancer and under-ascertainment. Unfortunately, there are still too few reliable data sources, particularly in Sub-Saharan Africa, and additional data were not available for this dissertation.

Conclusion

Taken together, the reported lower incidence rates for some childhood cancers in South Africa compared to developed countries, most pronounced for Black children, might be at least to some extent related to under-diagnosis and under-reporting. Since the actual incidence of childhood cancer in South Africa and other Sub-Sahara African countries is

unknown, the extent of under-ascertainment is difficult to quantify at present. It is very likely that the extent of under-ascertainment varies between i) cancer types with greater under-diagnosis likely occurring in cancer types with unspecific symptoms such as leukaemia, ii) age groups with greater under-diagnosis likely occurring in infants, and iii) race with the greatest likely under-diagnosis in South African Blacks.

Observed geographical differences in incidence rates have been used to put forward aetiological hypotheses to explain the apparent cancer excess in high-income countries, for instance related to lack of immunological training due to "over-hygiene" resulting in delayed exposure to infections or related to modern technology such as those producing EMFs (see Chapter 2.1 & 2.2). The South African findings suggest the need to be cautious in interpreting geographical differences in many childhood cancers. Further research on the geographical variation of childhood cancer incidence rates is needed to quantify the extent of under-reporting and under-diagnosis compared to true differences in incidence rates between more-developed and less-developed countries.

7.2 The role of social and family factors in survival from childhood cancer

The second objective was to investigate the role of social and family factors on survival from childhood cancer or certain types of childhood cancer in two countries with presumed uniform and free access to health care services, namely Germany and Denmark.

Interpretation of key findings

Table 4 presents an overview of the key findings observed from the four independently conducted studies on social and family factors and survival from childhood cancers in Denmark and Germany. Despite the highly specialized treatment of children with cancer and universal healthcare coverage in Denmark and Germany, social and family characteristics were found to be associated with survival from childhood cancers, although not consistently so between Germany and Denmark and across cancer types.

No strong impact of socioeconomic factors on survival from ALL was observed for either Germany or Denmark. The beneficial effect of maternal higher education in Denmark was only observed among children with non-CNS solid tumours. The superior survival among children with having cohabitating parents was seen mainly for children with CNS tumours and less so for children with non-CNS solid tumours. Increasing birth order and having

siblings was associated with inferior survival among childhood haematological cancer patients in Denmark, with the associations being rather suggestive for ALL and NHL but stronger and statistically significant for AML. Similarly, associations with family factors were rather suggestive for survival from ALL in German children. Poorer survival was only observed for children having 3 or more siblings. In contrast to the findings from Denmark, highest survival in Germany was seen for second-born children. A non-linear relationship was found for parental age at child's diagnosis, with poorer ALL survival for children with young parents and particular with older fathers. In Denmark, children with older parents showed a tendency towards lower survival from ALL, while for survival from AML young maternal age was related to a poorer prognosis.

With respect to the *a priori* defined hypotheses regarding the relationship between socioeconomic position and survival from childhood cancer (see Chapter 5.1.2), the hypothesis that children from families with higher parental education have better survival compared to children from families with lower parental education is supported for children with non-CNS solid tumours in Denmark. The hypothesis that children from families with higher monthly income have better survival finds no support based on the analyses of survival from ALL in Germany, and very weak support for survival from haematological malignancies or CNS tumours in Denmark.

My findings with respect to family factors confirm several of the hypotheses outlined in Chapter 5.1. Firstborn children have better survival from ALL and AML compared to later born children in Denmark. Findings from Germany and Denmark support the hypothesis that only children have better survival compared to children with siblings. The hypothesis that children with cohabiting parents have better survival than children with single parents is support by the Danish study among children with a CNS or non-CNS solid tumour.

On the contrary, the hypothesis that children living in more rural areas have worse survival than children living in urban areas finds no support both from either the findings from Denmark or Germany. Findings for parental age and survival from childhood cancers are inconclusive. Finally, the supplementary hypothesis that children of higher birth order have a higher childhood cancer risk compared to children of lower birth order finds no support, since the results from the Danish cohort study did not indicate an association between birth order and risk of any childhood cancer.

Table 4: Overview of key findings on social and family factors and survival from childhood cancers in Denmark and Germany. Interpretation is based on models that at least adjusted for age, sex and if necessary on cancer type.*

Article	**Article III**	**Article IV**	**Article V**				**Article VI**		
Region	West Germany		Denmark				Denmark	Denmark	Denmark
Children's age	< 15 years		< 20 years						
Cancer type	ALL		Childhood cancer	Haem. malignancies	CNS tumours	Non-CNS solid tumours	ALL	AML	NHL
N	647		3,797	1,401	986	1,353	1,011	213	163
Year of diagnosis	October 1992 - September1994		1990-2009				1973-2006		
Paternal occupational training									
Maternal education									
Paternal education									
Income									
Birth order									
Cohabitation status									
Number of full siblings									
Number of all siblings									
Maternal age at birth									
Maternal age at diagnosis									
Paternal age at diagnosis									
Place of residence									

**red:* no association; *orange:* inconclusive, tendency in a subcategory but no trend; *light blue:* non-significant association; *blue:* significant association in categorical and/ or trend analyses*

The role of social and family factors in survival from childhood cancer

Out of the broad range of social and family factors under study, the observed associations between family factors and survival from childhood cancers are particularly interesting, especially in that associations with socioeconomic factors were not very pronounced. Whereas parental education and income did not appear to impact survival from childhood haematological malignancies in Denmark and ALL in Germany, strains on families and their social resources (as measured by birth order, number of siblings and parental age at child's diagnosis in this dissertation) appeared to be more relevant than the socioeconomic situation of the family, at least for survival from haematological malignancies. For survival from non-CNS solid tumours, both maternal education and number of siblings appeared to be relevant. Little is known about the role of family factors on survival (see Chapter 3.4), particularly their interaction with socioeconomic circumstances.

The well documented impact of social factors on cancer outcome in adults [136, 138, 167] is associated with differences in the time of diagnosis, in the biological characteristics of the tumour, treatments given and individual factors, such as lifestyle or the presence of comorbidities [138, 166, 171]. However, for childhood cancers dissimilarities in survival would be expected to be less likely related to co-morbidities and children's lifestyle, but more likely related to delayed diagnosis for some social groups [208], adherence to treatment recommendations [180], communication barriers with health professionals as well as psycho-social effects [209].

Treatment of lymphoblastic malignancies (ALL and NHL) usually lasts several years, and poor adherence to oral maintenance therapy may have a negative impact on cure rates [210]. As soon as the child is discharged from hospital (typically after about 8-9 months [33, 122]), parents are responsible for complying with the recommendations for the continuation of a highly demanding therapy, including daily drug administration and frequent medical outpatient appointments. Accordingly, findings from the UK indicated that ALL survival dissimilarities by socioeconomic position emerge about the time when treatment management requires parental/child's adherence, i.e. from the time of oral treatment in the outpatient setting. Investigators hypothesized that this dissimilarity may be due to treatment adherence [21]. In Germany, children with 3 or more siblings showed inferior survival and these dissimilarities emerged about 1.5 years after diagnosis, a time by which

treatment management had usually moved from hospital to home [33, 123]. Similarly in Denmark, children with siblings as well as children of higher birth order showed worse survival. The pattern of diverging survival curves after the beginning of home-administered therapy seen in the UK was, however, not reflected in the survival curves for Danish children. Moreover, I observed an even stronger relationship between the number of siblings and AML survival and AML is entirely treated in hospital. Thus, family resources might not only be of relevance for the period of the home-administered maintenance therapy for ALL, but for the entire treatment period of AML and ALL. Smaller families may be able to devote more time to assisting the sick child and may thus be better at coping with and managing the cancer experience [180, 211].

However, and in contrast to the findings from Germany, the associations seen between number of siblings and leukaemia survival in Denmark (both ALL and AML) were mainly attributed to the effect of birth order. According to the adrenal hypothesis [212], higher birth order [38] and more social contacts [213] could suggest that the lymphoblastic malignancies emerged in spite of high glucocorticosteroid exposure and thus were more glucocorticosteroid-resistant when diagnosed, a feature associated with poor prognosis [214]. Nevertheless, this explanation would only apply for the observed relationship between birth order and survival from ALL. However, the relationship between survival and birth order noticed for children with AML in Denmark was even stronger than for ALL and more pronounced for cases diagnosed since 1990 characterised by a standardised treatment approach [31, 32, 120]. Perhaps firstborns and children with fewer siblings might receive more attention from their parents, possibly positively affecting abilities to cope with the cancer experience [211], the demanding therapy and associated uncertainties, but this is speculation.

The observed relationship between parental cohabitation status and survival from CNS and non-CNS solid tumours in Denmark implies that living with a partner might facilitate sharing of the prolonged attention and practical work required in caring for a child with cancer and also for coping with the associated mental challenges and anxiety [22, 211]. Furthermore, cohabitation might enable one parent to reduce his or her working hours to be at the hospital [211].

The poorer survival from AML and NHL reported in the Danish study for children with young mothers (for the latter also for children with young fathers) and from ALL in the German study for children with young fathers may possibly also reflect the capacity to cope with the cancer diagnosis and related circumstances, which may be particularly challenging for young parents [211]. In an investigation from Brazil younger parents of children with cancer reported higher levels of stress and anxiety [215]. This might also explain the better survival from AML and NHL among children with older mothers. However, as the parental age-survival relationship appeared to be reversed for ALL among Danish children, interpretation of these findings remains unclear at present.

While the financial situation of a family does not appear to be strongly relevant to survival, parental educational might have a potential effect on survival – as seen among Danish children with non-CNS solid tumours. Families depend on information and guidance from health personnel, but general health literacy, communication and cognitive skills may differ by level of education, resulting in different understanding by parents who receive the same information [180]. The problem might be exacerbated for children with cancers that require multidisciplinary treatment, like non-CNS solid tumours.

Whether children lived in urban or more rural areas in Germany or Denmark was not found to be of relevance for their survival. This is plausible as a dense network of paediatric clinics cover both countries, with relatively short distances to the treating centre from most places. Further, treatment is highly standardised [31-33, 120, 123] (see Chapter 3.1), irrespective of the treating hospital.

As described in Chapter 5.1.2, family factors such as birth order, parental age or place of residence have been proposed as risk factors for some childhood cancers, especially for ALL, either operating directly (parental age) or indirectly as proxy of other exposures (birth order as proxy of infectious contacts) (see Chapter 2.2). It could therefore be hypothesized that if such factors increase the risk of developing ALL they may also increase the risk of subsequent relapse and consequently impact survival through similar mechanisms, namely promoting the aberrant leukaemic clone. The only factor for which this has been already investigated is magnetic fields, where studies on risk show a weak positive association, but

no association was observed with survival [36]. Similarly I did not observe an association between birth order and risk of ALL in the same Danish population in which I observed the association with survival. Moreover, advanced parental age has been associated with an increased risk of most childhood cancers, although findings are not fully consistent [10, 40, 112-115] (see Chapter 2.2). However, these increased cancer risks reported in the literature do not correspond to the diverse patterns observed for survival and parental age in my studies.

International context

The findings indicate that some social and family circumstances are associated with better survival. However, the impact of the different indicators differed by cancer type and between countries, even between neighbouring Germany and Denmark as investigated in the present analysis. This illustrates why findings from previous studies only including leukaemia [24, 26, 148], lymphomas [29] or ALL [21, 28, 146] cancer cases are markedly limited by patient selection (only certain cancer types) or sample size, with limited power.

While survival from non-CNS solid tumours was superior among Danish children of mothers with higher educational attainment, parental education and income did not appear to strongly impact survival from childhood haematological malignancies and CNS tumours in Denmark and ALL in Germany. On the contrary, among studies from other European countries, mainly investigating leukaemia or ALL alone, parental education, income or occupation did matter [21, 22, 24, 26, 146] (see Chapter 3.4).

Family characteristics such as number of siblings, birth order and parental age have been postulated to be related to the occurrence of childhood cancer [10, 37-39, 92, 112, 113, 216] (see Chapter 2.2), but evidence of their role as prognostic factors for leukaemia and in particular lymphoma and solid tumours is sparse and with conflicting findings [22, 23, 26, 146, 147, 162] (see Chapter 3.4). In line with the findings of this dissertation research, a large Norwegian study on children with cancer reported that having no siblings was associated with mortality reductions of almost 20% [22]. In contrast, a study from Greece on children diagnosed with ALL in the late 1990s-early 2000s observed better prognosis for children with increasing number of siblings [146]. However, this finding was not confirmed in a recent

follow-up study [26] (see Chapter 3.4). Likewise and in significant contrast to the findings from Denmark, no relationship between survival from AML and number of siblings was observed there [26].

To my knowledge, so far no earlier investigation had addressed the possible importance of parental age at the child's cancer diagnosis for childhood cancer survival. Although only somewhat comparable, analyses of mother's age at child's birth from Norway did not indicate a relationship with childhood cancer survival, whereas the most recent findings from Greece indicated better survival from AML with older maternal age [22, 26] (see Chapter 3.4). This trend is similar to what was observed for maternal age at child's AML diagnosis in Denmark. As for ALL survival, however, old parental age was related to inferior prognosis.

The large Norwegian study did not find an association between parental marital status and survival [22], whereas in Denmark I observed an association in children with CNS tumours but also noticed indications of an association in children with non-CNS solid tumours. Notably however, the definition of marital status in the Norwegian study did not include cohabiting unmarried parents, which in the Danish study constituted some 19%. Single parenthood was also reported as a critical factor for childhood leukaemia prognosis in Greece [26]. Apart from methodological differences between studies, socio-cultural aspect of the respective countries might also affect these associations.

With respect to place of residence, a study from Australia reported better leukaemia survival for children living in major cities compared to those living elsewhere. However, no evidence of geographical variation in survival was observed for children with lymphoma [23]. Living in rural areas was also associated with less favourable prognosis in recent multi-national findings from Bulgaria, Turkey and Russia [162]. This may likely contrast the smaller size of Germany and Denmark, the excellent infrastructure and the lack of real remote areas. In Greece, an earlier study found indications of a trend of poorer survival with increasing remoteness [146]. This was not confirmed in more recent years, which was suggested to be linked to improvements in motorway infrastructure [26] (see Chapter 3.4).

However, dissimilarities in welfare systems, including access to health care and public family support, coverage and distance to treatment facilities, lifestyle and socio-cultural aspects, treatment protocols as well as methodological differences between studies make an international comparison challenging. An essential question is to what extent the observed differences across studies are real (reflecting different impact of social and family characteristic due to differences in health care and social stratification, true overall health inequity) or to what extent differences can be explained by features of the studies, including differences in data sources, data collection, cancer type, and diagnostic period.

Strengths, limitations and methodological considerations

These are the first studies in Germany and Denmark on this topic among very few investigations from Europe. The population- and register-based Danish cohort studies with minimal risk of bias were an excellent data source for the investigation. With the national and register-based approach these studies covered virtually all Danish childhood cancer cases with a complete follow-up and thus provided a factual reflection of the situation in Denmark. Through the unique registries in Denmark a broad range of social and family factors were available with high validity excluding any kind of information bias and again with virtually no missing information. For the analysis part taking place in Denmark, individual level SEP markers were available and both married and cohabiting parents could be identified. Thus, this is one out of few studies that could take into account the joint influence of family and social factors, acknowledging that these factors operate together.

An inherent limitation is the low power of epidemiologic studies for rare outcomes, in this case the fortunately low incidence of childhood cancers (see Chapter 2.1). The cohorts studied reflect the population size of Denmark and West Germany and thus include the maximum population available at national level.

Several estimates failed to reach statistical significance despite clear patterns of risk by social factors. Since diagnostic periods and respective treatment protocols as well as the model adjustments differ notably between studies, risk estimates and therefore the magnitudes of associations are not directly comparable across studies, but give indications about differences or similarity of patterns between Denmark and Germany.

Further major limitations apply to specific studies. One is the diagnostic time period of the German study. Data of survival studies are by default historical by the time they are analysed, but the cases in the German studies were diagnosed between October 1992 and September 1994. Since then treatment protocols have improved considerably [33, 123] and the German health care system went through a series of reforms [185], although financial compensation for diagnosis and treatment of childhood cancers is not known to have been changed by these reforms. Nevertheless, it cannot be excluded that the most recent improvements of treatment may have offset or attenuated the relationship between family characteristics and ALL survival found here. Unfortunately, no more recent dataset was available for Germany as no new analytical studies have been carried out since the conduct of the nationwide studies in the 1990s and restricted epidemiological studies (such as in the vicinity of nuclear installations) were not useful for my research questions.

The German study focusing on socioeconomic factors had 18% missing data due to non-participation in the original case-control study; a further 6.5 % of the participating families did not specify their monthly family income and 5.3% did not provide information on maternal education. Poorer survival was noticed in non-participants suggesting that families where the child had died where less likely to participate and potentially not invited to participate by their treating physician. As non-participation in epidemiological studies is possibly associated with lower socioeconomic position, the results might theoretically be biased. However, sensitivity analyses assuming the worst case scenario that every non-participant had lowest maternal education level and lowest family income also yielded no association between socioeconomic factors and ALL survival.

No sex and/ or age group specific analyses were undertaken in any of the survival studies due to very small numbers in subgroups and subcategories. Age was found to be a predictor of treatment compliance with exceptionally poor compliance in adolescents [180]. Thus, patterns for the relationship between social and family factors and childhood cancer survival might vary by age group. Similarly, although there is little evidence for paediatric patient sex being related to compliance with a possible exception for adolescent girls [180], the role of family and social factors in childhood cancer survival might be different for girls and boys. Nevertheless, comparing crude and adjusted results in my analyses does not provide strong evidence that patterns differ by sex or age.

None of the investigations accounted for clinical and immunophenotypic features of the diseases, leaving open the possibility that factors predictive of the occurrence and the characteristics of the disease may confound the prognostic results. For instance, any risk factor associated with leukaemia cases diagnosed with high white blood cell count could appear as prognostic of the outcome if it was not adjusted for number of white blood cell count at diagnosis. However, the respective data were not available.

Conclusion

Social and family factors have the potential to impact survival from childhood cancer, although findings vary by cancer type and across countries. Despite the highly specialized and centralized treatment and free access for all children to all health services, not all children benefit equally from improvements in survival [11]. My findings suggest that cancer biology and treatment are not the only factors influencing survival and that some families may need extra supportive care during the demanding treatment and recovery of their child. Further studies are warranted to gain further knowledge on the impact of social and family factors on childhood cancer survival in other populations and to identify potential underlying mechanisms, particularly with regard to social differences in coping strategies, differential adherence to therapy and related interactions of families with paediatric oncologists in Germany, Denmark and elsewhere. Understanding the pathways leading to such associations is necessary in order to reduce health inequalities.

7.3 Social inequalities in childhood cancer and potential pathways

In the context of this dissertation I observed social inequalities in childhood cancer with respect to reported incidence differences between racial groups in South Africa and compared to Germany, and with respect to survival differences in Germany and Denmark. This work adds to the existing evidence on geographical differences in the reported incidence of childhood cancers (see Chapter 2.1) and on survival differences between social groups within European populations (see Chapter 3.4). Explanations or underlying pathways of these social inequalities cannot be derived from my research, however, as these investigations were not designed for this purpose.

Differences in the genetic make-up, environmental exposures and exposure to certain infectious diseases (see Chapter 2.1) as well as under-ascertainment of cases are discussed

as explanations for the observed geographical differences of childhood cancers [1, 19, 20]. In the context of social inequalities in survival, primarily adherence to and refusal of therapy [139, 145, 152, 180] are discussed in the literature. For developing countries, also malnutrition, variability in drug metabolism and access and utilization of health care and treatment are cited [1, 14, 140, 152]. Although there are some investigations on the impact of childhood cancer on the family life with respect to stress levels of parents of children with cancer, mental health of parents, important stressors and resources as well as coping strategies and behaviour [209, 211, 215, 217, 218], there is little evidence available on the role of those psychosocial aspects in pathways of survival inequalities.

A better understanding of the underlying pathways of those survival differences would help to develop strategies to diminish social inequalities in childhood cancer. The well documented impact of social factors on cancer outcome in adults (see Chapter 4.1) [136] is associated with differences in the time of diagnosis, in the tumour characteristics, in the treatments given and in individual factors, such as lifestyle or the presence of comorbidities [138, 170, 171]. However, in European countries differences in survival from childhood cancer would be expected to be less likely related to co-morbidities and children's lifestyle or early detection (as children are usually subjected to close parental and medical surveillance), but might include reasons such as adherence to treatment recommendations [180]. In low- and middle-income countries time of diagnosis and co-morbidities might indeed be important determinants [1]. Possibly a complex interplay of disease biology, pharmacogenetics, economic, social, psychosocial, family and cultural factors contribute to the observed inequalities in childhood cancer.

Based on the proposed theoretical framework by Hiatt and Breen (see Chapter 4.2) I developed a conceptual model specifically focusing on social inequalities in childhood cancer, illustrating potential pathways by which social and family factors might have an impact on the childhood cancer continuum (see Figure 7). In the model family factors are defined in a broader sense than in my investigations, to also encompass cultural factors and race. Potential key pathways of social inequalities may travel from social and/or family factors through individual risk factors to affect points along the childhood cancer continuum; moreover important routes might travel through factors related to health care including

psychosocial aspects at the time of diagnosis and treatment. The pathways related to health care are probably solely affecting inequalities in morbidity, survival and survivorship. As the drivers that influence social inequalities in childhood cancer incidence are likely to differ from those of inequalities in survival and survivorship, so are the pathways they take likely to differ. Social inequalities in the incidence of childhood cancers are most likely explained by differences in exposures to biological, genetic and/or environmental risk factors of childhood cancers.

Underlying mechanisms of social inequalities in survival are rather complex and might involve several pathways. Family factors are likely to have a particularly important role since children rely on their parents help and support. Possible mediating pathways may include different tumour biology, clinical prognostic factors, age, sex, malnutrition and comorbid conditions, and particularly affect the pathways related to treatment.

The impact of different pathways may vary between settings (such as between low-, middle- and high-income countries) and cancer types. The hypothesised pathways on survival differences related to access and utilization of health care, treatment and treatment adherence, abandonment or refusal of treatment might be of more relevance for developing countries or populations without universal access to health care [175]. Compliance will have greater potential effect upon outcome in malignancies for which outpatient oral chemotherapy plays a major role such as ALL [21, 51] than for those involving mainly inpatient therapy. However, again little is known about the mechanisms involved in compliance of children and adolescents in general and, in particular, in oncology [180].

Finally, social and family factors might similarly have an impact on health and life quality of childhood cancer survivors and their families. In turn, social inequalities might also be created or increased among children who survive after a cancer diagnosis. The cancer experience, its treatment and related psycho-social factors especially during childhood might have long-term consequences that disrupt educational attainment and social functioning of children/ adolescents and thus influence later socioeconomic position [170, 172]. However, inequalities in survivorship were not the focus of this dissertation.

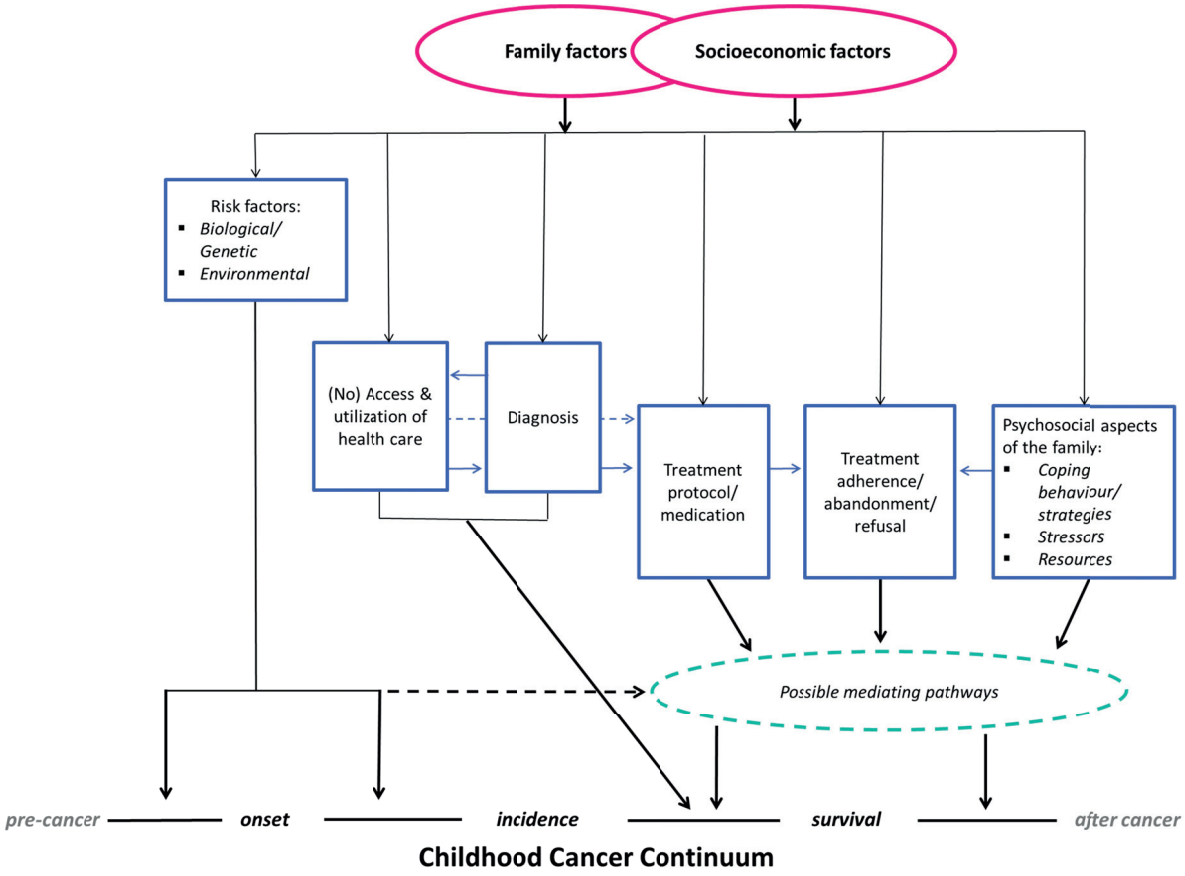

Figure 7: Conceptual model illustrating potential pathways of social inequalities in childhood cancer

8 Overall conclusions and perspectives

Social inequalities affect the health of children, for whom childhood cancer is one of the most dreaded diseases and the leading cause of disease-related deaths among children in high-income countries [1]. The Commission of Social Determinants of Health calls for global action on the social determinants of health to advance health equity and stresses the importance to promote health equity from the start of life [219].

Findings from this dissertation indicate substantial differences in the reported incidence of childhood cancers between South Africa and Germany as well as between racial groups within South Africa, with lowest rates observed among Black children and highest among White children. At least to some extent, these observed differences are most likely due to social inequalities in access and utilization of health care services rather than reflecting actual differences in cancer risks. More research is needed to understand the extent to which under-reporting and under-diagnosis drive not only the findings for South Africa but the global reported geographical patterns of childhood cancer. A better understanding of the actual incidence in low- and middle-income countries and the extent of under-diagnosis and under-reporting might bring more insight into the aetiology of childhood cancers. This, in turn, might also reveal specific pathways for under-diagnosis, identify social groups which are particularly affected, and uncover weaknesses in the respective health care systems. Since survival for many childhood cancers, when diagnosed at an early stage and treated according to high standard treatment protocols, is generally very good [11] it is essential to facilitate access to medical services for disadvantaged families, raise awareness on childhood cancers and its treatment options in the general population, train health care providers, and enhance diagnostic capacities.

Moreover, findings of this dissertation highlight social inequalities in survival from childhood cancer in Germany and Denmark, although not consistently across cancer types. Similarly, the evidence is rather inconsistent for entire Europe, with existing studies being also methodologically very heterogeneous (see Chapter 3.4). Different social and family factors may have different impact and importance, varying noticeably by country. A crucial question

is to what extent the observed differences across studies are real or to what extent differences can be explained by features of the studies. Therefore, first of all, further knowledge on a national level on various social and family factors by cancer type is required. Secondly, reduction of social inequality in disease and survival from diseases is an important public matter. Understanding the pathways and underlying mechanisms by which social and family factors may influence prognosis of childhood cancers would help to develop targeted strategies to diminish those social inequalities. However, this knowledge is very sparse. We need to distinguish which factors are involved in the development of inequalities and what the relative contribution of each of these factors is; we also need to identify where in the childhood cancer continuum the social differences are most pronounced.

In future studies, investigators should propose specific mechanisms and pathways *a priori* and identify measures of social factors and outcomes consistent with their hypotheses. Mixed methods approaches could be used with qualitative methods such as focus group discussions or expert interviews complementing a quantitative study design [211, 220]. Focus groups with for instance parents concerned, children with cancer (of a certain age), childhood cancer survivors, and health professionals including paediatric oncologists may reveal specific pathways for survival inequalities. The information learned from a qualitative study could be used for development of a structured questionnaire for a quantitative investigation [220], studying the importance of certain pathways and possible variability between populations.

Although my research findings on survival inequalities only concern Germany and Denmark, this is equally of relevance for less-developed countries. Since with high standard treatments 80% of all childhood cancer are potentially curable [11], yet about 91,000 deaths per year occur in low- and middle-income countries (which is 94% of the global mortality) [12], and survival inequalities are even more pronounced in less-developed countries [13, 139, 142, 143], improvement of health care and reduction of social inequalities are similarly of high priority for low- and middle-income countries.

Lastly, as a result of the improvements in survival the number of childhood cancer survivors continues to substantially increase [12]. Thus health and quality of life of childhood cancer survivors and the relationship with social and family factors are also likely to substantially

increase in terms of public health relevance. In the first instance this will be particularly so among high-income countries but will subsequently also affect low- and middle-income countries.

References

1. Magrath I, Steliarova-Foucher E, Epelman S, Ribeiro RC, Harif M, Li C-K, Kebudi R, Macfarlane SD, Howard SC: **Paediatric cancer in low-income and middle-income countries**. *The Lancet Oncology* 2013, **14**(3):e104-e116.
2. Steliarova-Foucher E, Frazier AL: **Chapter 1.3 Childhood cancer**. In: *World Cancer Report 2014.* Edited by Stewart B, Wild PW. Lyon: International Agency for Research on Cancer; 2014: 69-76.
3. Kaatsch P, Spix C: **German Childhood Cancer Registry - Annual Report 2012 (1980-2012).** Mainz: Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI) at the University Medical Center of the Johannes Gutenberg University 2013.
4. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A: **Childhood and adolescent cancer statistics, 2014**. *CA: A Cancer Journal for Clinicians* 2014, **64**(2):83-103.
5. McNally RJ, Parker L: **Environmental factors and childhood acute leukemias and lymphomas**. *Leukemia & Lymphoma* 2006, **47**(4):583-598.
6. Buffler P, Kwan M, Reynolds P, Urayama K: **Environmental and Genetic Risk Factors for Childhood Leukemia: Appraising the Evidence**. *Cancer Investigation* 2005, **23**(1):60-75.
7. Savage S, Schüz J: **Environmental Chemicals and Childhood Cancer**. In: *Encyclopedia of Environmental Health.* Edited by Nriagu J. Burlington: Elsevier Science & Technology; 2011: 336-347.
8. Spector LG, Pankratz N, Marcotte EL: **Genetic and Nongenetic Risk Factors for Childhood Cancer**. *Pediatric Clinics of North America* 2015, **62**(1):11-25.
9. Belson M, Kingsley B, Holmes A: **Risk factors for acute leukemia in children: a review**. *Environmental Health Perspectives* 2007, **115**(1):138-145.
10. Schüz J, Kaatsch P, Kaletsch U, Meinert R, Michaelis J: **Association of childhood cancer with factors related to pregnancy and birth.** *International Journal of Epidemiology* 1999, **28**(4):631-639.
11. Gatta G, Botta L, Rossi S, Aareleid T, Bielska-Lasota M, Clavel J, Dimitrova N, Jakab Z, Kaatsch P, Lacour B *et al*: **Childhood cancer survival in Europe 1999–2007: results of EUROCARE-5—a population-based study**. *The Lancet Oncology* 2014, **15**(1):35-47.
12. Pritchard-Jones K, Pieters R, Reaman GH, Hjorth L, Downie P, Calaminus G, Naafs-Wilstra MC, Steliarova-Foucher E: **Sustaining innovation and improvement in the treatment of childhood cancer: lessons from high-income countries**. *The Lancet Oncology* 2013, **14**(3):e95-e103.
13. Stones DK, De Bruin GP, Esterhuizen TM, Stefan DC: **Childhood cancer survival rates in two South African units**. *South African Medical Journal* 2014, **104**(7):501.
14. Hadley LG, Rouma BS, Saad-Eldin Y: **Challenge of pediatric oncology in Africa**. *Seminars in Pediatric Surgery* 2012, **21**(2):136-141.
15. Baade PD, Youlden DR, Valery PC, Hassall T, Ward L, Green AC, Aitken JF: **Trends in incidence of childhood cancer in Australia, 1983-2006**. *British Journal of Cancer* 2010, **102**(3):620-626.
16. Cancer Research UK: **Great Britain Cancer Incidence (1996-2005) Summary – Children, February 2014**
17. Parkin DM, Ferlay J, Hamdi-Cherif M, Sitas F, Thomas J, Wabinga H, Whelan SL: **Chapter 5: Childhood cancer.** In: *Cancer in Africa: Epidemiology and Prevention. IARC Scientific Publications No. 153.* Lyon: International Agency for Research on Cancer; 2003.
18. Chokunonga E, Borok MZ, Chirenje ZM, Nyakabau AM, Makunike-Mutasa R: **Cancer Incidence in Harare. Triennal Report 2010-2012.** Harare: National Cabcer Registry Zimbabwe; 2013.
19. Newton R: **Geographical variation in the incidence of acute lymphoblastic leukaemia in childhood-Is it real?** *Cancer Epidemiology* 2009, **33**(6):401-402.

20. Howard SC, Metzger ML, Wilimas JA, Quintana Y, Pui CH, Robison LL, Ribeiro RC: **Childhood cancer epidemiology in low-income countries**. *Cancer* 2008, **112**(3):461-472.
21. Lightfoot T, Johnston W, Simpson J, Smith A, Ansell P, Crouch S, Roman E, Kinsey S: **Survival from childhood acute lymphoblastic leukaemia: the impact of social inequality in the United Kingdom**. *European Journal of Cancer* 2012, **48**(2):263-269.
22. Syse A, Lyngstad TH, Kravdal O: **Is mortality after childhood cancer dependent on social or economic resources of parents? A population-based study**. *International Journal of Cancer* 2012, **130**(8):1870-1878.
23. Youlden DR, Baade PD, Valery PC, Ward LJ, Green AC, Aitken JF: **Differentials in Survival for Childhood Cancer in Australia by Remoteness of Residence and Area Disadvantage**. *Cancer Epidemiology Biomarkers & Prevention* 2011, **20**(8):1649-1656.
24. Coebergh JW, van der Does-van den Berg A, Hop W, van Weerden F, Rammeloo J, van Steensel H, van Wering E, Kamps WA: **Small influence of parental educational level on the survival of children with leukaemia in The Netherlands between 1973 and 1979**. *European Journal of Cancer* 1996, **32A**(2):286-289.
25. Walsh PM, Byrne J, Capra M, Comber H: **Childhood cancer survival in Ireland: Temporal, regional and deprivation-related patterns**. *European Journal of Cancer* 2011, **47**(12):1852-1862.
26. Sergentanis T, Dessypris N, Kanavidis P, Skalkidis I, Baka M, Polychronopoulou S, Athanassiadou F, Stiakaki E, Frangandrea I, Moschovi M *et al*: **Socioeconomic status, area remoteness, and survival from childhood leukemia**. *European Journal of Cancer Prevention* 2012:1.
27. Kent E, Sender L, Largent J, Anton-Culver H: **Leukemia survival in children, adolescents, and young adults: influence of socioeconomic status and other demographic factors.** *Cancer Causes & Control* 2009, **20**(8):1409-1420.
28. Gupta S, Sutradhar R, Guttmann A, Sung L, Pole JD: **Socioeconomic status and event free survival in pediatric acute lymphoblastic leukemia: A population-based cohort study**. *Leukemia Research* 2014, **38**(12):1407-1412.
29. Darmawikarta D, Pole JD, Gupta S, Nathan PC, Greenberg M: **The association between socioeconomic status and survival among children with Hodgkin and non-Hodgkin lymphomas in a universal health care system**. *Pediatric Blood & Cancer* 2013, **60**(7):1171-1177.
30. Statistics South Africa: **General household survey 2006, July 2006.** Pretoria: Statistics South Africa; 2007.
31. Schmiegelow K, Forestier E, Hellebostad M, Heyman M, Kristinsson J, Soderhall S, Taskinen M, Nordic Society of Paediatric H, Oncology: **Long-term results of NOPHO ALL-92 and ALL-2000 studies of childhood acute lymphoblastic leukemia**. *Leukemia* 2010, **24**(2):345-354.
32. Márky I, Björk O, Forestier E, Jónsson ÓG, Perkkiö M, Schmiegelow K, Storm-Mathiesen I, Gustafsson G: **Intensive chemotherapy without radiotherapy gives more than 85% event-free survival for non-Hodgkin lymphoma without central nervous involvement: a 6-year population-based study from the nordic society of pediatric hematology and oncology.** *Journal of Pediatric Hematology/ Oncology* 2004, **26**(9):555-560.
33. Moricke A, Zimmermann M, Reiter A, Henze G, Schrauder A, Gadner H, Ludwig WD, Ritter J, Harbott J, Mann G *et al*: **Long-term results of five consecutive trials in childhood acute lymphoblastic leukemia performed by the ALL-BFM study group from 1981 to 2000**. *Leukemia* 2010, **24**(2):265-284.
34. Greaves M: **Infection, immune responses and the aetiology of childhood leukaemia**. *Nature Reviews Cancer* 2006, **6**(3):193-203.
35. Greaves M: **Commentary: Birth order and risk of childhood acute lymphoblastic leukaemia (ALL)**. *International Journal of Epidemiology* 2001:1438-1439.
36. Schuz J, Grell K, Kinsey S, Linet MS, Link MP, Mezei G, Pollock BH, Roman E, Zhang Y, McBride ML *et al*: **Extremely low-frequency magnetic fields and survival from childhood acute**

lymphoblastic leukemia: an international follow-up study. *Blood Cancer Journal* 2012, **2**:e98.

37. Von Behren J, Spector LG, Mueller BA, Carozza SE, Chow EJ, Fox EE, Horel S, Johnson KJ, McLaughlin C, Puumala SE *et al*: **Birth order and risk of childhood cancer: a pooled analysis from five US States**. *International Journal of Cancer* 2011, **128**(11):2709-2716.
38. Hjalgrim LL, Rostgaard K, Hjalgrim H, Westergaard T, Thomassen H, Forestier E, Gustafsson G, Kristinsson J, Melbye M, Schmiegelow K: **Birth weight and risk for childhood leukemia in Denmark, Sweden, Norway, and Iceland**. *Journal of the National Cancer Institute* 2004, **96**(20):1549-1556.
39. Schuz J, Schmidt LS, Kogner P, Lahteenmaki PM, Pal N, Stokland T, Schmiegelow K: **Birth characteristics and Wilms tumors in children in the Nordic countries: a register-based case-control study**. *International Journal of Cancer* 2011, **128**(9):2166-2173.
40. Dockerty J, Draper GJ, Vincent TJ, Rowan S, Bunch K: **Case-control study of parental age, parity and socioeconomic level in relation to childhood cancers**. *International Journal of Epidemiology* 2001, **30**(6):1428-1437.
41. Oksuzyan S, Crespi CM, Cockburn M, Mezei G, Kheifets L: **Birth weight and other perinatal characteristics and childhood leukemia in California**. *Cancer Epidemiology* 2012, **36**(6):e359-365.
42. The World Bank: **Health Nutrition and Population Statistics.** The World Bank Group; 2015. [http://databank.worldbank.org/data/views/variableSelection/selectvariables.aspx?source=health-nutrition-and-population-statistics] [03.02.2015].
43. GBD 2013 Mortality and Causes of Death Collabrorators: **Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013**. *The Lancet* 2015, **385**(9963):117-171.
44. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF *et al*: **Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013**. *The Lancet* 2014, **384**(9945):766-781.
45. Li J, Thompson TD, Miller JW, Pollack LA, Stewart SL: **Cancer incidence among children and adolescents in the United States, 2001-2003**. *Pediatrics* 2008, **121**(6):e1470-1477.
46. Stewart B, Wild CP (editors): **World Cancer Report 2014**, Lyon: International Agency for Research on Cancer; 2014.
47. Pizzo PA, Poplack DG: **Principles and Practice of Pediatric Oncology, sixth edition**, Philadelphia: Lippincott Williams & Wilkins; 2010.
48. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S, (editors): **International Classification of Diseases for Oncology, third edition** Geneva: World Health Organisation; 2000.
49. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P: **International Classification of Childhood Cancer, third edition**. *Cancer* 2005, **103**(7):1457-1467.
50. Birch JM, Mardsen HB: **Classification scheme for childhood cancer**. *International Journal of Cancer* 1987, **40**(5):620-624.
51. Stanulla M, Schrappe M: **Treatment of Childhood Acute Lymphoblastic Leukemia**. *Seminars in Hematology* 2009, **46**(1):52-63.
52. Inaba H, Greaves M, Mullighan CG: **Acute lymphoblastic leukaemia**. *The Lancet* 2013, **381**(9881):1943-1955.
53. American Cancer Society: **Learn About Cancer.** American Cancer Society; 2015. [http://www.cancer.org/cancer/index] [04.03.2015].
54. Allen CE, Kelly KM, Bollard CM: **Pediatric Lymphomas and Histiocytic Disorders of Childhood**. *Pediatric Clinics of North America* 2015, **62**(1):139-165.
55. Chintagumpala M, Gajjar A: **Brain Tumors**. *Pediatric Clinics of North America* 2015, **62**(1):167-178.

56. Irwin MS, Park JR: **Neuroblastoma: Paradigm for Precision Medicine**. *Pediatric Clinics of North America* 2015, **62**(1):225-256.
57. Rodriguez-Galindo C, Orbach DB, VanderVeen D: **Retinoblastoma**. *Pediatric Clinics of North America* 2015, **62**(1):201-223.
58. Kesminiene A, Schüz J: **Chapter 2.8 Radiation: ionizing, ultraviolet, and electromagnetic** In: *World Cancer Report 2014.* Edited by Stewart B, Wild CP. Lyon: International Agency for Research on Cancer; 2014: 143-150.
59. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin D, Forman D, Bray F: **GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11**. In., Lyon, France: International Agency for Research on Cancer; 2013.
60. Kaatsch P, Steliarova-Foucher E, Crocetti E, Magnani C, Spix C, Zambon P: **Time trends of cancer incidence in European children (1978-1997): report from the Automated Childhood Cancer Information System project**. *European Journal of Cancer* 2006, **42**(13):1961-1971.
61. Stiller CA, Marcos-Gragera R, Ardanaz E, Pannelli F, Almar Marques E, Canada Martinez A, Steliarova-Foucher E: **Geographical patterns of childhood cancer incidence in Europe, 1988-1997. Report from the Automated Childhood Cancer Information System project**. *European Journal of Cancer* 2006, **42**(13):1952-1960.
62. Smith MA, Seibel NL, Altekruse SF, Ries LAG, Melbert DL, O'Leary M, Smith FO, Reaman GH: **Outcomes for Children and Adolescents With Cancer: Challenges for the Twenty-First Century**. *Journal of Clinical Oncology* 2010, **28**(15):2625-2634.
63. Moreno F, Loria D, Abriata G, Terracini B, network R: **Childhood cancer: incidence and early deaths in Argentina, 2000-2008**. *European Journal of Cancer* 2013, **49**(2):465-473.
64. Wiangnon S, Kamsa-Ard S, Jetsrisuparb A, Sriplung H, Sontipong S, Sumitsawan Y, Martin N: **Childhood Cancer in Thailand: 1995-1997**. *Asian Pacific Journal of Cancer Prevention* 2003, **4**(4):337-343.
65. Pritchard-Jones K, Kaatsch P, Steliarova-Foucher E, Stiller CA, Coebergh JWW: **Cancer in children and adolescents in Europe: Developments over 20 years and future challenges**. *European Journal of Cancer* 2006, **42**(13):2183-2190.
66. Parkin DM: **The global health burden of infection-associated cancers in the year 2002**. *International Journal of Cancer* 2006, **118**(12):3030-3044.
67. Magrath I: **Epidemiology: clues to the pathogenesis of Burkitt lymphoma**. *British Journal of Haematology* 2012, **156**(6):744-756.
68. Carozza SE, Puumala SE, Chow EJ, Fox EE, Horel S, Johnson KJ, McLaughlin CC, Reynolds P, Von Behren J, Mueller BA *et al*: **Parental educational attainment as an indicator of socioeconomic status and risk of childhood cancers**. *British Journal of Cancer* 2010, **103**(1):136-142.
69. Chow EJ, Puumala SE, Mueller BA, Carozza SE, Fox EE, Horel S, Johnson KJ, McLaughlin CC, Reynolds P, Von Behren J *et al*: **Childhood cancer in relation to parental race and ethnicity: a 5-state pooled analysis**. *Cancer* 2010, **116**(12):3045-3053.
70. Swaminathan R, Rama R, Shanta V: **Childhood cancers in Chennai, India, 1990-2001: incidence and survival**. *International Journal of Cancer* 2008, **122**(11):2607-2611.
71. Dietrich M, Block G, Pogoda JM, Buffler P, Hecht S, Preston-Martin S: **A review: dietary and endogenously formed N-nitroso compounds and risk of childhood brain tumors**. *Cancer Causes Control* 2005, **16**(6):619-635.
72. Vinson F, Merhi M, Baldi I, Raynal H, Gamet-Payrastre L: **Exposure to pesticides and risk of childhood cancer: a meta-analysis of recent epidemiological studies**. *Occupational and Environmental Medicine* 2011, **68**(9):694-702.
73. Schuz J, Ahlbom A: **Exposure to electromagnetic fields and the risk of childhood leukaemia: a review**. *Radiation Protection Dosimetry* 2008, **132**(2):202-211.
74. Azevedo-Silva F, Reis Rde S, Santos Mde O, Luiz RR, Pombo-de-Oliveira MS: **Evaluation of childhood acute leukemia incidence and underreporting in Brazil by capture-recapture methodology**. *Cancer Epidemiology* 2009, **33**(6):403-405.

75. Swaminathan R, Sankaranarayanan R: **Under-diagnosis and under-ascertainment of cases may be the reasons for low childhood cancer incidence in rural India**. *Cancer Epidemiology* 2010, **34**(1):107-108.
76. Mostert S, Njuguna F, Kemps L, Strother M, Aluoch L, Buziba G, Kaspers G: **Epidemiology of diagnosed childhood cancer in Western Kenya**. *Archives of Disease in Childhood* 2012, **97**(6):508-512.
77. Bhopal SS, Mann KD, Pearce MS: **Registration of cancer in girls remains lower than expected in countries with low/middle incomes and low female education rates**. *British Journal of Cancer* 2012, **107**(1):183-188.
78. Institute for Health Metrics and Evaluation (IHME): **Millennium Development Goals (MDGs) Visualization.** Seattle: IHME, University of Washington; 2014. [http://vizhub.healthdata.org/mdg.] [22.02.2015].
79. Mori H, Colman SM, Xiao Z, Ford AM, Healy LE, Donaldson C, Hows JM, Navarrete C, Greaves M: **Chromosome translocations and covert leukemic clones are generated during normal fetal development**. *Proceedings of the National Academy of Sciences of the United States of America* 2002, **99**(12):8242-8247.
80. Ross JA, Spector LG, Robison LL, Olshan AF: **Epidemiology of leukemia in children with Down syndrome**. *Pediatric Blood & Cancer* 2005, **44**(1):8-12.
81. Malkin D: **Li-fraumeni syndrome**. *Genes Cancer* 2011, **2**(4):475-484.
82. Carozza SE, Langlois PH, Miller EA, Canfield M: **Are children with birth defects at higher risk of childhood cancers?** *American Journal of Epidemiology* 2012, **175**(12):1217-1224.
83. Kinlen L: **Evidence for an infective cause of childhood leukaemia: comparison of a Scottish new town with nuclear reprocessing sites in Britain.** *The Lancet* 1988, **332**(8624):1323-1327.
84. Kinlen LJ: **An examination, with a meta-analysis, of studies of childhood leukaemia in relation to population mixing**. *British Journal of Cancer* 2012, **107**(7):1163-1168.
85. Greaves M: **Molecular genetics, natural history and the demise of childhood leukaemia.** *European Journal of Cancer* 1999, **35**(14):1941-1953.
86. Gilham C, Peto J, Simpson J, Roman E, Eden TO, Greaves MF, Alexander FE, Investigators U: **Day care in infancy and risk of childhood acute lymphoblastic leukaemia: findings from UK case-control study**. *BMJ* 2005, **330**(7503):1294.
87. Infante-Rivard C, Fortier I, Olson E: **Markers of infection, breast-feeding and childhood acute lymphoblastic leukaemia.** *British Journal of Cancer* 2000, **83**(11):1559-1564.
88. Dockerty JD, Skegg DC, Elwood JM, Herbison GP, Bercroft DM, Lewis ME: **Infections, vaccinations, and the risk of childhood leukaemia.** *British Journal of Cancer* 1999, **80**(9):1483-1489.
89. Kwan ML, Buffler PA, Abrams B, Kiley VA: **Breastfeeding and the risk of childhood leukemia: a meta-analysis**. *Public Health Reports* 2004, **119**(6):521-535.
90. Urayama KY, Buffler PA, Gallagher ER, Ayoob JM, Ma X: **A meta-analysis of the association between day-care attendance and childhood acute lymphoblastic leukaemia**. *International Journal of Epidemiology* 2010, **39**(3):718-732.
91. Rudant J, Lightfoot T, Urayama KY, Petridou E, Dockerty JD, Magnani C, Milne E, Spector LG, Ashton LJ, Dessypris N *et al*: **Childhood Acute Lymphoblastic Leukemia and Indicators of Early Immune Stimulation: A Childhood Leukemia International Consortium Study**. *American Journal of Epidemiology* 2015.
92. Schmidt LS, Kamper-Jorgensen M, Schmiegelow K, Johansen C, Lahteenmaki P, Trager C, Stokland T, Grell K, Gustafson G, Kogner P *et al*: **Infectious exposure in the first years of life and risk of central nervous system tumours in children: analysis of birth order, childcare attendance and seasonality of birth**. *British Journal of Cancer* 2010, **102**(11):1670-1675.
93. Turner MC, Wigle DT, Krewski D: **Residential pesticides and childhood leukemia: a systematic review and meta-analysis**. *Environmental Health Perspectives* 2010, **118**(1):33-41.

94. Bailey HD, Fritschi L, Infante-Rivard C, Glass DC, Miligi L, Dockerty JD, Lightfoot T, Clavel J, Roman E, Spector LG *et al*: **Parental occupational pesticide exposure and the risk of childhood leukemia in the offspring: findings from the childhood leukemia international consortium**. *International Journal of Cancer* 2014, **135**(9):2157-2172.
95. Wigle DT, Turner MC, Krewski D: **A systematic review and meta-analysis of childhood leukemia and parental occupational pesticide exposure.** *Environmental Health Perspectives* 2009, **117**(10):1505-1513.
96. Kwan ML, Metayer C, Crouse V, Buffler PA: **Maternal illness and drug/medication use during the period surrounding pregnancy and risk of childhood leukemia among offspring**. *American Journal of Epidemiology* 2007, **165**(1):27-35.
97. Klimentopoulou A, Antonopoulos CN, Papadopoulou C, Kanavidis P, Tourvas AD, Polychronopoulou S, Baka M, Athanasiadou-Piperopoulou F, Kalmanti M, Sidi V *et al*: **Maternal smoking during pregnancy and risk for childhood leukemia: a nationwide case-control study in Greece and meta-analysis**. *Pediatric Blood & Cancer* 2012, **58**(3):344-351.
98. Milne E, Greenop KR, Scott RJ, Bailey HD, Attia J, Dalla-Pozza L, de Klerk NH, Armstrong BK: **Parental prenatal smoking and risk of childhood acute lymphoblastic leukemia**. *American Journal of Epidemiology* 2012, **175**(1):43-53.
99. Latino-Martel P, Chan DS, Druesne-Pecollo N, Barrandon E, Hercberg S, Norat T: **Maternal alcohol consumption during pregnancy and risk of childhood leukemia: systematic review and meta-analysis**. *Cancer Epidemiology Biomarkers & Prevention* 2010, **19**(5):1238-1260.
100. Cheng J, Su H, Zhu R, Wang X, Peng M, Song J, Fan D: **Maternal coffee consumption during pregnancy and risk of childhood acute leukemia: a metaanalysis**. *American Journal of Obstetrics and Gynecology* 2014, **210**(2):151 e151-151 e110.
101. Goh YI, Bollano E, Einarson TR, Koren G: **Prenatal multivitamin supplementation and rates of pediatric cancers: a meta-analysis**. *Clinical Pharmacology & Therapeutics* 2007, **81**(5):685-691.
102. International Agency for Research on Cancer: **Non-Ionizing Radiation, Part 1: Static and Extremely Low-Frequency (ELF) Electric and Magnetic Fields, VOLUMNE 80.** *IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS.* Lyon, France; 2002.
103. Caughey RW, Michels KB: **Birth weight and childhood leukemia: a meta-analysis and review of the current evidence**. *International Journal of Cancer* 2009, **124**(11):2658-2670.
104. Hjalgrim LL: **Birth Weight as a Risk Factor for Childhood Leukemia: A Meta-Analysis of 18 Epidemiologic Studies**. *American Journal of Epidemiology* 2003, **158**(8):724-735.
105. Harder T, Plagemann A, Harder A: **Birth weight and risk of neuroblastoma: a meta-analysis**. *International Journal of Epidemiology* 2010, **39**(3):746-756.
106. Chu A, Heck JE, Ribeiro KB, Brennan P, Boffetta P, Buffler P, Hung RJ: **Wilms' tumour: a systematic review of risk factors and meta-analysis**. *Paediatric and Perinatal Epidemiology* 2010, **24**(5):449-469.
107. Schmidt LS, Schuz J, Lahteenmaki P, Trager C, Stokland T, Gustafson G, Hjalgrim L, Sehested A, Johansen C, Schmiegelow K: **Fetal growth, preterm birth, neonatal stress and risk for CNS tumors in children: a Nordic population- and register-based case-control study**. *Cancer Epidemiology Biomarkers & Prevention* 2010, **19**(4):1042-1052.
108. Harder T, Plagemann A, Harder A: **Birth weight and subsequent risk of childhood primary brain tumors: a meta-analysis**. *American Journal of Epidemiology* 2008, **168**(4):366-373.
109. de Fine Licht S, Schmidt LS, Rod NH, Schmiegelow K, Lahteenmaki PM, Kogner P, Trager C, Stokland T, Schuz J: **Hepatoblastoma in the Nordic countries**. *International Journal of Cancer* 2012, **131**(4):E555-561.
110. Ross JA, Perentesis JP, Robinson LL, Davies SM: **Big babies and infant leukemia: a role for insulin-like growth factor-1?** *Cancer Causes & Control* 1996, **7**(5):553-559.
111. Lunde A, Melve KK, Gjessing HK, Skjaerven R, Irgens LM: **Genetic and environmental influences on birth weight, birth length, head circumference, and gestational age by use of**

population-based parent-offspring data. *American Journal of Epidemiology* 2007, **165**(7):734-741.
112. Larfors G, Hallbook H, Simonsson B: **Parental age, family size, and offspring's risk of childhood and adult acute leukemia**. *Cancer Epidemiology Biomarkers & Prevention* 2012, **21**(7):1185-1190.
113. Johnson KJ, Carozza SE, Chow EJ, Fox EE, Horel S, McLaughlin CC, Mueller BA, Puumala SE, Reynolds P, Von Behren J *et al*: **Parental age and risk of childhood cancer: a pooled analysis**. *Epidemiology* 2009, **20**(4):475-483.
114. Yip BH, Pawitan Y, Czene K: **Parental age and risk of childhood cancers: a population-based cohort study from Sweden**. *International Journal of Epidemiology* 2006, **35**(6):1495-1503.
115. Crump C, Sundquist J, Sieh W, Winkleby MA, Sundquist K: **Perinatal and familial risk factors for acute lymphoblastic leukemia in a Swedish national cohort**. *Cancer* 2014.
116. Smith A, Roman E, Simpson J, Ansell P, Fear NT, Eden T: **Childhood leukaemia and socioeconomic status: fact or artefact? A report from the United Kingdom childhood cancer study (UKCCS)**. *International Journal of Epidemiology* 2006, **35**(6):1504-1513.
117. Kroll ME, Stiller CA, Murphy MF, Carpenter LM: **Childhood leukaemia and socioeconomic status in England and Wales 1976-2005: evidence of higher incidence in relatively affluent communities persists over time**. *British Journal of Cancer* 2011, **105**(11):1783-1787.
118. Youlden DR, Baade PD, Valery PC, Hassall TE, Ward LJ, Green AC, Aitken JF: **Area-based differentials in childhood cancer incidence in Australia, 1996-2006**. *Pediatric Blood & Cancer* 2012, **58**(3):390-394.
119. Adam M, Rebholz CE, Egger M, Zwahlen M, Kuehni CE: **Childhood leukaemia and socioeconomic status: what is the evidence?** *Radiation Protection Dosimetry* 2008, **132**(2):246-254.
120. Lie SO, Abrahamsson J, Clausen N, Forestier E, Hasle H, Hovi L, Jonmundsson G, Mellander L, Siimes MA, Yssing M *et al*: **Long-term results in children with AML: NOPHO-AML Study Group--report of three consecutive trials**. *Leukemia* 2005, **19**(12):2090-2100.
121. Pui CH, Carroll WL, Meshinchi S, Arceci RJ: **Biology, Risk Stratification, and Therapy of Pediatric Acute Leukemias: An Update**. *Journal of Clinical Oncology* 2011, **29**(5):551-565.
122. Mitchell C, Richards S, Harrison CJ, Eden T: **Long-term follow-up of the United Kingdom medical research council protocols for childhood acute lymphoblastic leukaemia, 1980–2001**. *Leukemia* 2009, **24**(2):406-418.
123. Escherich G, Horstmann MA, Zimmermann M, Janka-Schaub GE: **Cooperative study group for childhood acute lymphoblastic leukaemia (COALL): long-term results of trials 82,85,89,92 and 97**. *Leukemia* 2010, **24**(2):298-308.
124. O'Leary M, Krailo M, Anderson JR, Reaman GH, Children's Oncology G: **Progress in childhood cancer: 50 years of research collaboration, a report from the Children's Oncology Group**. *Seminars in Oncology* 2008, **35**(5):484-493.
125. Vassal G, Fitzgerald E, Schrappe M, Arnold F, Kowalczyk J, Walker D, Hjorth L, Riccardi R, Kienesberger A, Jones KP *et al*: **Challenges for children and adolescents with cancer in Europe: the SIOP-Europe agenda**. *Pediatric Blood & Cancer* 2014, **61**(9):1551-1557.
126. Steliarovafoucher E, Stiller C, Kaatsch P, Berrino F, Coebergh J, Lacour B, Perkin M: **Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCIS project): an epidemiological study**. *The Lancet* 2004, **364**(9451):2097-2105.
127. Basta NO, James PW, Gomez-Pozo B, Craft AW, McNally RJQ: **Survival from childhood cancer in northern England, 1968–2005**. *British Journal of Cancer* 2011, **105**(9):1402-1408.
128. Johnston WT, Lightfoot TJ, Simpson J, Roman E: **Childhood cancer survival: A report from the United Kingdom Childhood Cancer Study**. *Cancer Epidemiology* 2010, **34**(6):659-666.
129. Baade PD, Youlden DR, Valery PC, Hassall T, Ward L, Green AC, Aitken JF: **Population-based survival estimates for childhood cancer in Australia during the period 1997–2006**. *British Journal of Cancer* 2010, **103**(11):1663-1670.

130. Bao PP, Zheng Y, Wang CF, Gu K, Jin F, Lu W: **Time trends and characteristics of childhood cancer among children age 0-14 in Shanghai**. *Pediatric Blood & Cancer* 2009, **53**(1):13-16.
131. Donadieu J, Auclerc M, Baruchel A, Perel Y, Bordigoni P, Landman-Parker J, Leblanc T, Cornu G, Sommelet D, Leverger G *et al*: **Prognostic study of continuous variables (white blood cell count, peripheral blast cell count, haemoglobin level, platelet count and age) in childhood acute lymphoblastic leukaemia. Analysis of a population of 1545 children treated by the French Acute Lymphoblastic Leukaemia Group (FRALLE).** *British Journal of Cancer* 2000, **83**(12):1617-1622.
132. Pui C, Boyett J, Relling M, Harrison P, Rivera G, Behm F, Sandlund J, Ribeiro R, Rubnitz J, Gajjar A *et al*: **Sex differences in prognosis for children with acute lymphoblastic leukemia.** *Journal of Clinical Oncology* 1999, **17**(3):818-824.
133. Tarlock K, Meshinchi S: **Pediatric Acute Myeloid Leukemia: Biology and Therapeutic Implications of Genomic Variants**. *Pediatric Clinics of North America* 2015, **62**(1):75-93.
134. Institute NC: **Childhood Non-Hodgkin Lymphoma Treatment (PDQ®). General Information About Childhood Non-Hodgkin Lymphoma (NHL).** 2015. [13.01.2015].
135. Yanagisawa T, Bartels U, Bouffet E: **Role of prognostic factors in the management of pediatric solid tumors**. *Annals of the New York Academy of Sciences* 2008, **1138**:32-42.
136. Dalton SO, Schüz J, Engholm G, Johansen C, Kjær SK, Steding-Jessen M, Storm HH, Olsen JH: **Social inequality in incidence of and survival from cancer in a population-based study in Denmark, 1994–2003: Summary of findings**. *European Journal of Cancer* 2008, **44**(14):2074-2085.
137. Sprague BL, Trentham-Dietz A, Gangnon RE, Ramchandani R, Hampton JM, Robert SA, Remington PL, Newcomb PA: **Socioeconomic status and survival after an invasive breast cancer diagnosis**. *Cancer* 2011, **117**(7):1542-1551.
138. Woods LM, Rachet B, Coleman MP: **Origins of socio-economic inequalities in cancer survival: a review**. *Annals of Oncology* 2006, **17**(1):5-19.
139. Mostert S, Sitaresmi MN, Gundy CM, Janes V, Sutaryo, Veerman AJP: **Comparing childhood leukaemia treatment before and after the introduction of a parental education programme in Indonesia**. *Archives of Disease in Childhood* 2010, **95**(1):20-25.
140. Viana M, Fernandes R, de Oliveira B, Murao M, de Andrade Paes C, Duarte A: **Nutritional and socio-economic status in the prognosis of childhood acute lymphoblastic leukemia**. *Haematologica* 2001, **86**(2):113-120.
141. Gupta S, Bonilla M, Fuentes SL, Caniza M, Howard SC, Barr R, Greenberg ML, Ribeiro R, Sung L: **Incidence and predictors of treatment-related mortality in paediatric acute leukaemia in El Salvador**. *British Journal of Cancer* 2009, **100**(7):1026-1031.
142. Gupta S, Wilejto M, Pole J, Guttermann A, Sung L: **Low socioeconomic status is associated with worse survival in children with cancer: a systematic review**. *PloS One* 2014, **9**(2).
143. Tang Y, Xu X, Song H, Yang S, Shi S, Wei J: **Long-term outcome of childhood acute lymphoblastic leukemia treated in China**. *Pediatric Blood & Cancer* 2008, **51**(3):380-386.
144. Gómez-Almaguer D, Ruiz-Argüelles GJ, Ponce-de-León S: **Nutritional status and socio-economic conditions as prognostic factors in the outcome of therapy in childhood acute lymphoblastic leukemia.** *International Journal of Cancer Supplement* 1998, **11**:52-55.
145. Arora R, Pizer B, Eden T: **Understanding Refusal and Abandonment in the Treatment of Childhood Cancer**. *Indian Pediatrics* 2010, **47**(12):1005-1010.
146. Charalampopoulou A, Petridou ET, Spyridopoulos T, Dessypris N, Oikonomou A, Athanasiadou-Piperopoulou F, Baka M, Kalmanti M, Polychronopoulou S, Trichopoulos D: **An integrated evaluation of socioeconomic and clinical factors in the survival from childhood acute lymphoblastic leukaemia: a study in Greece**. *European Journal of Cancer Prevention* 2004, **13**(5):397–401.
147. Petridou ET, Kosmidis H, Haidas S, Tong D, Revinthi K, Flytzani V, Papaioannou D, Trichopoulos D: **Survival from childhood leukemia depending on socioeconomic status in Athens.** *Oncology* 1994, **51**(5):391-395.

148. Njoku K, Basta N, Mann KD, McNally RJ, Pearce MS: **Socioeconomic variation in survival from childhood leukaemia in northern England, 1968-2010**. *British Journal of Cancer* 2013, **108**(11):2339-2345.
149. Son M, Kim J, Oh J, Kawachi I: **Inequalities in childhood cancer mortality according to parental socioeconomic position: A birth cohort study in South Korea**. *Social Science & Medicine* 2011, **72**(1):108-115.
150. Schillinger JA, Grosclaude PC, Honjo S, Quinn MJ, Sloggett A, Coleman MP: **Survival after acute lymphocytic leukaemia: effects of socioeconomic status and geographic region.** *Archives of Disease in Childhood* 1999, **80**(4):311-317.
151. Metzger ML, Castellino SM, Hudson MM, Rai SN, Kaste SC, Krasin MJ, Kun LE, Pui CH, Howard SC: **Effect of race on the outcome of pediatric patients with Hodgkin's lymphoma**. *Journal of Clinical Oncology* 2008, **26**(8):1282-1288.
152. Bhatia S: **Influence of race and socioeconomic status on outcome of children treated for childhood acute lymphoblastic leukemia**. *Current Opinion in Pediatrics* 2004, **16**(1):9-14.
153. Goggins WB, Lo FFK: **Racial and ethnic disparities in survival of US children with acute lymphoblastic leukemia: evidence from the SEER database 1988–2008**. *Cancer Causes & Control* 2012, **23**(5):737-743.
154. Rubnitz JE, Lensing S, Razzouk BI, Pounds S, Pui CH, Ribeiro RC: **Effect of race on outcome of white and black children with acute myeloid leukemia: the St. Jude experience**. *Pediatric Blood & Cancer* 2007, **48**(1):10-15.
155. Barnholtz-Sloan JS, Severson RK, Stanton B, Hamre M, Sloan AE: **Pediatric brain tumors in non-Hispanics, Hispanics, African Americans and Asians: differences in survival after diagnosis**. *Cancer Causes Control* 2005, **16**(5):587-592.
156. Children's Oncology G, Aplenc R, Alonzo TA, Gerbing RB, Smith FO, Meshinchi S, Ross JA, Perentesis J, Woods WG, Lange BJ *et al*: **Ethnicity and survival in childhood acute myeloid leukemia: a report from the Children's Oncology Group**. *Blood* 2006, **108**(1):74-80.
157. Baker KS, Anderson JR, Lobe TE, Wharam MD, Qualman SJ, Raney RB, Ruymann FB, Womer RB, Meyer WH, Link MP *et al*: **Children from ethnic minorities have benefited equally as other children from contemporary therapy for rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma Study Group.** *Journal of Clinical Oncology* 2002, **20**(22):4428-4433.
158. Pui CH, Boyett JM, Hancock ML, Pratt CB, Meyer WH, Christ WM: **Outcome of treatment for childhood cancer in black as compared with white children. The St Jude Children's Research Hospital experience, 1962 through 1992.** *JAMA* 1995, **273**(8):633-637.
159. Bhatia S: **Disparities in cancer outcomes: lessons learned from children with cancer**. *Pediatric Blood & Cancer* 2011, **56**(6):994-1002.
160. Bhatia S: **Racial and ethnic differences in survival of children with acute lymphoblastic leukemia**. *Blood* 2002, **100**(6):1957-1964.
161. Kadan-Lottick N, Ness K, Bhatia S, Gurney J: **Survival variability by race and ethnicity in childhood acute lymphoblastic leukemia**. *JAMA* 2003, **290**(15):2008-2014.
162. Petridou ET, Dimitrova N, Eser S, Kachanov D, Karakilinc H, Varfolomeeva S, Belechri M, Baka M, Moschovi M, Polychronopoulou S *et al*: **Childhood leukemia and lymphoma: time trends and factors affecting survival in five Southern and Eastern European Cancer Registries**. *Cancer Causes Control* 2013, **24**(6):1111-1118.
163. Hsieh MH, Meng MV, Walsh TJ, Matthay KK, Baskin LS: **Increasing incidence of neuroblastoma and potentially higher associated mortality of children from nonmetropolitan areas: analysis of the surveillance, epidemiology, and end results database.** *Journal of Pediatric Hematology/ Oncology* 2009, **31**(12):942-946.
164. Marmot M: **Social determinants of health inequalities**. *The Lancet* 2005, **365**(9464):1099-1104.

165. Bray F: **Chapter 1.2 Transitions in human development and the global cancer burden**. In: *World Cancer Report 2014.* Edited by Stewart B, Wild PW. Lyon: International Agency for Research on Cancer; 2014: 54-68.
166. Larsen SB, Olsen A, Lynch J, Christensen J, Overvad K, Tjonneland A, Johansen C, Dalton SO: **Socioeconomic position and lifestyle in relation to breast cancer incidence among postmenopausal women: a prospective cohort study, Denmark, 1993-2006**. *Cancer Epidemiology* 2011, **35**(5):438-441.
167. Jansen L, Eberle A, Emrich K, Gondos A, Holleczek B, Kajuter H, Maier W, Nennecke A, Pritzkuleit R, Brenner H *et al*: **Socioeconomic deprivation and cancer survival in Germany: an ecological analysis in 200 districts in Germany**. *International Journal of Cancer* 2014, **134**(12):2951-2960.
168. Kogevinas M, Pearce N, Susser M, Boffetta P (editors): **Social inequalities and cancer. IARC Scientific Publications No. 138**, Lyon, France: Interantional Agency for Research on Cancer; 1997.
169. Coleman MP, Quaresma M, Berrino F, Lutz J-M, De Angelis R, Capocaccia R, Baili P, Rachet B, Gatta G, Hakulinen T *et al*: **Cancer survival in five continents: a worldwide population-based study (CONCORD)**. *The Lancet Oncology* 2008, **9**(8):730-756.
170. Merletti F, Galassi C, Spadea T: **The socioeconomic determinants of cancer**. *Environmental Health* 2011, **10 Suppl 1**:S7.
171. Frederiksen BL, Dalton SO, Osler M, Steding-Jessen M, de Nully Brown P: **Socioeconomic position, treatment, and survival of non-Hodgkin lymphoma in Denmark--a nationwide study**. *British Journal of Cancer* 2012, **106**(5):988-995.
172. Solar O, Irwin A: **A conceptual framework for action on the social determinants of health. Social Determinants of Health Discussion Paper 2 (Policy and Practice)**, Geneva, Switzerland: World Health Organization; 2010.
173. Voigtlander S, Mielck A, Razum O: **[Impact of small-area context on health: proposing a conceptual model]**. *Gesundheitswesen* 2012, **74**(11):702-709.
174. Mielck A: **Soziale Ungleichheit und Gesundheit: Einführung in die aktuelle Diskussion.**, Bern: Hans Huber; 2005.
175. Hiatt RA, Breen N: **The social determinants of cancer: a challenge for transdisciplinary science**. *American Journal of Preventive Medicine* 2008, **35**(2 Suppl):S141-150.
176. Koh HK (editor): **Toward the Elimination of Cancer Disparities**, New York: Springer; 2009.
177. Krieger N, Williams DR, Moss NE: **Measuring social class in US public health research: concepts, methodologies, and guidelines**. *Annual Review of Public Health* 1997, **18**:341-378.
178. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G: **Indicators of socioeconomic position (part 1)**. *Journal of Epidemiology and Community Health* 2006, **60**(1):7-12.
179. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G: **Indicators of socioeconomic position (part 2)**. *Journal of Epidemiology and Community Health* 2006, **60**(2):95-101.
180. Tebbi C: **Treatment compliance in childhood and adolescence**. *Cancer* 1993, **71**(10 Suppl):3441-3449.
181. Dorrington RE: **Alternative South African midyear estimates, 2013. CARe Monograph No. 13.**, Cape Town: Centre for Actuarial Research, University of Cape Town; 2013.
182. Krieger N: **A glossary for social epidemiology**. *Journal of Epidemiology and Community Health* 2001, **55**(10):693-700.
183. The World Bank: **Countries and Economies.** The World Bank Group; 2015. [http://data.worldbank.org/country] [04.03.2015].
184. Denmark.dk. The official website of Denmark: **Welfare.** 2015. [http://denmark.dk/en/society/welfare/] [04.03.2015].
185. Busse R, Riesberg A: **Health care systems in transition: Germany.** Copenhagen: WHO Regional Office for Europe on behalf of the European Observatory on Health Systems and Policies; 2004.

186. Singh E, Underwood JM, Nattey C, Babb C, Sengayi M, Kellett P: **South African National Cancer Registry: Effect of withheld data from private health systems on cancer incidence estimates**. *South African Medical Journal* 2015, **105**(2):107.
187. **NATIONAL HEALTH ACT 61 OF 2003. REGULATIONS RELATING TO CANCER REGISTRATION. Government Notice R380 in Government Gazette 34248 dated 26 April 2011**. In.: Department of Health, Republic of South Africa; 2011.
188. Dube N, Girdler-Brown B, Tint K, Kellett P: **Repeatability of manual coding of cancer reports in the South African National Cancer Registry, 2010**. *South African Journal of Epidemiology and Infection* 2013, **28**(3):157-165.
189. Little R, Rubin D: **Statistical Analysis with Missing Data.**, New York: Wiley; 2002.
190. Debling D, Spix C, Blettner M, Michaelis J, Kaatsch P: **The cohort of long-term survivors at the German childhood cancer registry**. *Klinische Padiatrie* 2008, **220**(6):371-377.
191. Grabow D, Spix C, Blettner M, Kaatsch P: **Strategy for long-term surveillance at the German Childhood Cancer Registry - an update**. *Klinische Padiatrie* 2011, **223**(3):159-164.
192. Statistisches Bundesamt: **Fachserie 1 Reihe 2.2. Bevölkerung und Erwerbstätigkeit. Bevölkerung mit Migrationshintergrund. – Ergebnisse des Mikrozensus 2012 –.** Wiesbaden: Statistisches Bundesamt; 2013.
193. Kaatsch P, Kaletsch U, Meinert R, Miesner A, Hoisl M, Schüz J, Michaelis J: **German case control study on childhood leukaemia--basic considerations, methodology and summary of the results.** *Klinische Padiatrie* 1998, **210**(4):185-191.
194. Schuz J, Forman MR: **Birthweight by gestational age and childhood cancer**. *Cancer Causes Control* 2007, **18**(6):655-663.
195. Thygesen LC, Daasnes C, Thaulow I, Bronnum-Hansen H: **Introduction to Danish (nationwide) registers on health and social issues: Structure, access, legislation, and archiving**. *Scandinavian Journal of Public Health* 2011, **39**(7 Suppl):12-16.
196. Pedersen CB: **The Danish Civil Registration System**. *Scandinavian Journal of Public Health* 2011, **39**(7 Suppl):22-25.
197. Segi M: **Cancer mortality for selected sites in 24 countries (1950-57)**, Sendai: Department of Public Health, Tohoku University School of Medicine; 1960.
198. Dorrington RE: **Personal Communication, Alternative South African midyear estimates, 2000**. In., Centre for Actuarial Research, University of Cape Town; 2013.
199. Clark TG, Bradburn MJ, Love SB, Altman DG: **Survival Analysis Part I: Basic concepts and first analyses**. *British Journal of Cancer* 2003, **89**(2):232-238.
200. Bradburn MJ, Clark TG, Love SB, Altman DG: **Survival Analysis Part II: Multivariate data analysis – an introduction to concepts and methods**. *British Journal of Cancer* 2003, **89**(3):431-436.
201. Bradburn MJ, Clark TG, Love SB, Altman DG: **Survival Analysis Part III: Multivariate data analysis – choosing a model and assessing its adequacy and fit**. *British Journal of Cancer* 2003, **89**(4):605-611.
202. Stefan DC, Stones D, Dippenaar A, Kidd M: **Ethnicity and characteristics of Hodgkin lymphoma in children**. *Pediatric Blood & Cancer* 2009, **52**(2):182-185.
203. MacDouglass MG: **Acute Childhood Leukaemia in Johannesburg**. *Leukemia Research* 1985, **9**(6):765-767.
204. Hesseling PB, Hartley P, Zietsman L, van Lill S, Preston-Martin S, Wessels G: **Incidence of acute lymphoblastic leukaemia in white and coloured children in the Western Cape.** *South African Medical Journal* 2004, **94**(7):533-536.
205. National Cancer Registry South Africa: **Cancer in South Africa 2006. Full Report.**
206. Peltzer K: **Utilization and practice of traditional/complementary/alternative medicine (TM/CAM) in South Africa.** *African Journal of Traditional, Complementary and Alternative Medicines* 2009, **6**(2):175-185.

207. Moradi A, Semnani S, Roshandel G, Mirbehbehani N, Keshtkar A, Aarabi M, Moghaddami A, Cheraghali F: **Incidence of Chidlhood Cancers in Golestan Province of Iran**. *Iranian Journal of Pediatrics* 2010, **20**(3):335-342.
208. Ahrensberg JM, Schroder H, Hansen RP, Olesen F, Vedsted P: **The initial cancer pathway for children - one-fourth wait more than 3 months**. *Acta Paediatrica* 2012, **101**(6):655-662.
209. Gage-Bouchard EA, Devine KA, Heckler CE: **The relationship between socio-demographic characteristics, family environment, and caregiver coping in families of children with cancer**. *Journal of Clinical Psychology in Medical Settings* 2013, **20**(4):478-487.
210. Bhatia S, Landier W, Shangguan M, Hageman L, Schaible AN, Carter AR, Hanby CL, Leisenring W, Yasui Y, Kornegay NM *et al*: **Nonadherence to oral mercaptopurine and risk of relapse in Hispanic and non-Hispanic white children with acute lymphoblastic leukemia: a report from the children's oncology group**. *Journal of Clinical Oncology* 2012, **30**(17):2094-2101.
211. Patterson JM, Holm KE, Gurney JG: **The impact of childhood cancer on the family: a qualitative analysis of strains, resources, and coping behaviors**. *Psychooncology* 2004, **13**(6):390-407.
212. Schmiegelow K, Vestergaard T, Nielsen SM, Hjalgrim H: **Etiology of common childhood acute lymphoblastic leukemia: the adrenal hypothesis**. *Leukemia* 2008, **22**(12):2137-2141.
213. Kamper-Jorgensen M, Woodward A, Wohlfahrt J, Benn CS, Simonsen J, Hjalgrim H, Schmiegelow K: **Childcare in the first 2 years of life reduces the risk of childhood acute lymphoblastic leukemia**. *Leukemia* 2008, **22**(1):189-193.
214. Schmiegelow K, Nyvold C, Seyfarth J, Pieters R, Rottier MM, Knabe N, Ryder LP, Madsen HO, Svejgaard A, Kaspers GJ: **Post-induction residual leukemia in childhood acute lymphoblastic leukemia quantified by PCR correlates with in vitro prednisolone resistance**. *Leukemia* 2001, **15**(7):1066-1071.
215. dos Santos Alves DF, de Brito Guirardello E, Kurashima AY: **Stress related to care: the impact of childhood cancer on the lives of parents.** *Revista Latino-Americana de Enfermagem* 2013, **21**(1):356-362.
216. Johnson KJ, Carozza SE, Chow EJ, Fox EE, Horel S, McLaughlin CC, Mueller BA, Puumala SE, Reynolds P, Von Behren J *et al*: **Birth characteristics and childhood carcinomas**. *British Journal of Cancer* 2011, **105**(9):1396-1401.
217. Dockerty JD, Williams SM, McGee R, Skegg DC: **Impact of childhood cancer on the mental health of parents.** *Medical and Pediatric Oncology* 2000, **35**(5):475-483.
218. Patistea E, Makrodimitri P, Panteli V: **Greek parents' reactions, difficulties and resources in childhood leukaemia at the time of diagnosis**. *European Journal of Cancer Care* 2000, **9**(2):86-96.
219. Marmot M, Friel S, Bell R, Houweling TAJ, Taylor S: **Closing the gap in a generation: health equity through action on the social determinants of health**. *The Lancet* 2008, **372**(9650):1661-1669.
220. Tariq S, Woodman J: **Using mixed methods in health research**. *JRSM Short Reports* 2013, **4**(6):2042533313479197.

Appendix

Article I: Erdmann F, Kielkowski D, Schonfeld SJ, Kellett P, Stanulla M, Dickens C, Kaatsch P, Singh E, Schüz J: Childhood cancer incidence patterns by race, sex and age for 2000-2006: A report from the South African National Cancer Registry.

Article II: *Schonfeld SJ, Erdmann F, Wiggill T, Babb C, Kellett P, Singh E, Schüz J: Hematological malignancies in South Africa 2000-2006: Analysis of data reported to the National Cancer Registry.*

Article III: Erdmann F, Kaatsch P, Zeeb H, Roman E, Lightfoot T, Schüz J: Survival from childhood acute lymphoblastic leukaemia in West Germany: does socio-demographic background matter?

Article IV: Erdmann F, Kaatsch P, Schüz J: Family circumstances and survival from childhood acute lymphoblastic leukaemia in West Germany.

Article V: *Simony KS, Lund LW, Erdmann F, Andersen KK, Winther JF, Schüz J, Johanson C, Schmiegelow K, Dalton SO: Effect of socioeconomic position on survival after childhood cancer in Denmark.*

Article VI: Erdmann F, Winther JF, Dalton SO, Lightfoot T, Zeeb H, Simony KS, Deltour I, Ferro G, Bautz A, Schmiegelow K, Schüz J: Family characteristics and survival from childhood haematological malignancies in Denmark, 1973-2006.

Article VII: *Schüz J, Luta G, Erdmann F, Ferro G, Bautz A, Simony KS, Dalton SO, Lightfoot T, Winther JF: Birth order and the risk of childhood cancer in the Danish birth cohort of 1973-2010.*

Article I

Childhood cancer incidence patterns by race, sex and age for 2000 – 2006: A report from the South African National Cancer Registry

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Childhood cancer incidence patterns by race, sex and age for 2000–2006: A report from the South African National Cancer Registry

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Higher childhood cancer incidence rates are generally reported for high income countries although high quality information on descriptive patterns of childhood cancer incidence for low or middle income countries is limited, particularly in Sub-Saharan Africa. There is a need to quantify global differences by cancer types, and to investigate whether they reflect true incidence differences or can be attributed to under-diagnosis or under-reporting. For the first time, we describe childhood cancer data reported to the pathology report-based National Cancer Registry of South Africa in 2000–2006 and compare our results to incidence data from Germany, a high income country. The overall age-standardized incidence rate (ASR) for South Africa in 2000–2006 was 45.7 per million children. We observed substantial differences by cancer types within South Africa by racial group; ASRs tended to be 3–4-fold higher in South African Whites compared to Blacks. ASRs among both Black and White South Africans were generally lower than those from Germany with the greatest differences observed between the Black population in South Africa and Germany, although there was marked variation between cancer types. Age-specific rates were particularly low comparing South African Whites and Blacks with German infants. Overall, patterns across South African population groups and in comparison to Germans were similar for boys and girls. Genetic and environmental reasons may probably explain rather a small proportion of the observed differences. More research is needed to understand the extent to which under-ascertainment and under-diagnosis of childhood cancers drives differences in observed rates.

Epidemiology

Worldwide, country-specific estimates of the annual incidence rates of childhood cancer in 0–14 year olds range from about 50 to 200 new cases per million children for 2012.[1] The incidence is well described for economically developed countries,[2,3] with recent incidence rates of 164, 178 and 157 per million children reported in Germany,[4] US Whites[5] and Australia,[6] respectively. In contrast, high quality data from low or middle income countries and, in particular, from Sub-Saharan Africa are limited.[7] Childhood cancer incidence rates of 35, 120 and 174 per million were reported from The Gambia,[8] Harare in Zimbabwe[9] and Kyadono in Uganda,[8] with substantial variation in the spectrum of cancer types.[10] Particularly for leukemia, the most common childhood cancer type in developed countries, reported rates were considerably lower in Sub-Saharan Africa.[10]

Childhood cancer is a heterogeneous group of malignancies. Little is known about the aetiology of these cancers, but it appears that both genetic and environmental factors play a role.[11,12] The early age at diagnosis indicates that childhood cancer might originate *in utero*, and that factors prior to birth, including preconception and/or fetal environmental exposures, as well as those in early childhood may be important determinants.[11,13,14] Observed geographical differences in incidence rates have been used to support several hypotheses for the association between exposures related to modern lifestyle and the risk of childhood cancer.[14] These include factors related to social contacts and opportunities for infection in

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What's new?

Reported geographical and racial differences in childhood cancer incidence contribute to hypotheses regarding the possible risk factors for the disease. Analysis of data from the National Cancer Registry of South Africa uncovered marked differences in childhood cancer incidence within South African populations, with significantly higher rates in Whites compared to Blacks. Compared to data from Germany (representing childhood cancer incidence in Western countries) lower rates were even found in South African Whites, with the greatest differences being noted for the Black population. Under-diagnosis and under-reporting may drive in part the observed patterns. These findings are highly informative for future policy making and improving access to health care services in South Africa.

early life,[14] but also maternal diet during pregnancy,[15] parental occupational exposures prior to conception or during pregnancy,[12,16] and exposures to electromagnetic fields.[17]

While the risk factors for childhood cancer are not well understood, there is evidence that social factors, in particular wealth, are related to the reported incidence of childhood cancer.[7,18] This is consistent with the higher reported incidence in high income countries compared to low and middle income countries, especially Sub-Saharan Africa, and is particularly strong for leukemia.[7,8]

Recent studies from Brazil and India suggest, however, that under-reporting of acute lymphoblastic leukemia (ALL) may be sufficiently large to account for most, if not all, of the observed differences between these countries compared with Europe and North America.[19,20] The extent to which under-reporting may explain lower rates reported in Sub-Saharan Africa is not known.[7] Thus, there is a need to understand the contribution of true differences versus under-diagnosis or under-reporting in reported childhood cancer incidence rates in Sub-Saharan Africa.[21,22]

This study describes for the first time childhood cancer data reported to the pathology-based South African National Cancer Registry (NCR) for the time period 2000–2006, a period during which the cancer registry operated under stable and defined conditions. As race is correlated with wealth and socioeconomic circumstances in South Africa,[23] particular emphasis was given to investigating differences by racial groups. We focused on South African Black and White populations as they represent the extremes of the socioeconomically disadvantaged and advantaged groups respectively. In addition, these groups have sufficiently large numbers of cancer to conduct robust analyses, whereas numbers are much more limited among the Indian/Asian and mixed ancestry populations. Furthermore, we compared our results to data from Germany, as a representative of a high income country[3,24] and that has a long-established population-based childhood cancer registry. Comparisons of reported incidence rates in South Africa and Germany provide a basis for considering the potential impact of differences in diagnosis, reporting and risk factor distributions by sex, age, race and diagnostic groups.

Material and Methods

Population structure and access to health care in South Africa

National statistics in South Africa classify the population using broad population groups, largely reflecting pre- 1994 legislative groupings: "Black African," "White," "Colored" (a heterogeneous mixed ancestry population with Khoisan, Black African, European and Asian ethnic origins), "Indian/Asian" (the majority of whom are of Indian origin) and "Other." Thus, from hereafter this report uses the terminology of "population group" rather than "race." Among the 14.5 million children under the age of 15 years living in the country in 2006, 83.7% were Black African, 8.8% mixed ancestry, 1.9% Indian/Asian and 5.6% White[25] (Supporting Information Table 1). South Africa is an upper-middle income country[24] with healthcare provided by both public and private facilities. According to the household survey of 2006,[23] 14.7% of the population was covered by a medical aid scheme giving access to private health care services. Medical aid coverage differs by population group and is generally affordable for the more affluent section of the South African population. In 2006, 63.1% of Whites had medical aid compared to 7.2% of Blacks.[23] Public sector health services are available at the primary, secondary, and tertiary levels at a nominal fee calculated on income and thus at little or no cost to those who cannot afford it.[26] Pathology services are provided by the National Health Laboratory Service (NHLS) in public sector hospitals and a number of private laboratories provide pathology services to private healthcare institutions.

The South African National Cancer Registry

The South African NCR was established in 1986 as a pathology-based surveillance system under the then South African Institute for Medical Research, located in Johannesburg. The NCR, currently a division of the NHLS, collates all cases of malignancies including nonmelanoma skin cancers but not benign tumors. Copies of pathology reports confirming a cancer diagnosis (based on histology, cytology and hematology) were submitted to the NCR on a voluntary basis until 2011, by laboratories serving both the public and private sectors. Although reporting was voluntary, laboratories were actively followed up. Over time, and mainly from 2006 onwards, many private laboratories discontinued their voluntary contribution because of concerns about disclosure of confidential patient information to the NCR. For this reason, our analysis is restricted to the years 2000–2006. New legislation introduced in April 2011 makes the reporting of diagnosed cancer cases to the NCR by health professionals and laboratories mandatory.[27]

Table 1. Childhood cancer cases reported to the South African NCR in 2000–2006 according to population group, sex, age group and reporting laboratory (public *vs.* private)

			All	Black	Mixed ancestry	Indian/Asian	White	Race missing
Childhood cancer	N		4,601	3,125	399	148	689	240
Sex *(120 missing)*	Boys	N	2,474	1,659	231	84	384	116
		%	*55.2*	*54.7*	*58.9*	*57.5*	*56.6*	*50.2*
	Girls	N	2,007	1,374	161	62	295	115
		%	*44.8*	*45.3*	*41.1*	*42.5*	*43.5*	*49.8*
Age groups	<1 year	N	289	186	36	13	43	11
		%	*6.3*	*6.0*	*9.0*	*8.8*	*6.2*	*4.6*
	1–4 years	N	1,569	1,063	132	63	235	76
		%	*34.1*	*34.0*	*33.1*	*42.6*	*34.1*	*31.7*
	5–9 years	N	1,306	901	115	37	170	83
		%	*28.4*	*28.8*	*28.8*	*25*	*24.7*	*34.6*
	10–14 years	N	1,437	975	116	35	241	70
		%	*31.2*	*31.2*	*29.1*	*23.7*	*35.9*	*29.2*
Reported laboratory	NHLS[1]	N	3,995	2,878	356	116	458	187
		%	*86.8*	*92.1*	*89.2*	*78.4*	*66.5*	*77.9*
	Private laboratory	N	606	247	43	32	231	53
		%	*13.2*	*7.9*	*10.8*	*21.6*	*33.5*	*22.1*

[1]The NHLS is a national network of public laboratories and the largest diagnostic pathology service in South Africa.

Data reported to the NCR include: patient's name and surname, sex, age at diagnosis, population group, diagnosis and tumor information (topography, morphology), date of diagnosis and name of the reporting laboratory. Diagnosis is coded by trained coders based on primary organ site and morphological type according to the International Classification of Diseases for Oncology, third edition (ICD-O-3).[28] Only primary incident cases with histological, cytological or hematological confirmation are recorded. Each multiple primary cancer is recorded as an additional case. Doubtful, *in situ* or borderline cancers are excluded. For multiple notifications of the same cancer, only one record is kept.

Since the beginning of the 1990s an increasing number of reports were received without information on population group, with 54% of childhood cancer cases missing data in 2000–2006. The NCR used a hot-deck imputation method to determine population group for those with this information missing. The algorithm makes use of a reference database of approximately 1.4 million surnames with known population group. Surnames which do not appear in the database are classified as unknown. The database is continually updated with the addition of each new patient whose population group is known, and information from other sources is also used to improve quality and completeness. In a former validation study (unpublished and herewith reported for the first time), cases reported to the cancer registry from 1990–1995 ($N = 277{,}130$) with known information on population group, were also used for the hot desk imputation method, and the proportions by population group were very similar; the original distribution was 53% Whites, 40% Blacks, 2% Indian/Asian and 5% with mixed ancestry, compared to the imputed distribution of 50% Whites, 41% Blacks, 2% Indian/Asian, 7% with mixed ancestry and 0.01% unknown (Chi-square test p-value = 0.94 for distribution differences).

The German Childhood Cancer Registry

Our reference registry for comparison with high income country incidence, the nationwide German Childhood Cancer Registry (GCCR), was established in 1980 and collects all malignancies and benign brain tumors diagnosed before age 15 (approximately 1,800 new cases each year in a population of about 11.5 million children). As most childhood cancer patients are enrolled in clinical trials in Germany, a network of pediatric oncology centers guarantees the coverage of virtually all cases. The GCCR was chosen as a reference registry because of (in order of importance) the very high estimated level of completeness of nationwide registration (>95% since 1987[4]), the assumed high comparability of genetic make-up between German and White South African children, and the ability of the registry to provide data in a structure comparable to that of the South African database with respect to the time period (2000–2006) and included diagnoses (*e.g.*, exclusion of benign brain tumors which are not recorded in the NCR). Information on racial group is not collected by the

Table 2. Childhood cancer reported to the South African NCR and to the GCCR in 2000–2006 by population group, sex ratio and age specific, crude and age-standardized incidence rates[1]

		SA[2] all	SA[2] Black	SA[2] Mixed ancestry	SA[2] Indian/ Asian	SA[2] White	Germany
	N	4,601	3,125	399	148	689	11,669
	M/F[3]	1.2	1.2	1.4	1.4	1.3	1.3
Age specific incidence[4]	< 1 year	41.39	31.51	59.54	112.11	119.77	249.8
	1–4 years	59.81	48.50	56.37	134.68	155.71	191.3
	5–9 years	38.48	31.92	38.43	57.48	81.99	106.9
	10–14 years	39.81	32.44	37.92	48.34	106.84	106.6
	Crude incidence[5]	44.56	36.29	44.34	75.84	111.17	138.8
	ASR[6]	45.70	37.17	45.47	82.97	114.96	144.4

[1]Sex ratio is based on cases with known sex. Total number (N) and rates include cases with sex missing.
[2]SA: South Africa
[3]M/F: sex ratio—male cases/female cases
[4]Age specific incidence: age group specific incidence rates per 1,000,000 population aged 0–14 years.
[5]Crude incidence: crude incidence rate per 1,000,000 population aged 0–14 years.
[6]ASR: age-standardized incidence rate (using the world standard population) per 1,000,000 population aged 0–14 years.

GCCR, but racial diversity is very low in Germany, with German children usually being Caucasian and with larger migrant groups living in Germany originating elsewhere in Europe or in Turkey.[29]

Case definition

Childhood cancer was defined as a cancer diagnosed at ages younger than 15 years. Data on pediatric cancer cases for 2000 to 2006 was obtained from the NCR and recoded using the International Classification of Childhood Cancer, third edition (ICCC-3)[30] which classifies tumors coded according to the IDC-O-3 nomenclature into 12 major diagnostic groups: I. Leukemias, myeloproliferative disease and myelodisplastic diseases (*leukemias*), II. Lymphomas and reticuloendothelial neoplasms (*Lymphomas*), III.CNS and miscellaneous intracranial and intraspinal neoplasms (malignant *CNS tumors*), IV. Neuroblastoma and other peripheral nervous cell tumors (*Sympathetic nervous system tumors*), V. Retinoblastomas (*Retinoblastomas*), VI. Renal tumors (*Renal tumors),* VII. Hepatic tumors (*Hepatic tumors*), VIII. Malignant bone tumors (*Malignant bone tumors*), IX. Soft tissue and other extraosseous sarcomas (*Soft tissue sarcomas*), X. Germ cell tumors, trophoblastic tumors, and neoplasm of gonads (*Germ cell tumors*), XI. Other malignant epithelial neoplasms and melanomas (*Malignant epithelial neoplasms*), and XII. Other and unspecified malignant neoplasms (*Other and unspecified malignant tumors*). All cancer cases among children who were clearly not South Africa residents (*e.g.*, specimens sent to South African laboratories from other countries) were excluded.

Statistical methods

Frequencies, sex ratios, and age specific and age-standardized rates (ASRs; per 1,000,000 children) were used to analyze the incidence data of childhood cancer in South Africa. Subgroup analyses were performed by major ICCC-3 group[30] as well as by subtypes of leukemia, lymphoma and soft tissue sarcoma, by age group (grouped into <1, 1–5, 6–9 and 10–14 years), sex and population group (Black, White, mixed ancestry and Indian/Asian). Because of small case numbers, comparisons by population group were largely restricted to Blacks and Whites, while results for the mixed ancestry and Indian/Asian populations are shown in supplemental material. The directly age-standardized incidence rates (ASR) per 1,000,000 were estimated using the weights (by age groups 0, 1–4, 5–9, 10–14 years) of the Segi world standard population.[31] The Alternative South African mid-year population estimates were used as the denominator[25,32] for calculating incidence rates. These mid-year population estimates are similar in magnitude to the official mid-year estimates but maintain an age distribution that is consistent with that of the most recent Census in 2011.[25] We therefore considered them as the more appropriate population estimates for the purposes of studying differences by age group. The incidence rate proportion in South Africa compared to the reference registry of Germany was calculated to investigate differences for specific subgroups of childhood cancer. For this purpose, the ASRs in Germany in the respective subcategories (by cancer type and by sex) as well as age-specific rates were set to 100% and these were compared to the reported rates among South African Whites and Blacks separately. The German childhood cancer incidence rates presented here were calculated by the GCCR.

All statistical analyses were performed using Stata 13[33] and Microsoft Excel 2010.

Results

Characteristics of reported childhood cancer cases

Newly diagnosed cancer cases (4601) under the age of 15 years were reported to the NCR during the period 2000 to

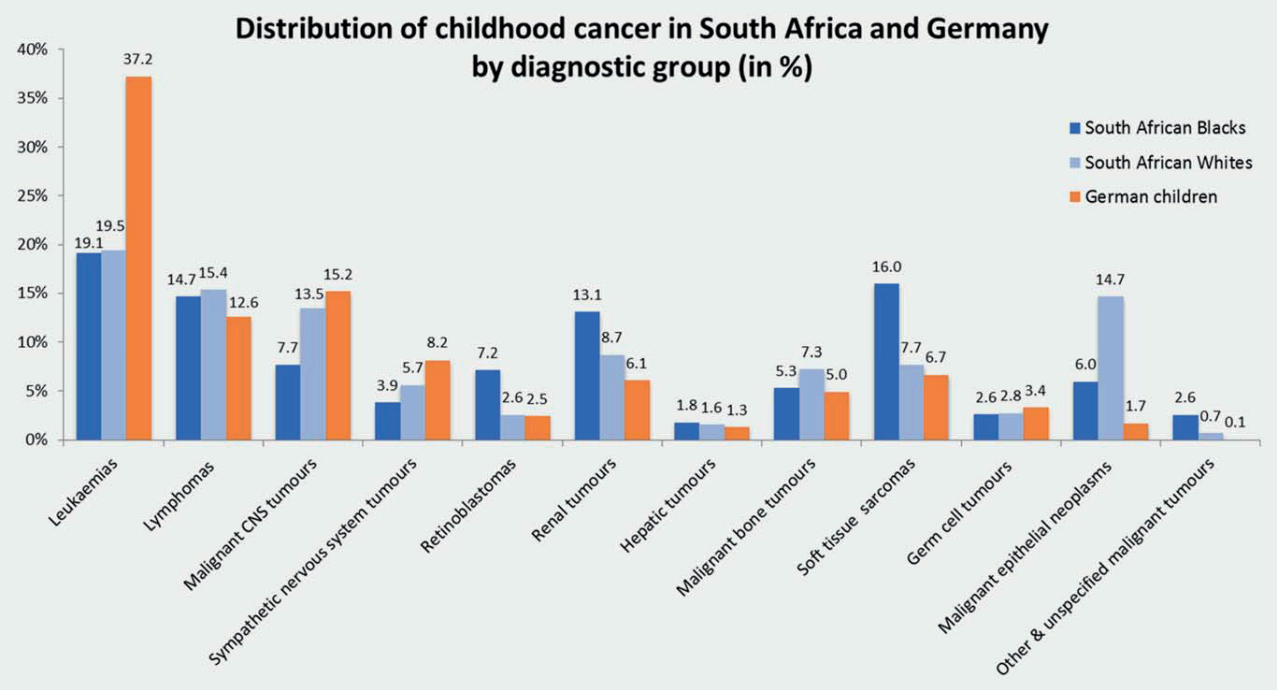

Figure 1. Distribution of childhood cancer (2000–2006) by major diagnostic group (in %) based on cases reported to the South African NCR among Blacks and Whites *vs*. childhood cancer reported to the GCCR.

2006; with a greater number of cases among males than females (55% *vs*. 45%; sex ratio: 2:1). The percentage of cases reported by the public laboratories of the NHLS ranged from 92% among Black children to 66.5% among Whites (Table 1). The overall ASR was 45.7 per million children, 37.2/million among Black, 45.5/million among mixed ancestry, 83/million among Indian/Asian and 115/million among White South African children (Table 2). The highest age-specific incidence rate was observed for children aged 1–4 years (59.8/million), with considerable differences by population group (highest in Whites and lowest in Blacks). In comparison, the ASR in Germany during 2000 and 2006 was 144.4/million with the highest age-specific incidence rate of 250/million children observed in infants less than one year of age (Table 2).

Reported childhood cancer for South African Blacks and Whites and Germans

Figure 1 presents the percentage distribution of the major diagnostic groups of pediatric cancers for South African Blacks and Whites and Germans. The distribution of cancer types varied substantially between these population groups, with the distribution among South African Whites being only slightly closer to the distribution reported from Germany than to Black South Africans. Among Black South Africans, the most commonly reported cancer types were leukemias, soft tissue sarcomas, and lymphomas, while among White South Africans the most common cancer types were leukemias, lymphomas, and malignant epithelial neoplasms. The high proportion of malignant epithelial neoplasm among South African Whites is primarily explained by their higher incidence of skin cancers (data not shown).

As shown in Table 3, incidence rates differed considerably by age and diagnostic group. The highest rates were reported for leukemia with an ASR of 8.5/million in South Africa and 54.5/million in Germany. Among South Africans, the incidence rate patterns varied substantially between Blacks and Whites. With few exceptions, reported rates were lower among Blacks than Whites across the diagnostic groups. ASRs tended to be 3 to 4-fold higher in South African Whites compared to Blacks. Table 4 shows a more detailed presentation of the reported leukemia, lymphoma and soft tissue sarcoma incidence. The observed low incidence of leukemia in South African Whites compared to German children is more pronounced in ALL than in acute myeloid leukemia. Also the age patterns varied substantially in ALL between Black and White South African children. Unlike most other cancer types, the ASR for Kaposi sarcoma was higher among Blacks than Whites (1.8 *vs*. 0.3/million).

Figures 2*a–c* show the childhood cancer incidence rates in South Africa (by (*i*) major diagnostic group, (*ii*) age group and (*iii*) sex) stratified by Blacks and Whites as a proportion of the corresponding incidence rate in Germany (incidence rate proportions). The observed incidence rates of lymphomas, hepatic, renal and malignant bone tumors, and malignant epithelial neoplasm among South African Whites exceed the corresponding ASRs of German children. In contrast, ASRs for leukemias, tumors of the sympathetic nervous

Table 3. Childhood cancer reported to the South African NCR compared to the GCCR in 2000–2006 by major diagnostic group, population group (all, Blacks *vs*. Whites), sex ratio, and age specific, crude and age-standardized rates[1]

				Age specific incidence[4]							
ICCC-3 diagnostic group[2]	Race	N	M/F[3]	<1 year	1–4 years	5–9 years	10–14 years	Crude incidence[5]	ASR[6]	Germany ASR[6]	Germany M/F[3]
Leukemias	All	875	1.3	7.2	9.6	8.1	8.3	8.5	8.5	54.5	1.2
	Black	598	1.2	5.9	6.4	6.6	7.9	6.9	6.9		
	White	134	1.3	22.3	37.8	20.7	11.5	21.6	23.5		
Lymphomas	All	725	2.1	1.3	6.3	8.4	7.3	7.0	6.9	15.7	2
	Black	458	1.9	0.8	5.3	6.2	5.4	5.3	5.3		
	White	106	2.7	5.6	11.9	16.4	23.1	17.1	16.1		
Malignant CNS tumors	All	431	1.2	2.3	5.3	4.5	3.4	4.2	4.3	21.5	1.3
	Black	240	1.3	1.2	3.5	3.3	2.1	2.8	2.9		
	White	93	1.2	8.4	21.9	11.6	14.6	15.0	15.4		
Sympathetic nervous system tumors	All	209	1.3	6.0	4.5	1.1	0.4	2.0	2.3	14.0	1.2
	Black	121	1.1	3.9	2.7	1.0	0.3	1.4	1.6		
	White	39	1.8	22.3	18.6	1.0	0.4	6.3	7.9		
Retinoblastomas	All	278	1.3	4.6	7.9	1.0	0.2	2.7	3.2	4.3	1.2
	Black	225	1.4	4.4	7.7	0.9	0.2	2.6	3.1		
	White	18	1.6	5.6	8.6	1.4	0.0	2.9	3.6		
Renal tumors	All	542	1.1	6.2	12.6	3.9	1.0	5.2	5.9	9.8	0.9
	Black	410	1.1	4.4	11.4	3.6	1.0	4.8	5.3		
	White	60	1.1	11.1	25.8	6.3	1.8	9.7	11.4		
Hepatic tumors	All	87	1.6	2.3	1.3	0.4	0.6	0.8	0.9	2.1	1.6
	Black	57	1.6	1.7	0.8	0.4	0.6	0.7	0.7		
	White	11	1.8	8.4	4.0	0.5	0.4	1.8	2.2		
Malignant bone tumors	All	260	0.9	0.6	0.4	1.4	5.5	2.5	2.2	5.9	1.1
	Black	167	0.9	0.3	0.2	0.9	4.5	1.9	1.7		
	White	50	1.0	0.0	2.0	6.3	15.1	8.1	7.0		
Soft tissue sarcomas	All	630	1.3	4.7	7.4	5.7	5.8	6.1	6.2	9.5	1.2
	Black	499	1.3	4.4	6.9	5.8	5.2	5.8	5.9		
	White	53	1.0	11.1	12.6	3.9	9.8	8.6	8.8		
Germ cell tumors	All	118	0.3	1.1	1.1	0.9	1.4	1.1	1.1	4.7	0.8
	Black	82	0.2	0.8	0.8	0.8	1.2	1.0	0.9		
	White	19	0.3	2.8	2.0	2.9	4.0	3.1	2.9		
Malignant epithelial neoplasms	All	350	0.9	3.7	2.0	2.3	5.3	3.4	3.2	2.1	0.8
	Black	187	0.8	2.2	1.2	1.7	3.4	2.2	2.1		
	White	101	1.1	22.3	10.6	9.6	25.3	16.3	15.5		
Other & unspecified malignant tumors	All	96	1.0	1.4	1.5	0.7	0.6	0.9	1.0	0.1	1.2
	Black	81	1.0	1.4	1.6	0.7	0.6	0.9	1.0		
	White	5	1.0	0.0	0.0	1.4	0.9	0.8	0.7		

[1]Sex ratio is based on cases with known sex. Total number (N) and rates include cases with sex missing.
[2]Diagnostic groups defined using the International Classification of Childhood Cancer Third Edition (ICCC-3)
[3]M/F: sex ratio—male cases/female cases
[4]Age specific incidence: age group specific incidence rates per 1,000,000 population aged 0–14 years.
[5]Crude incidence: crude incidence rate per 1,000,000 population aged 0–14 years.
[6]ASR: age-standardized incidence rate (using the world standard population) per 1,000,000 population aged 0–14 years.

Table 4. leukemias, Lymphomas and soft tissue sarcomas reported to the South African NCR compared to the GCCR in 2000–2006 by diagnostic subgroup, population group (all, Blacks *vs*. Whites), sex ratio, and age specific, crude and age-standardized incidence rate[1]

ICCC-3 diagnostic group[2]		Race	N	M/F[3]	Age specific incidence[4]				Crude incidence[5]	ASR[6]	Germany ASR[6]	Germany M/F[3]
					<1 year	1–4 years	5–9 years	10–14 years				
Leukemias	Lymphoid leukemia	All	498	1.5	2.4	5.9	5.0	4.4	4.8	4.9	43.4	1.2
		Black	324	1.5	1.9	3.5	4.0	4.2	3.8	3.7		
		White	81	1.8	13.9	24.5	12.5	5.8	13.1	14.4		
	Acute myeloid leukemia	All	226	0.9	3.2	2.1	1.9	2.3	2.2	2.2	7.2	1.1
		Black	175	0.9	2.2	1.9	1.8	2.3	2.0	2.0		
		White	21	0.8	8.4	4.6	2.4	2.7	3.4	3.6		
	Other & unspecified	All	151	1.1	1.6	1.6	1.2	1.6	1.5	1.5	3.9	1.3
		Black	99	1.1	1.9	1.0	0.8	1.5	1.1	1.1		
		White	32	1.0	–	8.6	5.8	3.1	5.2	5.4		
Lymphomas	Hodgkin Lymphoma	All	241	2.2	0.4	1.0	3.1	3.0	2.3	2.2	6.2	1.4
		Black	171	2.1	0.3	1.1	2.7	2.3	2.0	1.9		
		White	27	4.4	–	0.7	3.9	8.0	4.4	3.8		
	Non-Hodgkin Lymphoma	All	227	1.8	0.3	2.1	2.0	2.8	2.2	2.1	6.3	2.2
		Black	150	1.7	0.3	1.9	1.6	2.1	1.7	1.7		
		White	34	2.4	–	2.7	4.3	9.3	5.5	4.9		
	Burkitt Lymphoma	All	182	2.7	0.3	2.3	2.6	0.9	1.8	1.8	3.0	4.7
		Black	91	2.8	–	1.8	1.3	0.4	1.1	1.1		
		White	31	1.7	5.6	4.6	6.3	4.0	5.0	5.0		
	Other & unspecified	All	75	1.4	0.3	0.9	0.7	0.7	0.7	0.7	0.1	1.0
		Black	46	1.1	0.2	0.5	0.6	0.5	0.5	0.5		
		White	14	5.0	–	4.0	1.9	1.8	2.3	2.4		
Soft tissue sarcomas	Rhabdomyo sarcomas	All	281	1.2	1.0	4.0	2.7	2.1	2.7	2.8	5.4	1.4
		Black	212	1.1	0.7	3.6	2.6	1.9	2.5	2.5		
		White	30	1.0	2.8	11.3	2.9	2.7	4.8	5.4		
	Kaposi sarcoma	All	166	2.1	0.7	2.2	1.9	1.0	1.6	1.7	0.0	0.0
		Black	152	2.0	0.8	2.5	2.3	1.0	1.8	1.8		
		White	2		–	–	–	0.9	0.3	0.3		
	Other & unspecified	All	183	1.0	3.0	1.2	1.1	2.6	1.8	1.7	1.1	4.0
		Black	135	1.0	2.9	0.9	1.0	2.3	1.6	1.5		
		White	21	0.9	8.4	1.3	1.0	6.2	3.4	3.2		

[1]Sex ratio is based on cases with known sex. Total number (N) and rates include cases with sex missing.
[2]Diagnostic groups defined using the International Classification of Childhood Cancer Third Edition (ICCC-3)
[3]M/F: sex ratio—male cases/female cases
[4]Age specific incidence: age group specific incidence rates per 1,000,000 population aged 0–14 years.
[5]Crude incidence: crude incidence rate per 1,000,000 population aged 0–14 years.
[6]ASR: age-standardized incidence rate (using the world standard population) per 1,000,000 population aged 0–14 years.

system and germ cell tumors were markedly lower than among German children. Among Black South African children, the observed rates were noticeably lower across all diagnostic groups (except for malignant epithelial neoplasms; Fig. 2*a*). Looking at incidence rates by age group, the incidence among South African children (both Black and White) under the age of 1 was particularly low when compared to German infants (Fig. 2*b*). Incidence rate proportions were similar for boys and girls (Fig. 2*c*).

Reported childhood cancer for South African Indian/Asian and children with mixed ancestry

This study focused primarily on Black and White South African children as the numbers of cases were highest for these

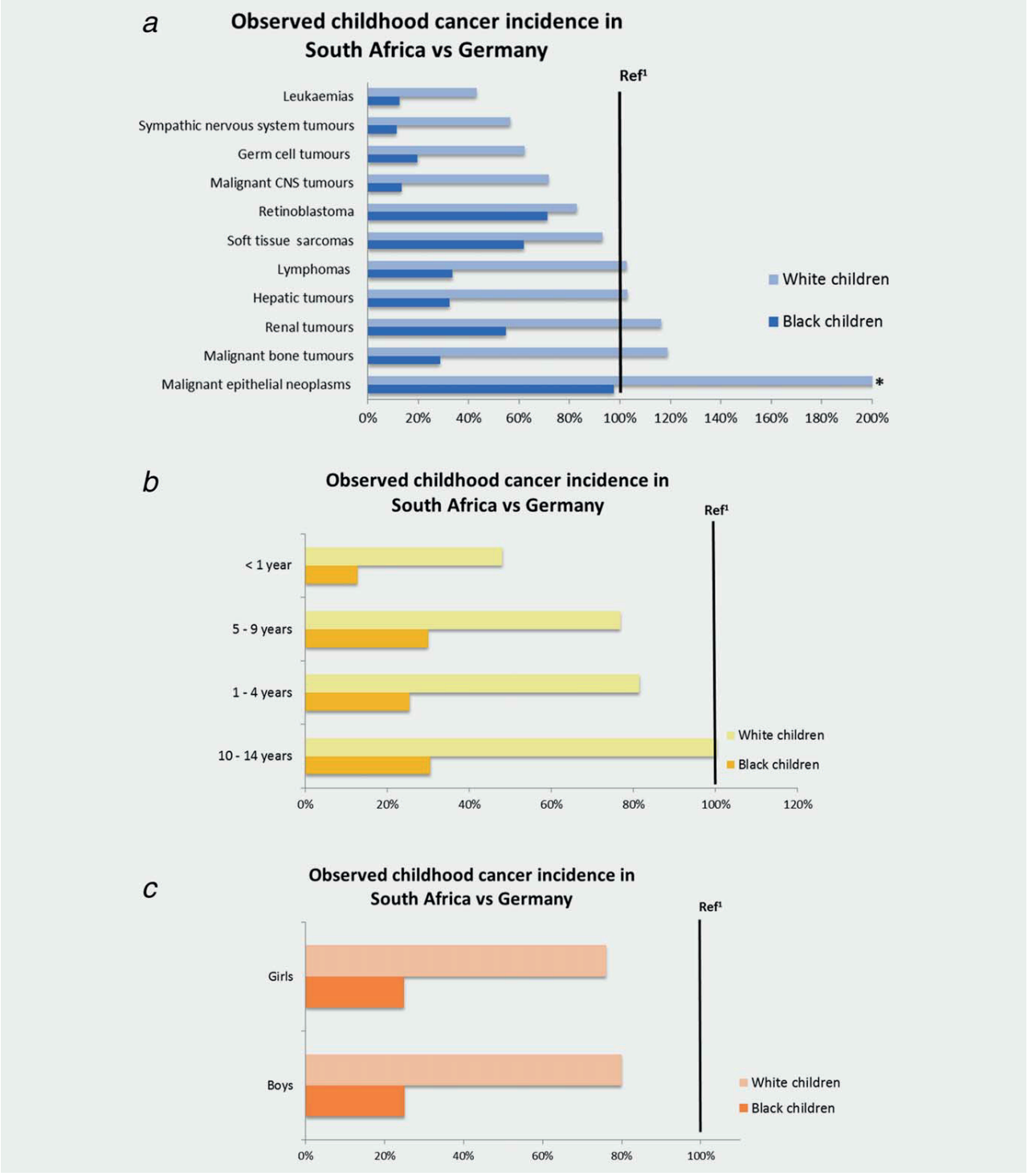

Figure 2. (*a*) Proportion of age-standardized childhood cancer incidence rates (2000–2006) by major diagnostic group based on cases reported to the South African National Cancer Registry stratified by Black and White children in relation to the age-standardized childhood cancer incidence rates of Germany, sorted from lowest to highest proportion of White South African childhood incidence with German children as a reference. [1]Ref: age-standardised incidence rates (using the world standard population) of Germany were set to 100% as reference points. *Truncated, the proportion of age standardized incidence rate of malignant epithelial neoplasm among White children in South Africa in relation to the incidence rate for Germany is 736%. (*b*) Proportion of age-standardized childhood cancer incidence rates (2000–2006) by age group based on cases reported to the South African National Cancer Registry stratified by Black and White children in relation to the age-standardized childhood cancer incidence rates of Germany, sorted from lowest to highest proportion of White South African childhood incidence with German children as a reference. [1]Ref: age-standardised incidence rates (using the world standard population) of Germany were set to 100% as reference points. (*c*) Proportion of age-standardized childhood cancer incidence rates (2000–2006) by sex based on cases reported to the South African National Cancer Registry stratified by Black and White children in relation to the age-standardized childhood cancer incidence rates of Germany. [1]Ref: age-standardised incidence rates (using the world standard population) of Germany were set to 100% as reference points.

population groups. The reported childhood cancer incidence in the Indian/Asian and in mixed ancestry groups by diagnostic group, age and sex are shown in Supporting Information Table 2. Considering all four population groups, the second highest rates (following the White population) were generally observed among the Indian/Asian population followed by those among children of mixed ancestry and lowest rates in Black children.

Discussion

Key findings

This study describes for the first time the reported childhood cancer incidence in South Africa on a national level, based on data from the South African National Cancer Registry, addressing variation in incidence overall, and by age, sex and population group. Key findings include substantial differences in the reported incidence rates and the distribution of pediatric cancer types within South African population groups, and between South African and German children, as well as a particularly low incidence rate in South African infants compared to German infants. Rates among South African Whites were much closer overall to the reported rates from Germany than among Black South Africans, but with marked variation across cancer types. Some cancer types were slightly more common in South African Whites than in German children. Patterns across the South African population groups and in comparison with Germany were generally similar for boys and girls.

Observed differences between Black and White South Africans

Overall, as well as for the major diagnostic groups including leukemias and lymphomas, White South Africans had approximately threefold higher ASRs than Black South Africans, with mixed ancestry and Indian/Asian children falling in between. ASRs were 4–5-times greater among Whites than Blacks for malignant CNS tumors and malignant bone tumors whereas rates were relatively close for retinoblastomas and soft tissue sarcomas.

Differences by population group in South African children have been also observed in previous regional studies[34–36] as well as in the annual reports of NCR.[37] In a study from 1974 to 1983 in Johannesburg, significant differences in the incidence of childhood leukemia between Black and White children were found with much lower rates in Black children.[35] A more recent study from the Western Cape observed that children with mixed ancestry showed a lower incidence of ALL than White children.[36]

Observed differences in incidence likely reflect a combination of variation in access to and utilization of health care services, in environmental exposures as well as in genetic susceptibility. Significant variations in incidence rates according to race were also reported in the United States. US White children had an approximately 1.5-fold higher rate of childhood cancer than Blacks, particularly pronounced for leukemia (1.8-fold higher) but less so for lymphomas (1.3-fold higher).[38] A large population based case-control study of more than 13,000 cases confirmed that compared to Whites, Black children have a decreased risk of childhood cancer in the United States. Among both the Black population and children of mixed White/Black ancestry, cancer rates were approximately 28% lower than that of Whites, whereas estimates for White/Asian as well as White/Hispanic children did not differ from those for Whites.[39] Authors speculated that different racial/ethnic groups may vary in terms of their environmental exposures, and that there might be important interactions between selected exposures and underlying genetic susceptibility.[39] However, incidence rate differences between racial groups in the United States were much smaller than the ones we observed in South Africa. Thus, genetic susceptibility and variability in environmental exposures can probably account for a smaller proportion of the large observed differences in South Africa than other factors.

Observed differences across the South African populations may be explained by socioeconomic and/or cultural factors related to access or utilization of health care services and health care seeking behavior. In South Africa, population group is strongly correlated with socioeconomic circumstances (such as education, income and medical aid), with low socioeconomic status most frequent among Blacks.[23] Higher unemployment in Blacks[23] may be related to a lack of financial resources available for seeking medical help. Only 7% of the Black population and 16% of the population with mixed ancestry were covered by medical aid compared to 29% of the Indian/Asians and 63% of Whites. The postapartheid bill of rights grants everyone the right to basic education, but as a consequence of the previous regime, in 2006 21.5% of the Black population had no schooling, compared to 7.4% of Whites.[28] Lack of parental education and low awareness of cancer, particularly in children, might delay or inhibit seeking of medical help. Furthermore, some parents may believe cancer is incurable and, therefore, not seek medical care.

The nonspecific nature of many early symptoms (*e.g.*, for leukemia which often presents as infection) may result in delayed diagnosis or failure to detect the disease.[21] This could explain the smaller population differences for cancer types with clearly visible symptoms than for cancer types with more nonspecific symptoms.

A greater proportion of Black South African families live in rural/remote areas[23] and may not access to a medical centre due to inadequate public transport infrastructure or inability to pay for transport and accommodation when their child is ill. Therefore, cancer diagnosis may be delayed. Moreover, primary healthcare facilities and local/regional hospitals may lack awareness of and experience in diagnosing pediatric cancer.[20] For instance, the observed lower incidence of ALL in children with mixed ancestry compared to White children in Western Cape was particularly pronounced in children from rural areas.[36]

In addition, as traditional medicine and cultural beliefs continue to play an important role in healthcare delivery in South Africa.[40] Therefore, parents may rely on traditional healers using herbs or witchcraft rather than attending a medical centre for diagnosis.

Observed much lower survival rates among Black children compared to Whites, recently estimated to be 48.5% in Black and 62.8% in White children,[41] adds to the evidence that the lower incidence rates among Black children may be, at least in part, due to under-ascertainment than necessarily reflect a lower cancer risk.

Observed differences between South Africa and Germany

Comparing Germans with South African Whites, the overall childhood cancer ASR in Germany was 1.25-fold higher, but variation across diagnostic groups was large. While the difference was striking for leukemias, being more than twofold higher in Germany and also markedly higher for sympathetic nervous system tumors, germ cell tumors and malignant CNS tumors, ASRs were similar for some other types such as soft tissue sarcomas, lymphomas and hepatic tumors, and even somewhat higher in South African Whites for renal tumors and malignant bone tumors. An eightfold higher incidence in South African Whites was seen in malignant epithelial neoplasms driven by high numbers of skin cancers.

Incidence rate comparisons between South Africa and Germany also differed by age. German infants had a twofold higher incidence rate when compared to infant South African Whites and almost 10-fold compared to infant Blacks, whereas in 10–14 year olds the incidence rates of Germans and South Africans were almost identical. This suggests under-diagnosis among both Black and White South African children below the age of 1 may be a particular issue. Diagnosis in infants is difficult in general, however, in South Africa, with its overwhelming burden of infectious disease,[42] cancer may not be among the first diagnoses suspected and thus children, even in the private sector may not be diagnosed before they die.

In contrast to age, incidence rate proportions were similar for boys and girls and differences in diagnosis or reporting by sex appeared to not to play a great role in South Africa. This finding was unexpected, as recent evidence points out that rates of cancer registrations in girls remain lower than expected in low and middle income countries.[43] Explanations include that sick girls tend not to be taken for health care services as often or as early as boys. It is possible that when resources are limited, culture and economics favour boys.[43] Nonetheless, our data suggest this is not the case in South Africa.

International comparison

The observed distribution of childhood cancer types in South Africa is unique and differs from those observed in other Sub-Saharan African[9,10] and middle income countries,[44–46] as well as high income countries[5,6,47] including Germany (Supporting Information Table 3). In high-income countries, leukemias are the most frequent childhood cancer with ALL accounting for up to 25% of all pediatric cancers, followed by brain tumors and other solid tumors.[4–6,47] However, particularly in equatorial Africa, children are more susceptible to developing non-Hodgkin Lymphomas (Burkitt's lymphomas) and Kaposi sarcoma due to higher exposure to infectious diseases (namely Epstein-Barr virus, HIV and human herpes virus 8)[7,48,49] (Supporting Information Table 3). Such differences might be again the result of the cumulative effect of variable genetic predisposition, diverse burden of infectious diseases, environmental exposures and chronic immune stimulation, as well as incomplete diagnosis and registration. The difference between the reported and actual incidence of childhood malignancies in low-income countries is assumed to be most striking for leukemia, a disease with symptoms resembling those of infectious diseases including malaria and tuberculosis, and so children could die before their cancer is suspected or diagnosed.[8,21] For lymphomas and some solid tumors, visible symptoms might encourage parents to seek medical help and early death is less common.

South Africa is an upper middle income country,[24] with a relatively high level of wealth, and is therefore distinct for the Sub-Saharan region. Our study reveals that leukemias in South Africa, as in high income countries, are the most frequent reported cancers although rates are substantially lower, in particular for ALL. Under-diagnosis, due to clinicians being less experienced at recognizing leukemias in children may partly explain this finding. Findings from the Tygerberg and Bloemfontein hospitals highlight the need to increase parental awareness of childhood cancer on the one hand but also to increase the sensitivity of medical doctors and health professionals to the warning signs of childhood cancers.[36,41] Many Sub-Saharan African countries report few brain tumors and substantial underestimation is assumed.[8] In South Africa this seemed to be more pronounced in the Black population as the observed incidence rate in White children was more than 70% of that reported for Germany.

Strengths and weaknesses

This study presents, for the first time, the incidence of pediatric cancers in South Africa on a national level and is one of very few studies from Sub-Saharan Africa. The strengths of conducting this analysis in South Africa include the availability of cancer registry data, the large childhood population, and the diverse racial population, allowing us to investigate differences by population group which is an important determinant of socioeconomic circumstances in South Africa. The NCR captures data from all public sector pathologically confirmed cancers across the country and a large proportion of cancers diagnosed in the private sector. However, as many private laboratories discontinued reporting to the NCR in 2006 because of concerns about patient privacy, marginal under-reporting of pediatric cancer cases diagnosed in the private healthcare sector is likely during the study period.

There were only 120 cases in our study with information missing on sex and 240 cases for which population group could not be assigned. Although we cannot entirely exclude some bias, we do not envisage any systematic reason for the missing data. A major limitation of our study is the pathology-based reporting process of the NCR, as cancers without a pathology-based diagnosis are missed. This might be of particular concern for some brain tumor cases diagnosed solely by

medical imaging, but could also apply more generally to the situation of cancer patients who present at a late stage and for whom the cancer was too advanced to benefit from a more precise diagnosis. Possibly also some leukemia cases might have been diagnosed only on peripheral blood tests performed outside the tertiary laboratory structures. This would be expected to primarily concern children who died before referral to a tertiary hospital where bone marrow biopsies would have been analyzed and could explain why rates of leukemia were particularly low. Therefore, even if malignancies are accurately diagnosed, they may not be captured by the NCR resulting in under-reporting of the actual incidence of cancer.

As there have been an increasing number of pathology reports received without information on population group since the early the 1990s, an imputation method (surname algorithm) was used to assign population group to cases missing this information. Thus, misclassification of some cases with regard to population group cannot be excluded. However, previously conducted validation analyses of the imputation method have shown this method to be reasonably accurate. Another limitation of this study was the lack of data on stage at diagnosis which could provide further insight into differences in stage at diagnosis by population and age groups.[34]

Conclusions

Our study provides an overview of childhood cancer incidence in South Africa as reported to the NCR between 2000 and 2006. Studies based on more recent data will be important to see whether the observed differences by population group, and between South Africa and high income countries, persist. Considering that the differences by population group were much greater than those observed in other settings, as well as the marked differences between South African Whites and the German population, genetic and environmental reasons would seem likely to explain only a small proportion of the substantial observed differences in incidence rates within South Africa by population group, and between White South Africans and Germans. More research is needed to understand the extent to which under-reporting and under-diagnosis may drive the observed patterns. Survival for many childhood cancers, when diagnosed at an early stage, is generally very good, with recent survival probabilities for children with cancer exceeding 80% in several European countries.[50] In contrast, survival from childhood cancer is much lower in South Africa, with reported survival rates of less than 50% among African Blacks.[41] This underlines the importance of raising awareness, training healthcare providers, enhancing diagnostic capacities, and facilitating access to medical services for poor families, as most pediatric cancers are potentially curable.[50]

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References

1. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer, 2013.
2. Kaatsch P, Steliarova-Foucher E, Crocetti E, et al. Time trends of cancer incidence in European children (1978–1997): report from the Automated Childhood Cancer Information System project. *Eur J Cancer* 2006;42:1961–71.
3. Stiller CA, Marcos-Gragera R, Ardanaz E, et al. Geographical patterns of childhood cancer incidence in Europe, 1988–1997. Report from the Automated Childhood Cancer Information System project. *Eur J Cancer* 2006;42:1952–60.
4. Kaatsch P, Spix J, German Childhood Cancer Registry—Annual Report 2012 (1980–2012). Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), University Medical Center of the Johannes Gutenberg University, 2013.
5. Ward E, DeSantis C, Robbins A, et al. Childhood and adolescent cancer statistics, 2014. *CA Cancer J Clin* 2014;64:83–103.
6. Baade PD, Youlden DR, Valery PC, et al. Trends in incidence of childhood cancer in Australia, 1983–2006. *Br J Cancer* 2010;102:620–6.
7. Magrath I, Steliarova-Foucher E, Epelman S, et al. Paediatric cancer in low-income and middle-income countries. *Lancet Oncol* 2013;14:e104–e16.
8. Parkin DM, Ferlay J, Hamdi-Cherif M, et al. Chapter 5: Childhood cancer. Cancer in Africa: Epidemiology and Prevention IARC Scientific Publications No 153 ed. Lyon: International Agency for Research on Cancer, 2003.
9. Chokunonga E, Borok MZ, Chirenje ZM, et al. Cancer incidence in harare. Triennal Report 2010–2012. National Cancer Registry Zimbabwe, 2013.
10. Stewart B, Wild PW. Chapter 1.3 Childhood cancer World Cancer Report ed. Lyon: International Agency for Research on Cancer, 2014.
11. Savage S, Schüz J. Environmental Chemicals and Childhood Cancer. In: Nriagu J, ed. Encyclopedia of Environmental Health. Elsevier Science and Technology, Elsevier: Burlington, 2011. 336–47.
12. Buffler P, Kwan M, Reynolds P, Urayama K. Environmental and Genetic Risk Factors for Childhood Leukemia: appraising the Evidence. *Cancer Invest* 2005;23:60–75.
13. Schüz J, Kaatsch P, Kaletsch U, et al. Association of childhood cancer with factors related to pregnancy and birth. *Int J Epidemiol* 1999;28:631–9.
14. Greaves M. Infection, immune responses and the aetiology of childhood leukaemia. *Nat Rev Cancer* 2006;6:193–203.
15. Dietrich M, Block G, Pogoda JM, et al. A review: dietary and endogenously formed N-nitroso compounds and risk of childhood brain tumors. *Cancer Causes Control* 2005;16:619–35.
16. Vinson F, Merhi M, Baldi I, et al. Exposure to pesticides and risk of childhood cancer: a meta-analysis of recent epidemiological studies. *Occupat Environ Med* 2011;68:694–702.
17. Schuz J, Ahlbom A. Exposure to electromagnetic fields and the risk of childhood leukaemia: a review. *Radiat Protect Dosimetr* 2008;132:202–11.
18. Hadley LG, Rouma BS, Saad-Eldin Y. Challenge of pediatric oncology in Africa. *Semin Pediatr Surg* 2012;21:136–41.
19. Azevedo-Silva F, Reis Rde S, Santos Mde O, et al. Evaluation of childhood acute leukemia incidence and underreporting in Brazil by capture-recapture methodology. *Cancer Epidemiol* 2009;33:403–5.
20. Swaminathan R, Sankaranarayanan R. Under-diagnosis and under-ascertainment of cases may be the reasons for low childhood cancer incidence in rural India. *Cancer Epidemiol* 2010;34:107–8.
21. Howard SC, Metzger ML, Wilimas JA, et al. Childhood cancer epidemiology in low-income countries. *Cancer* 2008;112:461–72.
22. Newton R. Geographical variation in the incidence of acute lymphoblastic leukaemia in childhood-Is it real? *Cancer Epidemiol* 2009;33:401–2.
23. Statistics South Africa, General household survey 2006, July 2006. Statistics South Africa, 2007.
24. World Bank. How we Classify Countries, Vol. 2014: The World Bank Group, 2014.
25. Dorrington RE, Alternative South African mid-year estimates, 2013. Centre for Actuarial Research Monograph 13, University of Cape Town, 2013.
26. Coovadia H, Jewkes R, Barron P, et al. The health and health system of South Africa: historical roots of current public health challenges. *Lancet* 2009;374:817–34.

27. National Health Act 61 of 2003. Regulations Relating to Cancer Registration. Government Notice R380 in Government Gazette 34248 dated 26 April 2011: Department of Health, Republic of South Africa, 2011.
28. Fritz A, Percy C, Jack A, et al. International Classification of Diseases for Oncology, Third Edition ed. Geneva: World Health Organisation, 2000.
29. Statistisches Bundesamt, Fachserie 1 Reihe 2.2. Bevölkerung und Erwerbstätigkeit. Bevölkerung mit Migrationshintergrund. Ergebnisse des Mikrozensus 2012—Statistisches Bundesamt, 2013.
30. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. *Cancer* 2005;103:1457–67.
31. Segi M. Cancer mortality for selected sites in 24 countries (1950-57) ed. Sendai: Department of Public Health, Tohoku University School of Medicine, 1960.
32. Dorrington RE, personal communication. Alternative South African midyear estimates, 2000. Centre for Actuarial Research Monograph 13, University of Cape Town, 2013.
33. StataCorp. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP, 2013.
34. Stefan DC, Stones D, Dippenaar A, Kidd M. Ethnicity and characteristics of Hodgkin lymphoma in children. *Pediatr Blood Cancer* 2009;52:182–5.
35. MacDouglass MG. Acute childhood leukaemia in Johannesburg. *Leuk Res* 1985;9:765–7.
36. Hesseling PB, Hartley P, Zietsman L, et al. Incidence of acute lymphoblastic leukaemia in white and coloured children in the Western Cape. *South African Med J* 2004;94:533–6.
37. National Cancer Registry South Africa, Cancer in South Africa 2006. Full Report.
38. Li J, Thompson TD, Miller JW, et al. Cancer incidence among children and adolescents in the United States, 2001–2003. *Pediatrics* 2008;121:e1470–7.
39. Chow EJ, Puumala SE, Mueller BA, et al. Childhood cancer in relation to parental race and ethnicity: a 5-state pooled analysis. *Cancer* 2010;116:3045–53.
40. Peltzer K. Utilization and practice of traditional/complementary/alternative medicine (TM/CAM) in South Africa. *Afr J Tradit, Complement Alter Med* 2009;6:175–85.
41. Stones DK, De Bruin GP, Esterhuizen TM, Stefan DC. Childhood cancer survival rates in two South African units. *South African Medical Journal* 2014;104:501.
42. Institute for Health Metrics and Evaluation (IHME). Millennium Development Goals (MDGs). Seattle: IHME, University of Washington, 2014.
43. Bhopal SS, Mann KD, Pearce MS. Registration of cancer in girls remains lower than expected in countries with low/middle incomes and low female education rates. *Br J Cancer* 2012;107:183–8.
44. Wiangnon S, Kamsa-Ard S, Jetsrisuparb A, Sriplung H, Sontipong S, Sumitsawan Y, Martin N. Childhood Cancer in Thailand: 1995–1997. *Asian Pacific J Cancer Prev* 2003;4:337–43.
45. Moreno F, Loria D, Abriata G, et al. Childhood cancer: incidence and early deaths in Argentina, 2000–2008. *Eur J Cancer* 2013;49:465–73.
46. Moradi A, Semnani S, Roshandel G, et al. Incidence of Chidlhood Cancers in Golestan Province of Iran. *OIran J Pediatr* 2010;20:335–42.
47. Cancer Research UK, Great Britain Cancer Incidence (1996–2005) Summary—Children. February 2014.
48. Parkin DM. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 2006;118:3030–44.
49. Magrath I. Epidemiology: clues to the pathogenesis of Burkitt lymphoma. *Br J Haematol* 2012;156:744–56.
50. Gatta G, Botta L, Rossi S, et al. Childhood cancer survival in Europe 1999–2007: results of EUROCARE-5—a population-based study. *Lancet Oncol* 2014;15:35–47.

Supplementary Information Table 1: Population estimates of South Africa and childhood cancer cases reported to the South African National Cancer Registry in 2000-2006 by population group and calendar year.

Year		All		Black		Mixed ancestry		Indian/Asian		White		*Race missing*
		Mid-year estimates	Childhood cancer	Mid-year estimates	Childhood cancer	Mid-year estimates	Childhood cancer	Mid-year estimates	Childhood cancer	Mid-year estimates	Childhood cancer	Childhood cancer
2000	**N**	15,051,670.0	703	12,520,281.0	494	1,287,690.8	63	293,751.4	***25***	949,946.4	96	25
	%	*100*	*100*	*83.2*	*70.3*	*8.6*	*9.0*	*2.0*	*3.6*	*6.3*	*13.7*	*3.6*
2001	**N**	14,958,546.0	770	12,448,246.0	511	1,290,564.3	89	288,576.5	34	931,159.1	114	22
	%	*100*	*100*	*83.2*	*66.4*	*8.6*	*11.6*	*1.9*	*4.4*	*6.2*	*14.8*	*2.9*
2002	**N**	14,843,594.0	719	12,361,236.0	498	1,289,661.9	59	283,787.9	24	908,908.1	114	24
	%	*100*	*100*	*83.3*	*69.3*	*8.7*	*8.2*	*1.9*	*3.3*	*6.1*	*15.9*	*3.3*
2003	**N**	14,717,143.0	630	12,263,615.0	403	1,287,961.1	60	279,324.4	15	886,242.4	105	47
	%	*100*	*100*	*83.3*	*64*	*8.8*	*9.5*	*1.9*	*2.4*	*6.0*	*16.7*	*7.5*
2004	**N**	14,633,686.0	642	12,212,022.0	429	1,284,745.0	51	273,693.4	15	863,225.9	100	47
	%	*100*	*100*	*83.5*	*66.8*	*8.8*	*7.9*	*1.9*	*2.3*	*5.9*	*15.6*	*7.3*
2005	**N**	14,546,782.0	575	12,160,223.0	399	1,278,845.6	44	268,517.6	15	839,195.3	84	33
	%	*100*	*100*	*83.6*	*69.4*	*8.8*	*7.7*	*1.8*	*2.6*	*5.8*	*14.6*	*5.7*
2006	**N**	14,497,629.0	562	12,136,946.0	391	1,278,198.4	33	263,701.3	20	818,783.3	76	42
	%	*100*	*100*	*83.7*	*69.6*	*8.8*	*5.9*	*1.9*	*3.6*	5.6	13.5	*7.5*
Total	**N**	**103,249,048.0**	**4601**	**86,102,568.0**	**3125**	**8,997,667.0**	***399***	**1,951,352.5**	***148***	**6,197,460.5**	***689***	***240***
	%	**100**	**100**	**83.4**	**67.9**	**8.7**	**8.7**	**1.9**	**3.2**	***6.0***	***15***	**5.2**

Supplementary Information Table 2: Childhood cancer reported to the South African National Cancer Registry compared to the German Childhood Cancer Registry in 2000-2006 by diagnostic group, population group (all, Mixed ancestry vs. Indian/Asian), sex ratio, and age specific, crude, and age-standardized incidence rates.[1]

ICCC-3 diagnostic group[2]	Race	N	M/F[3]	Age specific incidence[4]				Crude incidence[5]	ASR[6]	Germany ASR[6]	Germany M/F[3]
				< 1 year	1 - 4 years	5 – 9 years	10 - 14 years				
Leukaemias	*All*	875	1.3	7.2	9.6	8.1	8.3	8.5	8.5	54.5	1.2
	Mixed ancestry	66	1.4	8.3	9.4	7.0	5.9	7.3	7.5		
	Indian/Asian	47	1.5	8.6	51.3	18.6	13.8	24.1	26.6		
Lymphomas	*All*	725	2.1	1.3	6.3	8.4	7.3	7.0	6.9	15.7	2
	Mixed ancestry	84	2.1	0.0	5.6	13.0	10.5	9.3	9.0		
	Indian/Asian	15	1.5	0.0	10.7	9.3	5.5	7.7	7.9		
Malignant CNS tumours	*All*	431	1.2	2.3	5.3	4.5	3.4	4.2	4.3	21.5	1.3
	Mixed ancestry	55	1.7	6.6	5.6	6.7	5.9	6.1	6.1		
	Indian/Asian	18	0.5	0.0	15.0	12.4	4.1	9.2	9.8		
Sympathetic nervous system tumours	*All*	209	1.3	6.0	4.5	1.1	0.4	2.0	2.3	14.0	1.2
	Mixed ancestry	29	1.4	9.9	7.3	1.0	1.0	3.2	3.6		
	Indian/Asian	10	9.0	34.5	10.7	1.6	0.0	5.1	6.5		
Retino-blastomas	*All*	278	1.3	4.6	7.9	1.0	0.2	2.7	3.2	4.3	1.2
	Mixed ancestry	16	0.7	1.7	5.6	0.7	0.0	1.8	2.1		
	Indian/Asian	7	0.8	25.9	8.6	0.0	0.0	3.6	4.7		
Renal tumours	*All*	542	1.1	6.2	12.6	3.9	1.0	5.2	5.9	9.8	0.9
	Mixed ancestry	41	1.4	14.9	9.8	3.0	0.0	4.6	5.2		
	Indian/Asian	9	1.3	8.6	15.0	1.6	0.0	4.6	5.8		
Hepatic tumours	*All*	87	1.6	2.3	1.3	0.4	0.6	0.8	0.9	2.1	1.6
	Mixed ancestry	13	1.2	3.3	3.4	1.0	0.0	1.4	1.6		
	Indian/Asian	2	1.0	8.6	2.1	0.0	0.0	1.0	1.3		
Malignant bone tumours	*All*	260	0.9	0.6	0.4	1.4	5.5	2.5	2.2	5.9	1.1
	Mixed ancestry	19	0.6	1.7	0.4	1.3	4.2	2.1	1.9		
	Indian/Asian	10	1.5	0.0	4.3	1.6	9.7	5.1	4.6		
Soft tissue sarcomas	*All*	630	1.3	4.7	7.4	5.7	5.8	6.1	6.2	9.5	1.2
	Mixed ancestry	38	2.2	3.3	5.1	2.7	5.2	4.2	4.2		
	Indian/Asian	11	1.5	8.6	6.4	4.7	5.5	5.6	5.8		
Germ cell tumours	*All*	118	0.3	1.1	1.1	0.9	1.4	1.1	1.1	4.7	0.8
	Mixed ancestry	7	0.4	1.7	1.7	0.3	0.3	0.8	0.9		
	Indian/Asian	6	2.0	8.6	6.4	1.6	1.4	3.1	3.6		
Malignant epithelial neoplasms	*All*	350	0.9	3.7	2.0	2.3	5.3	3.4	3.2	2.1	0.8
	Mixed ancestry	27	1.2	6.6	2.1	1.0	4.9	3.0	2.9		
	Indian/Asian	10	1.0	0.0	2.1	6.2	6.9	5.1	4.7		

Other & unspecified malignant tumours	***All***	96	1.0	1.4	1.5	0.7	0.6	0.9	1.0	0.1	1.2
	Mixed ancestry	4	0.3	1.7	0.4	0.7	0.0	0.4	0.5		
	Indian/Asian	3	2.0	8.6	2.1	0.0	1.4	1.5	1.7		

[1]Sex ratio is based on cases with known sex. Total number (N) and rates include cases with sex missing.
[2]Diagnostic groups defined using the International Classification of Childhood Cancer Third Edition (ICCC-3)
[3]M/F: sex ratio – male cases/female cases
[4]Age specific incidence: age group specific incidence rates per 1,000,000 population aged 0 – 14 years.
[5]Crude incidence: crude incidence rate per 1,000,000 population aged 0 – 14 years.
[6]ASR: age-standardized incidence rate (using the world standard population) per 1,000,000 population aged 0 – 14 years.

Supplementary Information Table 3: International comparison of reported age-standardized incidence rates of cancer in children (aged 0 – 14 years) from regions with different income level defined by the World Bank classification.

		UK[1]	Germany[2]	Australia[3]	Argentina[4]	Golestan, Iran[5]	Thailand[6]	South Africa[2]	The Gambia[7]	Harare, Zimbabwe[7]	Uganda[7]
Time period		1996 - 2005	2000 - 2006	1997 - 2006	2000 - 2008	2004 - 2006	1995 - 1997	2000 - 2006	1988 - 1998	1990 - 1997	1993 - 1997
World bank classification[8]		High income	High income	High income	Upper middle income	Upper middle income	Upper middle income	Upper middle income	Low income	Low income	Low income
ASR[9] by diagnostic group[10]	***All cancers***	147.1	144.4	157.5	128.5	99.3	93.0	45.7	34.7	111.3	173.9
	Leukaemias	48.1	54.5	53.1	47.5	42.7	36.9	8.5	2.7	21.6	7.9
	Lymphomas	13.3	15.7	15.4	15.6	9.9	8.9	6.9	13.7	13.8	65.3
	CNS tumours	35.6	*(21.5)*	35.7	23.5	*(9.2)*	*(14.2)*	*(4.3)*	0.2	11.9	1.8
	Sympathetic nervous system tumours	10.3	14.0	9.6	7.9	3.9	6.3	2.3	0.5	3.4	--
	Retinoblastomas	4.4	4.3	3.9	5.0	1	4.4	3.2	2.8	10.6	7.7
	Renal tumours	9.1	9.8	8.5	6.9	1.9	4.0	5.9	3.6	14.0	7.2
	Hepatic tumours	1.8	2.1	2.6	1.9	2.1	1.3	0.9	No data reported	No data reported	No data reported
	Malignant bone tumours	5.0	5.9	6.5	5.4	5.6	3.3	2.2	1.9	4.1	4.3
	Soft tissue sarcomas	9.6	9.5	8.4	7.7	7.3	3.9	6.2	1.0	14.0	58.6
	Germ cell tumours	4.8	4.7	6.4	4.1	3.8	2.9	1.1	0.2	2.0	1.3
	Malignant epithelial neoplasms	4.4	2.1	7.1	2.1	3.8	2.7	3.2	No data reported	No data reported	No data reported
	Other & unspecified malignant tumours	0.7	0.1	0.4	1.0	8.1	4.2	1.0	No data reported	No data reported	No data reported

[1] Cancer Research UK, Great Britain Cancer Incidence (1996-2005) Summary – Children, February 2014

[2] Results from present manuscript.

[3] Baade PD, Youlden DR, Valery PC, Hassall T, Ward L, Green AC, Aitken JF. Trends in incidence of childhood cancer in Australia, 1983-2006. *British journal of cancer* 2010;102: 620-6

[4] Moreno F, Loria D, Abriata G, Terracini B, network R. Childhood cancer: incidence and early deaths in Argentina, 2000-2008. *European journal of cancer* 2013;49: 465-73

[5] Moradi A, Semnani S, Roshandel G, Mirbehbehani N, Keshtkar A, Aarabi M, Moghaddami A, Cheraghali F. Incidence of Chidlhood Cancers in Golestan Province of Iran. OIran Journal of Pediatrics 2010;20: 335-42

[6] Wiangnon S, Kamsa-Ard S, Jetsrisuparb A, Sriplung H, Sontipong S, Sumitsawan Y, Martin N. Childhood Cancer in Thailand: 1995-1997. *Asian Pacific Journal of Cancer Prevention* 2003;4: 337-43

[7] World Bank. How we Classify Countries, vol. 2014: The World Bank Group, 2014

[8] Parkin DM, Ferlay J, Hamdi-Cherif M, Sitas F, Thomas J, Wabinga H, Whelan SL. Chapter 5: Childhood cancer. *Cancer in Africa: Epidemiology and Prevention IARC Scientific Publications No 153*ed. Lyon: International Agency for Research on Cancer, 2003

[9]ASR: age-standardized incidence rate (Segi world standard population except incidence rates of Australia by the WHO World Standard) per 1,000,000 children per year.

[10] Diagnostic groups defined using the International Classification of Childhood Cancer (depending on the publication, either ICCC or ICCC-3), including non-malignant intracranial and intraspinal tumours. An exception are the CNS tumour rates of South Africa, Germany, Iran and Thailand, these rates do not include non-malignant brain tumours.

Article II

Hematological malignancies in South Africa 2000-2006: Analysis of data reported to the National Cancer Registry

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BACKGROUND

Worldwide, leukemia, multiple myeloma, Hodgkin lymphoma (HL), and non-Hodgkin lymphoma (NHL) collectively accounted for an estimated 6.5% of new cancer cases in 2012 with the majority of these cases coming from NHL followed by leukemia [1]. While global estimates suggest 2- and 3-fold higher incidence rates of NHL and leukemia, respectively, in high income countries compared to Sub-Saharan Africa (1), there is little known about the incidence patterns of hematologic malignancies in this region, including South Africa. Similar to worldwide figures, hematologic malignancies contributed an estimated 6% of new cancer cases in South Africa in 2012 (1).

To date, the literature of hematologic malignancies in South Africa is largely based on hospital-based studies which report on patient and disease characteristics of leukemias and lymphomas (2-6), with a particular focus on the prevalence of HIV and the differences in cancer characteristics between HIV positive and negative patients. There is a well-established association between HIV and several types of hematologic malignancies, including but not restricted to the AIDS-defining subtypes of NHL (7-9). While hospital-based studies benefit from detailed patient information, there is also a need to estimate incidence and mortality rates, particularly at the national-level. Such data provide important information about the overall burden of disease which in turn inform cancer control strategies, and provide a basis for investigating underlying determinants of disease (*REF*).

Studies from the United Kingdom and United States show considerable variability in the incidence of hematologic malignancies by gender and age (10-12) as well as by race (10,11,13). It is unknown whether the incidence of these malignancies in South Africa follows similar patterns to those reported in higher income areas. Recently, it was reported that the

incidence of pediatric hematologic malignancies was approximately 3-times higher among White compared with Black African children within South Africa (14). As race is highly correlated with socioeconomic position and access to private health care services in South Africa (15), the authors hypothesized that differences in access and utilization of health care services likely explain at least some of the observed incidence differences (14). To our knowledge, these patterns have not been investigated among adults in South Africa.

In this report, we describe the incidence of adult cases of leukemia, multiple myeloma, HL, and NHL reported to the National Cancer Registry of South Africa (NCR-SA) between 2000 and 2006, by age, gender and race in South Africa.

METHODS

National Cancer Registry

A detailed description of the NCR-SA is provided in (16). Briefly, the NCR-SA (www.ncr.ac.za) is a pathology-based registry, receiving pathology reports from public and private laboratories throughout the country. The registry includes only incident, primary invasive cancers based on histologic, cytologic or hematologic confirmation. Trained coders at the registry code the diagnoses from pathology reports based on primary organ site and morphological type according to the International Classification of Diseases for Oncology, third edition (ICD-O-3) (17). Until 2011, reporting to the registry was done on a voluntary basis although all of the National Health Laboratory Services (NHLS) laboratories (i.e., public laboratories), have regularly reported to the registry over time. Reporting has been less complete from the private sector, particularly from 2005 onwards. In addition to basic demographic information about the patient (name, age and/or date of birth, gender) and tumor diagnosis information (topography, morphology, date of diagnosis), the registry extracts

information by race (Black African, White, Colored (i.e., mixed ancestry), and Asian/Indian) where available from the pathology reports. In the absence of race, they apply an algorithm, a hot deck imputation, which estimates this variable using a database of approximately 1.4 million surnames with known race (16). In 2000-2001 approximately 67% of case reports had missing race and thus a large proportion is imputed. If race cannot be estimated (i.e., surname with no match in the database), it is left as missing. A comparison of the distribution of race based on actual versus imputed data for a subset of 277130 cancer cases (contributing to the database) reported to the registry between 1990 and 1995 showed very good agreement between actual and imputed values. The distribution of original (imputed) data was as follows: 53% (50%) Whites, 40% (41%) Black Africans, 2% (2%) Indian/Asian and 5% (7%) mixed ancestry (chi-square test p-value=0.94 for distribution differences).

Hematologic malignancy cases

For the present report, we included all incident cases of leukemia, myeloma, HL and NHL reported to the NCR-SA that were diagnosed at ages ≥15 years between 2000 and 2006, a time period under which the cancer registry worked under stable and defined conditions. From all invasive cancers diagnosed, the initial selection was made of all cases with ICD-0-3 morphology codes of 9590 to 9999 (17). Using the Surveillance, Epidemiology and End Results (SEER) Program site recode (http://seer.cancer.gov/siterecode/icdo3_dwhoheme/index.html) which is based on the ICD-O-3 and the 2008 WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (18), hematologic malignancies were classified into broad groups of leukemia, myeloma, Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL). Leukemia cases could be further broken down into: acute lymphocytic leukemia, chronic lymphocytic leukemia, other lymphocytic leukemia, acute myeloid leukemia, acute monocytic leukemia, chronic myeloid

leukemia, other myeloid/monocytic, other acute leukemia, aleukemia, subleukemia, and NOS. As the registry does not routinely collect information of tumor grade, it was not possible to fully implement the more detailed classification of lymphoid neoplasms which is grade dependent for some categories (http://seer.cancer.gov/lymphomarecode/). Our analysis did not include myelodysplastic syndromes.

Population data

Consistent with the approach used in the annual reports of the NCR-SA for the years included in the present study , we used the Alternative South African mid-year population estimates (19) from the Centre for Actuarial Research, University of Cape Town, stratified by age, gender and population group for calculation of incidence rates. These mid-year population estimates are similar in magnitude to the official mid-year estimates but maintain an age distribution that is consistent with that of the most recent Census in 2011 and, as with the NCR for this time period, we considered them as the more appropriate population estimates for the purposes of studying differences by age group.

Statistical methods

Gender-specific crude incidence rates overall and stratified by race were estimated for the different classifications of hematologic malignancies described above. Most analyses were based on the first-level, broad classification of leukemia, myeloma, HL and NHL. Reflecting limited case numbers in individual age groups, age-specific rates were not estimated separately for males and females. Gender-specific age-standardized rates, overall and stratified by race, were calculated using the SEGI world standard (20) truncated for ages ≥15 (ASR 15+). The ASR 15+ is a weighted average of age-specific rates based with the following weights for each age group: 15-19 (0.13), 20-24 (0.12), 25-29 (0.12), 30-34 (0.09),

35-39 (0.09), 40-44 (0.09), 45-49 (0.09), 50-54 (0.07), 55-59 (0.06), 60-64 (0.06), 65-69 (0.04), 70-74 (0.03), 75-79 (0.01), 80+ (0.01).

Incidence rate ratios (IRRs) and 95% confidence intervals (CI) were estimated using Poisson regression models with the number of cases for a given category of hematologic malignancy as the outcome, the population size as the log offset and a log link function, overall and stratified by race, comparing rates among females to males. Similar models, stratified by gender, were used to compare incidence rates by race, using Black Africans as the reference group. All models were adjusted for age group (5-year categories) and calendar year (single year treated as a categorical variable). Models including all races and/or both males and females were further adjusted for race and gender. Hematologic patients with unknown race and/or gender (4.7%) were excluded from Poisson models as there were no corresponding population estimates for such groups. As under-ascertainment of cancers at older ages is a concern in many cancer studies (not specific to South Africa), sensitivity analyses were repeated by restricting the dataset to ages less than 75 years.

RESULTS

Between 2000 and 2006, there were a total of 14662 hematologic malignancies reported to the registry. There were 46 cases (0.3%) with unknown gender. Table 1 presents the distribution by race for the 14616 hematologic malignancy cases with known gender, by calendar year of diagnosis, reporting source (private vs. public), and year of diagnosis, separately for males and females. In all calendar years, approximately half of the cases were reported among Black Africans, one-third among Whites, 10% among individuals of mixed ancestry and 5% or less among Asians/Indians. The distribution of race differed substantially between public and private laboratories, with the White population accounting for approximately half of all cases

reported by private laboratories. With increasing age at diagnosis, the proportion of cases coming from the Black African population declined while that from the White population increased steadily. Similar patterns were observed for males and females with respect to calendar year, reporting source and age.

The distribution of cases, by the four major categories of hematologic malignancies is presented in Figure 1. Regardless of gender or race, NHL was the most commonly reported hematologic malignancy, accounting for approximately 50% or more of cases in most groups. In all groups, this was followed by leukemia, contributing 15-25% of cases in the various subgroups.

Crude and age-standardized incidence rates are presented for leukemia, myeloma, HL and NHL by race and gender in Table 2. Incidence rates varied markedly by race. In general, the lowest rates were observed among Black Africans and the highest among Whites. An exception was myeloma, for which rates were lowest among the Asian/Indian population among both males and females. Among males, the ASR of myeloma was similar for the White and Mixed ancestry groups. A more detailed breakdown of leukemia subtypes is presented in Supplemental Table 1. Among females, acute myeloid leukemia was the most common form of leukemia whereas the highest ASR for males was observed for chronic lymphocytic leukemia. As with the main groups, ASRs tended to be lowest among Black Africans and highest among Whites. For several subtypes of leukemia ASRs were similar in the White and Asian/Indian populations.

Figure 2 presents the incidence rate ratio comparing males vs. females. For the whole population combined, the reported incidence rate of hematologic malignancies was 1.2 to 1.5-

fold higher among males than females (Figure 2a). Similar patterns were observed across the four race groups (Figure 2b).

The incidence rate ratios for race are presented in Figure 3. For males and females combined, reported incidence rates of hematologic malignancies tended to be higher among White, Mixed ancestry and Asian/Indian populations than among the Black population (Figure 3a). The exception was for myeloma, for which no statistically significant difference was observed between the Asian/Indian and Black populations, in either males or females. The largest rate ratios were observed comparing the White and Black populations, ranging from 1.56 (95% CI 1.38-1.76) for myeloma to 3.77 (95% CI 3.38-4.21) for HL. Gender-specific patterns were similar to those observed for males and females combined (Figures 3b, 3c).

Age-specific rates of leukemia, myeloma, HL and NHL are presented in Figure 4(a-d) by race. With the exception of HL, incidence rates tended to increase with age until approximately age 75, followed by a decline at the oldest ages. For HL (Figure 4c), the patterns appeared quite different between races, most notably comparing the White and Black populations. Among Whites, there was an early peak in HL incidence rates at ages 20-29 and a later peak around age 70-75 with rates somewhat lower and generally stable in between. Among Black South Africans, there was an increase with HL with age until approximately age 30, at which point the rate plateaued followed by a subsequent decline beginning around age 60. For all four major types of hematologic malignancies investigated, incidence rates were consistently higher among Whites than Black Africans, irrespective of age, but these differences tended to increase with age (Figures 4a-d).

In sensitivity analyses restricted to ages less than 75, there were no marked changes in the results presented in Tables 1-2 or the Figures 1-3. Incidence rate ratios by racial group were

slightly attenuated at ages less than 75 compared with the full adult population, but the reduction was very minor and the interpretation unchanged. This observation is consistent with the patterns observed in age-specific rates whereby differences between the White and Black populations were most apparent at oldest ages.

DISCUSSION

Summary of key results

We estimated the incidence of adult hematologic malignancies (diagnosed at ages 15 years or older) reported to the National Cancer Registry of South Africa (NCR-SA) between 2000 and 2006, describing overall rates as well as those by age, gender and race. NHL was the most common hematologic malignancy reported to the NCR-SA during this time period, irrespective of gender and race. Incidence rates of reported hematologic malignancies were generally 20 to 50% higher among males than females. Our analyses suggested higher rates of reported hematologic malignancies among the White, mixed ancestry and Asian/Indian populations than among Black Africans, with differences most pronounced when comparing the White and Black African populations (IRRs ranging from 1.6 for myeloma to 3.8 for HL for males and females combined). These differences tended to become more marked with increasing age. With respect to age-specific rates, incidence rates increased with age for hematologic malignancies other than HL. For HL, among Whites, a bimodal peak was observed at ages 20-29 and 70-75. A different pattern was observed among Black South Africans; reported HL rates increased with age until approximately age 30, at which point the rate plateaued followed by a subsequent decline beginning around age 60.

Interpretation of key results

The observation that NHL, followed by leukemia, was the most common of these four broad categories of hematologic malignancies is consistent with worldwide patterns (1). The higher incidence rates among males than females are also consistent with gender patterns reported elsewhere (12,21).

With respect to race, age-adjusted incidence rates from the SEER-18 registries in the US for the period of 2000-2011 show a predominance among the White vs. Black populations with annual White to Black ratios (estimated using (22)) of 1.3-1.5 for total NHL, 1.2-1.4 for total leukemia and 1.1-1.3 for HL. These overall estimates are somewhat lower than those estimated in the NCR-SA data. Of note, previous analyses of the SEER data have shown that the magnitude and direction of these race rate ratios varies by subtype (10,11). The available data from the NCR-SA do not permit a full classification of NHLs as grade is not available but we were able to classify leukemia subtypes. Unlike SEER (10), there were no leukemia subtypes for which ASRs were higher among Black Africans than the White population (Supplemental Table 1). The apparently distinct age-specific patterns observed for HL between the White and Black populations in the NCR data is also reported in the SEER data where a clear bimodal pattern, classically associated with HL, is much more pronounced in the White than Black populations (23). Globally, the classic bimodal age pattern appears to be more a characteristic of more economically developed areas (24). In contrast to what is observed for NHL, HL and leukemia rates, the incidence of myeloma in the SEER data is approximately 2-fold greater among Blacks than Whites (13). This was not seen in the South African data; while the estimated IRR in the NCR-SA comparing the White and Black African populations was lower for myeloma (1.56) than for leukemia, HL or NHL, it remained above 1.

For any cancer site, differences in the underlying distribution of genetic and environmental risk factors as well as factors related to completeness of reporting and diagnosis drive demographic variations in the incidence patterns. The etiology of hematologic malignancies is largely unexplained, with few known determinants(24-26). Established environmental risk factors for leukemia include ionizing radiation and certain chemical exposures such as benzene (26). For NHL, there is clear evidence for an association with infectious diseases (HIV, Epstein Barr virus (EBV), Hepatitis C Virus (HCV), and Human T-Lymphotrophic Virus (HTLV-1)) (25) and increasing data to support a role for lifestyle, occupational and environmental factors (27). HL also has an infectious etiology -- EBV is one of few known risk factors (24). While we cannot exclude the possibility that differences in the distribution of or susceptibility to etiologic factors could explain the marked differences by race observed in the NCR-SA data, the known infectious and environmental risk factors would not seem likely explanations. In order for these factors to drive truly higher rates of disease within South African Whites versus Black Africans, they would need to be more prevalent in the White population.

Disparities in the completeness of diagnosis and reporting between race groups may have contributed to the observed incidence rate patterns. The NCR is a pathology-based registry and thus only hematologic malignancies with a histologic, cytologic or hematologic (bone marrow aspirate or trephine biopsy) confirmation are captured. Consequently, there is an inherent risk of under-estimating rates based on the registry data as cases diagnosed by other means (i.e., peripheral blood smear) are not reported. Problems of under-reporting may be compounded, however, by other factors that disproportionately affect Black Africans compared with Whites and contribute not only to under-reporting but also under-diagnosis of these cancers. First, a smaller proportion of Black Africans have access to a private medical

aid fund (7.2% vs 63.1% among Whites according to 2006 data) (28). Public medical services are chronically under-resourced and understaffed (29,30). As such, patients in the public sector may be less likely than those in the private sector to receive a comprehensive diagnostic work-up. Further, the system operates under a tiered structure by which patients are referred from primary health clinics to tertiary hospitals via other tiers and many patients are thought to be lost from the system before presenting at referral centers (31). Second, the burden of HIV is markedly higher among Blacks than Whites in South Africa (in 2012, it was estimated that 22.7% of the Black South African population ages 15-49 was infected with HIV compared with 0.6% among Whites) (32). While HIV is associated with increased risk of lymphomas, particularly subtypes of NHL (9), atypical presentation and histology of HIV-associated lymphomas may lead to misdiagnosis or delayed diagnosis (33). Competing mortality (9,34) and late-stage presentation of disease (3,35) may further reduce opportunity for lymphomas to develop and/or be diagnosed in populations with high HIV rates.

Strengths/limitations

This is the first country-wide study on hematologic malignancies in South Africa and one of very few studies from Sub-Saharan Africa. The study benefits from the large number of cases permitting detailed examination of rates and patterns by age, sex and race. The diverse racial population of South Africa enabled us to investigate differences by race which is an important determinant of socioeconomic circumstances and access to private health care in South Africa (15). Nonetheless, analyses of the Asian/Indian and mixed ancestry populations were less robust owing to smaller case numbers than in the Black and White populations, particularly when further examining age-specific patterns. Limitations include that, by definition, the cancer registry is limited to pathology-confirmed cancer cases and thus it is understood that it does not fully capture incident hematologic malignancies. Further, there was a decline in

reporting to the NCR by some private sector laboratories (beginning in 2005) (16) – this would be expected to have the greatest impact on the White population which could attenuate the observed rate ratios by race. In the absence of tumor grade, we were unable to fully classify lymphoid neoplasms following the WHO criteria. Previous studies of lymphoma and leukemia in the US suggest that racial differences may vary considerably by subtype (10,11). Race group had to be imputed for a substantial proportion of the dataset. The method however has been previously validated in the NCR and the limitation appears to be of minor importance, although some misclassification cannot be ruled out. While it is important to consider our results in the context of these limitations, the NCR provides the most comprehensive overview of these cancers in the country at this time.

Conclusions

The hematologic malignancies investigated here collectively account for an estimated 6% of new cancer cases and 8% of cancer deaths in South Africa (1). The consistency of patterns by age and gender with those reported in other populations (1,10,12,13,21,23) suggest that underlying risk factors for these cancers are unlikely to modify the age distribution or gender ratio. Differences between races, however, would appear to be more pronounced than those observed in some other settings. We hypothesize that challenges related to diagnosis and reporting of cancers play a role in the patterns by race while the set-up of the NCR (pathology-based) could lead to some degree of under-ascertainment, irrespective of race, gender or age. Despite challenges, it is important to analyze and report available national cancer incidence data to raise awareness of the cancer burden and to characterize patterns by demographic characteristics so as ultimately to improve the situation.

References

1. Ferlay J, Soerjomataram I, Ervik M *et al.* (2013) GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer.

2. Mantina H, Wiggill TM, Carmona S, Perner Y, Stevens WS(2010) Characterization of Lymphomas in a high prevalence HIV setting. *J Acquir Immune Defic Syndr* **53**: 656-60.

3. Patel M, Philip V, Fazel F(2011) Human Immunodeficiency Virus Infection and Hodgkin's Lymphoma in South Africa: An Emerging Problem. *Adv Hematol* **2011**: 578163.

4. Patel M, Philip V, Fazel F *et al.*(2012) Human immunodeficiency virus infection and chronic myeloid leukemia. *Leuk Res* **36**: 1334-8.

5. Sissolak G, Sissolak D, Jacobs P(2010) Human immunodeficiency and Hodgkin lymphoma. *Transfus Apher Sci* **42**: 131-9.

6. Abayomi EA, Somers A, Grewal R *et al.*(2011) Impact of the HIV epidemic and Anti-Retroviral Treatment policy on lymphoma incidence and subtypes seen in the Western Cape of South Africa, 2002-2009: preliminary findings of the Tygerberg Lymphoma Study Group. *Transfus Apher Sci* **44**: 161-6.

7. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM(2007) Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* **370**: 59-67.

8. Shiels MS, Engels EA(2012) Increased risk of histologically defined cancer subtypes in human immunodeficiency virus-infected individuals: clues for possible immunosuppression-related or infectious etiology. *Cancer* **118**: 4869-76.

9. Carbone A, Vaccher E, Gloghini A *et al.*(2014) Diagnosis and management of lymphomas and other cancers in HIV-infected patients. *Nat Rev Clin Oncol* **11**: 223-38.

10. Dores GM, Devesa SS, Curtis RE, Linet MS, Morton LM(2012) Acute leukemia incidence and patient survival among children and adults in the United States, 2001-2007. *Blood* **119**: 34-43.

11. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS(2006) Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. *Blood* **107**: 265-76.

12. Smith A, Howell D, Patmore R, Jack A, Roman E(2011) Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network. *Br J Cancer* **105**: 1684-92.

13. Waxman AJ, Mink PJ, Devesa SS *et al.*(2010) Racial disparities in incidence and outcome in multiple myeloma: a population-based study. *Blood* **116**: 5501-6.

14. Erdmann F, Kielkowski D, Schonfeld SJ *et al.*(2014) Childhood cancer incidence patterns by race, sex and age for 2000-2006: A report from the South African National Cancer Registry. *Int J Cancer*.(in press)

15. Statistics South Africa (2007) General household survey: 2006. Statistical Release P0318. Pretoria.

16. Singh E, Underwood JM, Nattey C, Babb C, Sengayi M, Kellett P(2015) South African National Cancer Registry: Effect of withheld data from private health systems on cancer incidence estimates. *S Afr Med J* **105**: 107-9.

17. Fritz A, Percy C, Jack A *et al.* (2000) *International Classification of Diseases for Oncology, 3rd Edition.* Geneva: World Health Organization.

18. Swerdlow SH, Campo E, Harris NL *et al.* (2008) *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.* Lyon: IARC.

19. Dorrington RE (2013) Alternative South African midyear estimates, 2013. Centre for Actuarial Research Monograph 13.University of Cape Town.

20. Segi M (1960) Cancer mortality for selected sites in 24 countries (1950-57). Sendai, Tohoku University School of Public Health.

21. Sant M, Allemani C, Tereanu C *et al.*(2010) Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. *Blood* **116**: 3724-34.

22. Anonymous (2015) Fast Stats: An interactive tool for access to SEER cancer statistics. Surveillance Research Program, National Cancer Institute. http://seer.cancer.gov/faststats. (Accessed on 2-10-2015).

23. Evens AM, Antillon M, schebrook-Kilfoy B, Chiu BC(2012) Racial disparities in Hodgkin's lymphoma: a comprehensive population-based analysis. *Ann Oncol* **23**: 2128-37.

24. Mueller NE, Grufferman S (2006) Hodgkin's Lymphoma. In: Schottenfeld D, Fraumeni JFFJr, eds. *Cancer Epidemiology and Prevention*.

25. Hartge P, Bracci PM, Wang SS, Devesa SS, Holly EA (2006) Non-Hodgkin's Lymphoma. In: Schottenfeld D, Fraumeni JFFJr, eds. *Cancer Epidemiology and Prevention*.

26. Linet MS, Devesa SS, Morgan GJ (2006) The Leukemias. In: Schottenfeld D, Fraumeni JFF, Jr, eds. *Cancer Epidemiology and Prevention*.Oxford University Press.

27. Morton LM, Slager SL, Cerhan JR *et al.*(2014) Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. *J Natl Cancer Inst Monogr* **2014**: 130-44.

28. Statistics South Africa (2011) General household survey: 2011. Statistical Release P0318.

29. Broomberg J, Chetty KS, Masobe P(1992) The role of private hospitals in South Africa. Part I. Current trends. *S Afr Med J* **82**: 329-34.

30. Mayosi BM, Benatar SR(2014) Health and health care in South Africa--20 years after Mandela. *N Engl J Med* **371**: 1344-53.

31. Clouse K, Hanrahan CF, Bassett J, Fox MP, Sanne I, Van RA(2014) Impact of systematic HIV testing on case finding and retention in care at a primary care clinic in South Africa. *Trop Med Int Health* **19**: 1411-9.

32. Shisana O, Rehle T, Simbayi LC *et al.* (2014) South African National HIV Prevalence, Incidence and Behaviour Survey, 2012. Cape Town: HSRC Press.

33. Wiggill TM, Mayne ES, Willem P(2013) Challenges in lymphoma diagnosis in HIV positive patients in the South African setting. *Transfus Apher Sci* **49**: 157-62.

34. Mbulaiteye SM, Bhatia K, Adebamowo C, Sasco AJ(2011) HIV and cancer in Africa: mutual collaboration between HIV and cancer programs may provide timely research and public health data. *Infect Agent Cancer* **6**: 16.

35. Wiggill TM, Mantina H, Willem P, Perner Y, Stevens WS(2011) Changing pattern of lymphoma subgroups at a tertiary academic complex in a high-prevalence HIV setting: a South African perspective. *J Acquir Immune Defic Syndr* **56**: 460-6.

Table 1: Distribution of confirmed cases of hematologic malignancies reported to NCR-SA by select characteristics, ages 15+

	Males											Females									
	Black		White		Mixed ancestry		Asian		Unknown		All	Black		White		Mixed ancestry		Asian		Unknown		All
	N	%	N	%	N	%	N	%	N	%	N	N	%	N	%	N	%	N	%	N	%	N
Year																						
2000	563	*50%*	365	*32%*	126	*11%*	37	*3%*	44	*4%*	1135	458	*50%*	278	*30%*	113	*12%*	38	*4%*	27	*3%*	914
2001	563	*49%*	397	*35%*	102	*9%*	40	*4%*	38	*3%*	1140	482	*50%*	338	*35%*	77	*8%*	43	*4%*	26	*3%*	966
2002	542	*49%*	365	*33%*	99	*9%*	57	*5%*	49	*4%*	1112	496	*52%*	317	*33%*	77	*8%*	33	*3%*	30	*3%*	953
2003	518	*48%*	376	*35%*	107	*10%*	37	*3%*	36	*3%*	1074	413	*48%*	287	*33%*	97	*11%*	34	*4%*	29	*3%*	860
2004	500	*46%*	366	*34%*	127	*12%*	36	*3%*	60	*6%*	1089	514	*49%*	332	*32%*	116	*11%*	34	*3%*	55	*5%*	1051
2005	466	*47%*	326	*33%*	115	*11%*	32	*3%*	63	*6%*	1002	499	*51%*	296	*30%*	96	*10%*	31	*3%*	64	*6%*	986
2006	635	*50%*	383	*30%*	141	*11%*	35	*3%*	68	*5%*	1262	585	*55%*	296	*28%*	110	*10%*	25	*2%*	56	*5%*	1072
Total	3787	*48%*	2578	*33%*	817	*10%*	274	*4%*	358	*5%*	7814	3447	*51%*	2144	*32%*	686	*10%*	238	*3%*	287	*4%*	6802
Reporting source																						
NHLS	3101	*57%*	1294	*24%*	618	*11%*	184	*3%*	201	*4%*	5398	2937	*60%*	1063	*22%*	531	*11%*	166	*3%*	171	*4%*	4868
Private	686	*28%*	1284	*53%*	199	*8%*	90	*4%*	157	*6%*	2416	510	*26%*	1081	*56%*	155	*8%*	72	*4%*	116	*6%*	1934
Total	3787	*48%*	2578	*33%*	817	*10%*	274	*4%*	358	*5%*	7814	3447	*51%*	2144	*32%*	686	*10%*	238	*3%*	287	*4%*	6802
Age																						
15-19	237	*64%*	67	*18%*	34	*9%*	20	*5%*	15	*4%*	373	170	*64%*	51	*19%*	29	*11%*	7	*3%*	8	*3%*	265
20-24	225	*56%*	82	*21%*	48	*12%*	26	*7%*	19	*5%*	400	181	*60%*	58	*19%*	32	*11%*	19	*6%*	11	*4%*	301
25-29	266	*65%*	83	*20%*	28	*7%*	11	*3%*	19	*5%*	407	337	*73%*	68	*15%*	24	*5%*	17	*4%*	16	*3%*	462
30-34	469	*69%*	82	*12%*	62	*9%*	23	*3%*	41	*6%*	677	429	*73%*	75	*13%*	37	*6%*	14	*2%*	29	*5%*	584
35-39	414	*63%*	137	*21%*	56	*8%*	17	*3%*	35	*5%*	659	361	*67%*	91	*17%*	43	*8%*	16	*3%*	26	*5%*	537
40-44	422	*59%*	156	*22%*	77	*11%*	25	*4%*	30	*4%*	710	341	*64%*	91	*17%*	61	*11%*	20	*4%*	24	*4%*	537
45-49	410	*58%*	167	*23%*	71	*10%*	34	*5%*	30	*4%*	712	340	*59%*	138	*24%*	51	*9%*	24	*4%*	27	*5%*	580
50-54	383	*48%*	253	*32%*	96	*12%*	28	*4%*	34	*4%*	794	303	*50%*	185	*30%*	65	*11%*	31	*5%*	27	*4%*	611
55-59	290	*42%*	271	*39%*	85	*12%*	23	*3%*	29	*4%*	698	263	*42%*	244	*39%*	70	*11%*	24	*4%*	21	*3%*	622
60-64	231	*33%*	310	*45%*	81	*12%*	30	*4%*	40	*6%*	692	238	*37%*	266	*42%*	87	*14%*	20	*3%*	28	*4%*	639
65-69	175	*29%*	312	*51%*	86	*14%*	14	*2%*	24	*4%*	611	164	*31%*	241	*46%*	67	*13%*	19	*4%*	30	*6%*	521

70-74	137	*28%*	279	*57%*	48	*10%*	12	*2%*	17	*3%*	493	157	*33%*	241	*50%*	51	*11%*	14	*3%*	17	*4%*	480
75-79	79	*23%*	219	*63%*	31	*9%*	6	*2%*	12	*3%*	347	91	*26%*	211	*59%*	28	*8%*	11	*3%*	14	*4%*	355
80+	49	*20%*	160	*66%*	14	*6%*	5	*2%*	13	*5%*	241	72	*23%*	184	*60%*	41	*13%*	2	*1%*	9	*3%*	308
Total	3787	*48%*	2578	*33%*	817	*10%*	274	*4%*	358	*5%*	7814	3447	*51%*	2144	*32%*	686	*10%*	238	*3%*	287	*4%*	6802

Supplemental Table 1: Crude and age-standardized rates of confirmed leukemia malignancies reported to the NCR-SA per 100,000 by population group and gender, ages 15+

		Black			White			Mixed ancestry			Asian			Unknown		
Gender	**Hematologic malignancy**	**N**	**Crude**	**ASR***	**N**	**Crude**	**ASR***	**N**	**Crude**	**ASR***	**N**	**Crude**	**ASR***	**N**	**Crude**	**ASR**
Females	Leukemia	758	0.85	0.97	390	2.78	2.39	123	1.2	1.4	59	1.84	1.84			
	Acute lymphocytic leukemia	89	0.10	0.10	25	0.18	0.17	13	0.12	0.13	7	0.22	0.21	7		
	Chronic lymphocytic leukemia	112	0.13	0.17	49	0.35	0.24	12	0.11	0.15	6	0.19	0.21	8		
	Other lymphocytic leukemia	20	0.02	0.02	18	0.13	0.11	4	0.04	0.05	2	0.06	0.06	0		
	Acute myeloid leukemia	213	0.24	0.27	100	0.71	0.64	45	0.43	0.49	22	0.69	0.65	15		
	Acute monocytic leukemia	12	0.01	0.01	14	0.10	0.09	2	0.02	0.02	0	0.00	0.00	4		
	Chronic myeloid leukemia	173	0.19	0.22	57	0.41	0.34	12	0.11	0.13	7	0.22	0.21	4		
	Other myeloid/monocytic	16	0.02	0.02	16	0.11	0.11	8	0.08	0.09	0	0.00	0.00	3		
	Other acute leukemia	37	0.04	0.04	25	0.18	0.15	8	0.08	0.08	2	0.06	0.06	1		
	Aleukemia, subleukemia, and NOS	86	0.10	0.11	86	0.61	0.54	19	0.18	0.21	13	0.41	0.45	22		
Males	Leukemia	864	1.06	1.32	568	4.32	3.86	162	1.70	2.26	71	2.31	2.40			
	Acute lymphocytic leukemia	130	0.16	0.14	45	0.34	0.37	14	0.15	0.15	12	0.39	0.40	6		
	Chronic lymphocytic leukemia	192	0.24	0.40	107	0.81	0.66	26	0.27	0.43	9	0.29	0.35	12		
	Other lymphocytic leukemia	18	0.02	0.04	33	0.25	0.21	13	0.14	0.23	4	0.13	0.13	1		
	Acute myeloid leukemia	160	0.20	0.21	122	0.93	0.86	46	0.48	0.64	20	0.65	0.63	10		
	Acute monocytic leukemia	10	0.01	0.02	17	0.13	0.12	5	0.05	0.06	2	0.07	0.06	0		
	Chronic myeloid leukemia	192	0.24	0.28	63	0.48	0.42	22	0.23	0.27	13	0.42	0.43	15		
	Other myeloid/monocytic	19	0.02	0.03	16	0.12	0.11	8	0.08	0.12	2	0.07	0.07	3		
	Other acute leukemia	46	0.06	0.07	26	0.20	0.17	3	0.03	0.02	2	0.07	0.06	4		
	Aleukemia, subleukemia, and NOS	97	0.12	0.14	139	1.06	0.94	25	0.26	0.33	7	0.23	0.27	21		

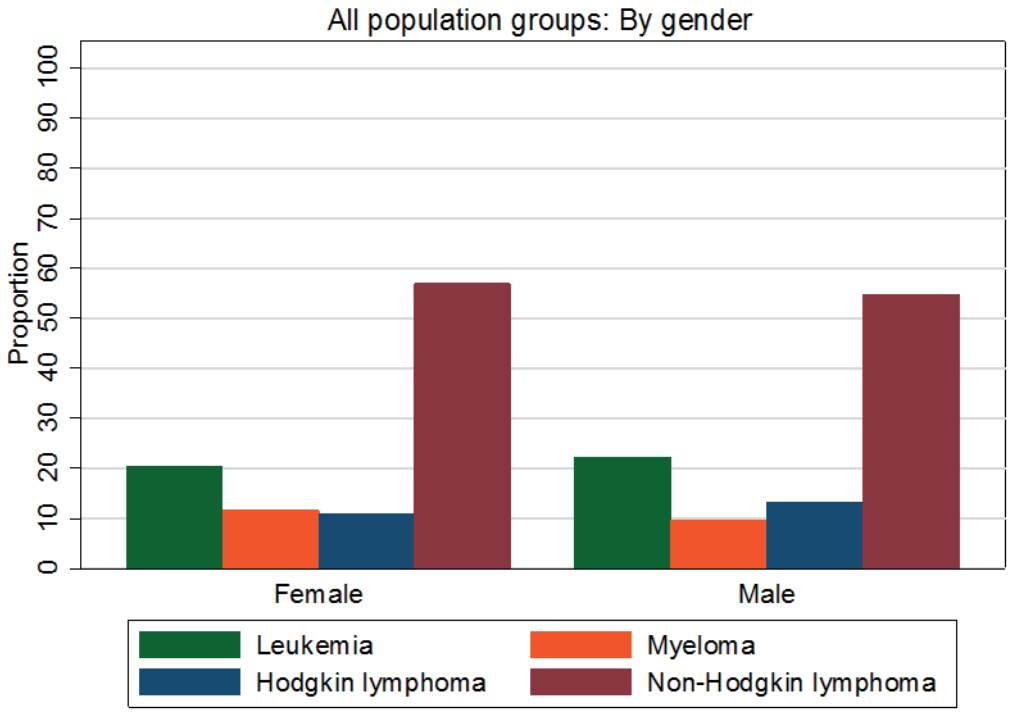
(continued)

		All			All excluding unknown		
Gender	**Hematologic malignancy**	**N**	**Crude**	**ASR***	**N**	**Crude**	**ASR**
Females	Leukemia	1394	1.19	1.32			
	Acute lymphocytic leukemia	141	0.12	0.12	134	0.11	0.11
	Chronic lymphocytic leukemia	187	0.16	0.20	179	0.15	0.19
	Other lymphocytic leukemia	44	0.04	0.04	44	0.04	0.04
	Acute myeloid leukemia	395	0.34	0.37	380	0.32	0.36
	Acute monocytic leukemia	32	0.03	0.03	28	0.02	0.03
	Chronic myeloid leukemia	253	0.22	0.24	249	0.21	0.23
	Other myeloid/monocytic	43	0.04	0.04	40	0.03	0.04
	Other acute leukemia	73	0.06	0.07	72	0.06	0.06
	Aleukemia, subleukemia, and NOS	226	0.19	0.22	204	0.17	0.20
					334	0.31	0.46
Males	Leukemia	1737	1.62	2.01	68	0.06	0.09
	Acute lymphocytic leukemia	207	0.19	0.18	348	0.32	0.37
	Chronic lymphocytic leukemia	346	0.32	0.48	34	0.03	0.04
	Other lymphocytic leukemia	69	0.06	0.09	290	0.27	0.32
	Acute myeloid leukemia	358	0.33	0.38	45	0.04	0.06
	Acute monocytic leukemia	34	0.03	0.04	77	0.07	0.08
	Chronic myeloid leukemia	305	0.28	0.34	268	0.25	0.32
	Other myeloid/monocytic	48	0.04	0.06	722	0.67	0.95
	Other acute leukemia	81	0.08	0.09	905	0.84	0.86
	Aleukemia, subleukemia, and NOS	289	0.27	0.34	91	0.08	0.09

ASR*: Age-standardized rate

Figure 1: Distribution of confirmed cases ages 15+ reported to NCR by type of hematologic malignancy, by gender (a) and by gender and racial group (b)

1a



1b

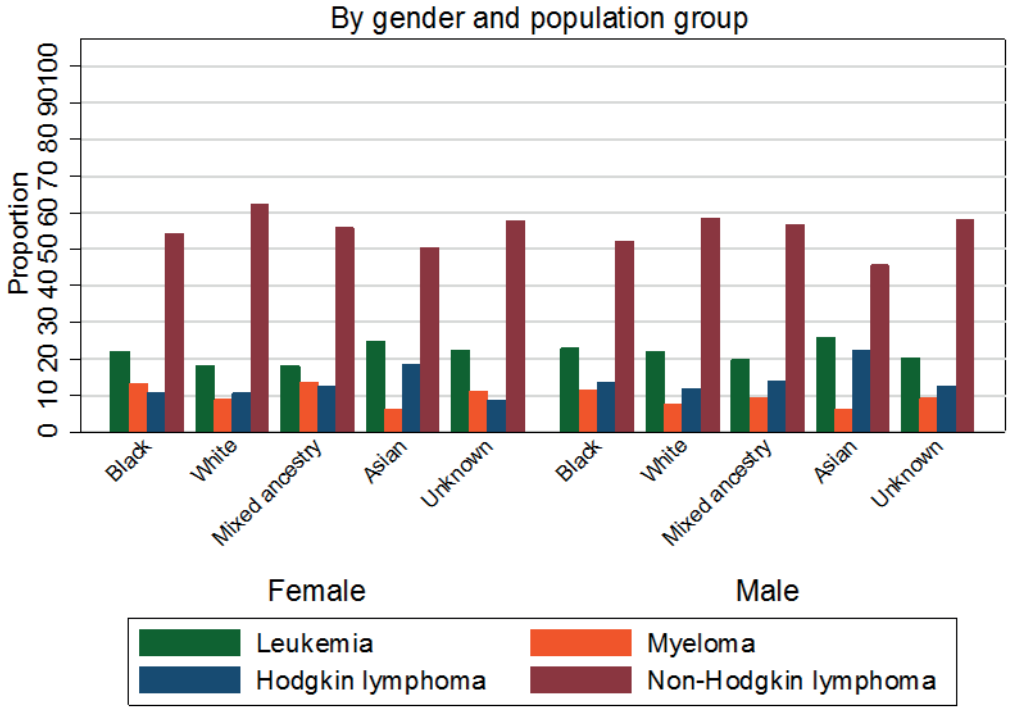
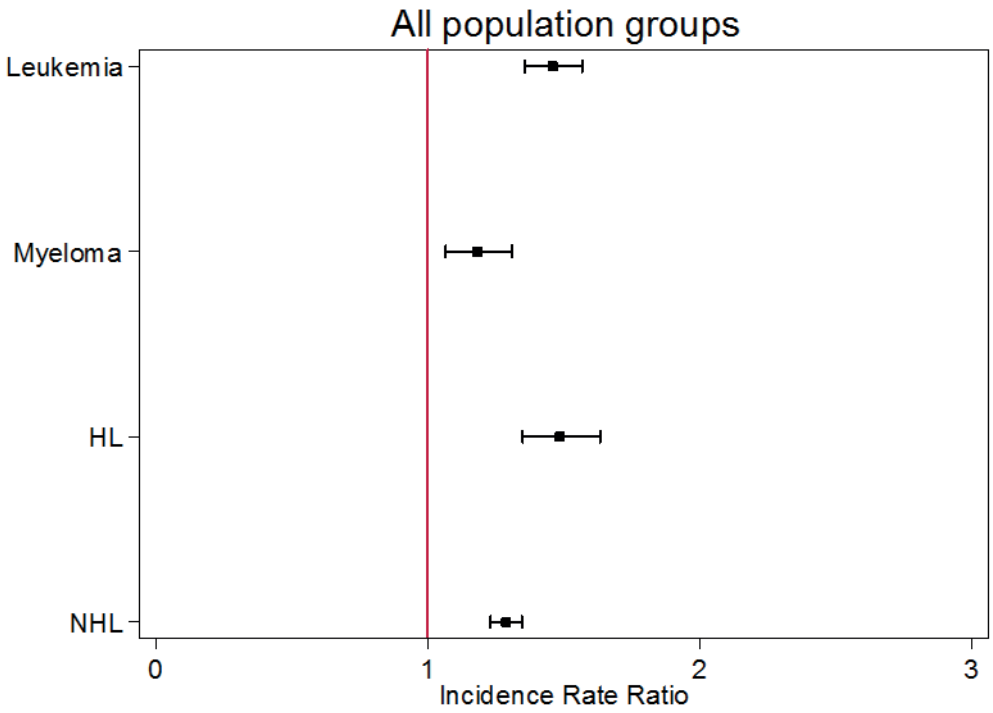


Figure 2: Male to female incidence rate ratios (IRR) of histologically confirmed cases reported to the NCR-SA, overall (a) and by racial group (b)

2a



2b

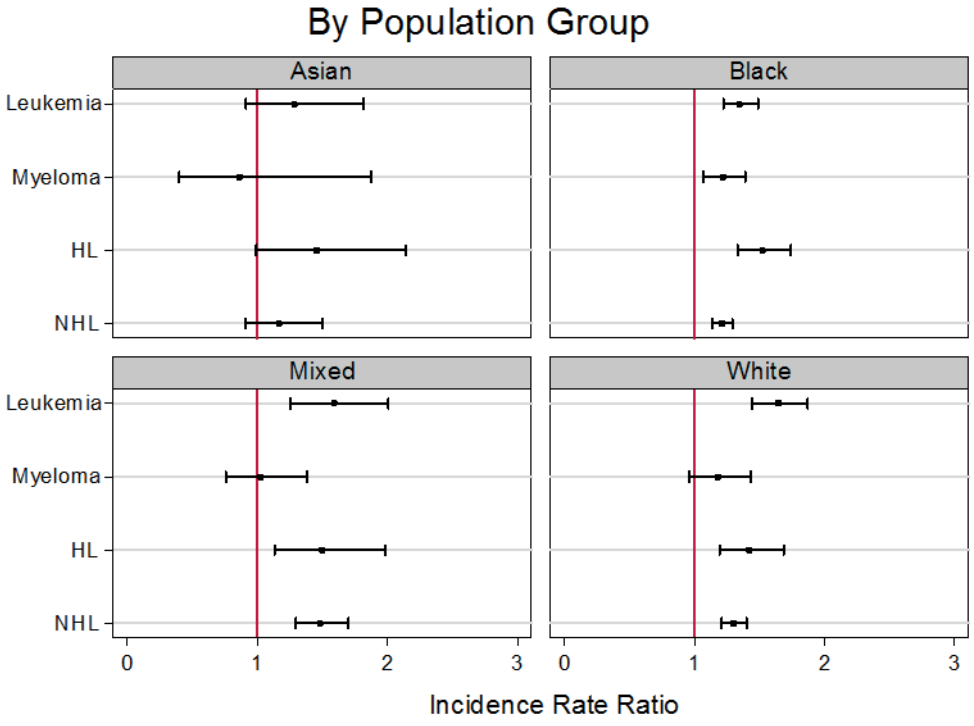
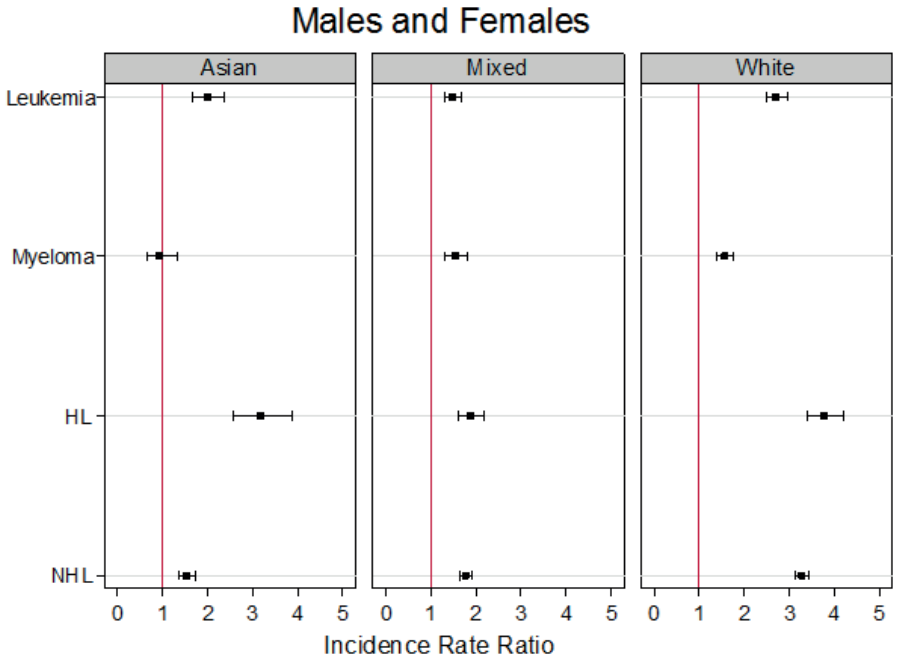
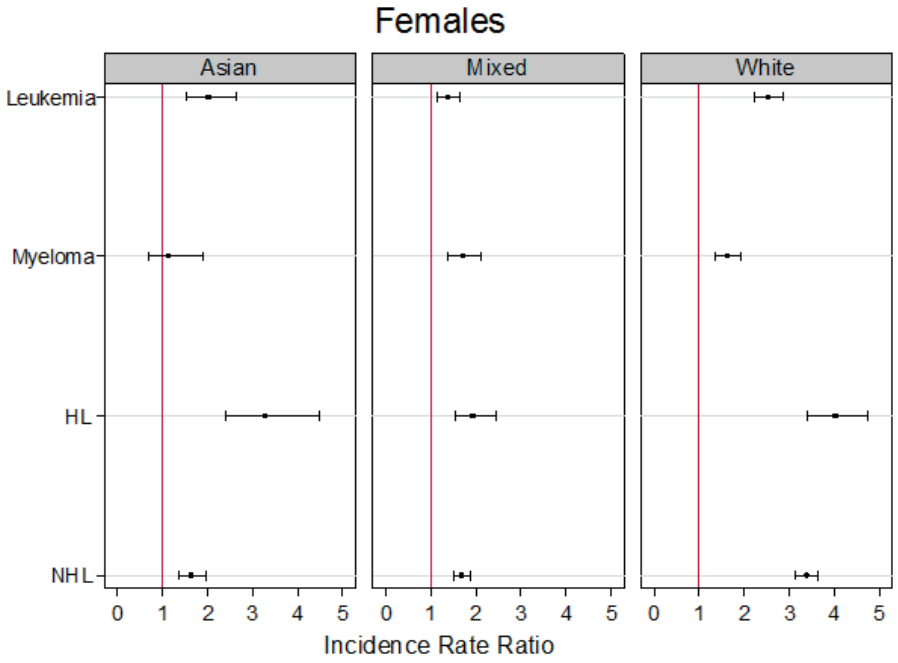


Figure 3: Incidence rate ratios compared with Black population of confirmed hematologic malignancy cases reported to NCR-SA, overall (3a) and by gender (3b females, 3c males)

3a



3b



(continued)

3c

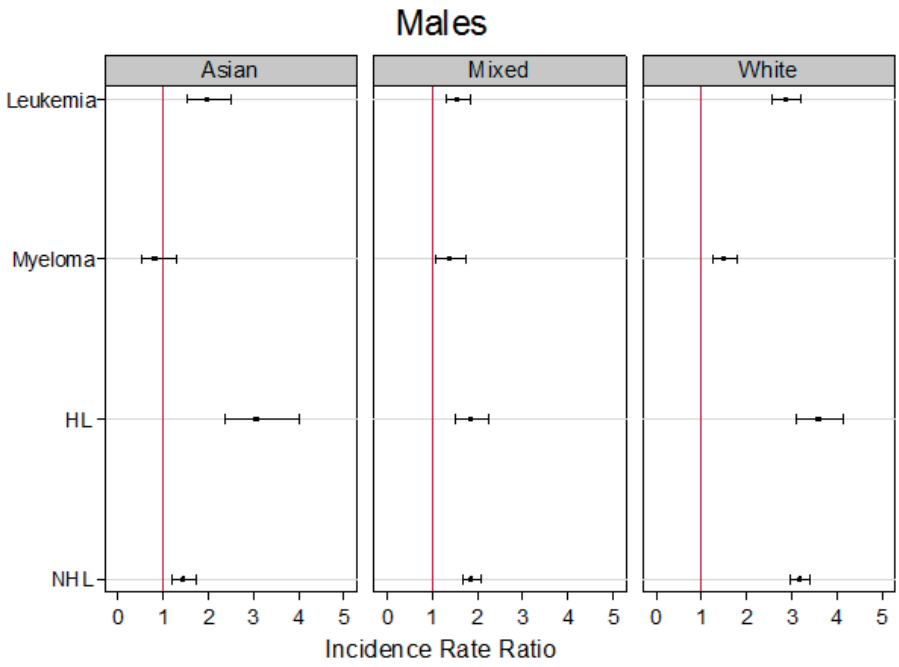
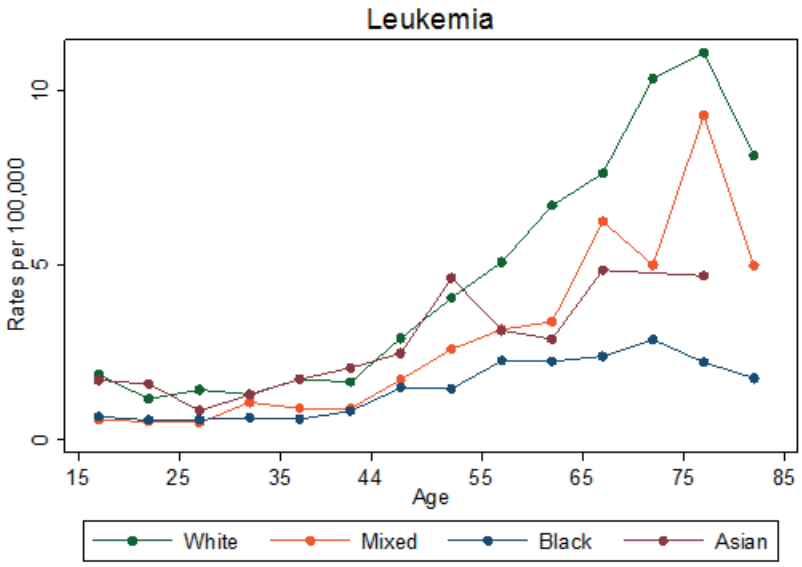
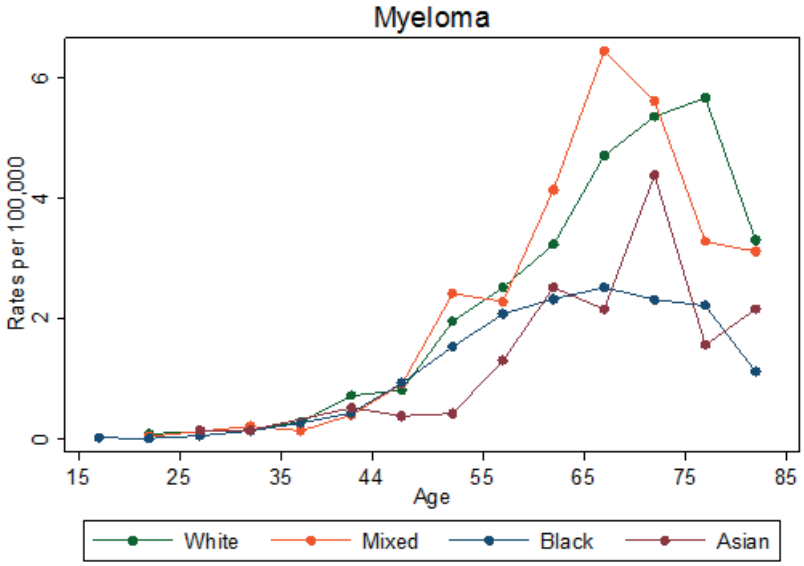

Males
Asian
Mixed
White
Leukemia
Myeloma
HL
NHL
0 1 2 3 4 5
Incidence Rate Ratio

Figure 4: Age-specific rates (per 100,000) of confirmed hematologic malignancies reported to the SA-NCR by population group, ages 15+, males and females combined

4a



4b



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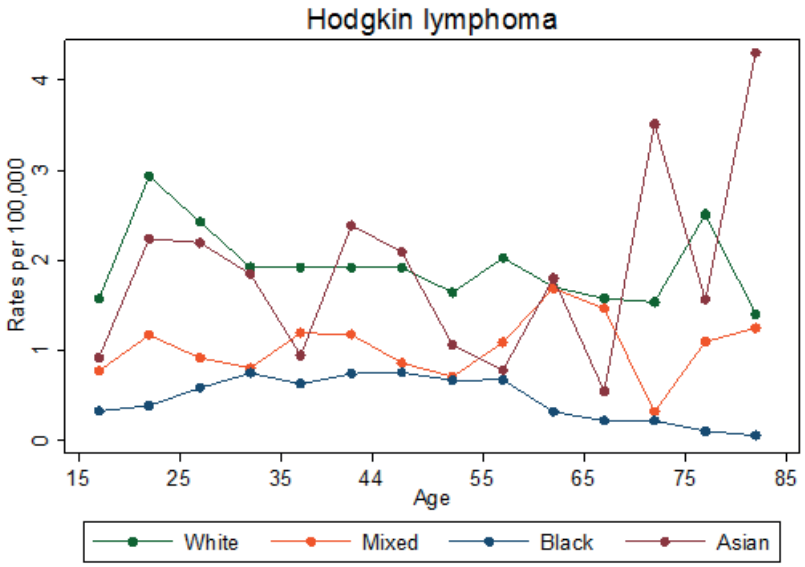
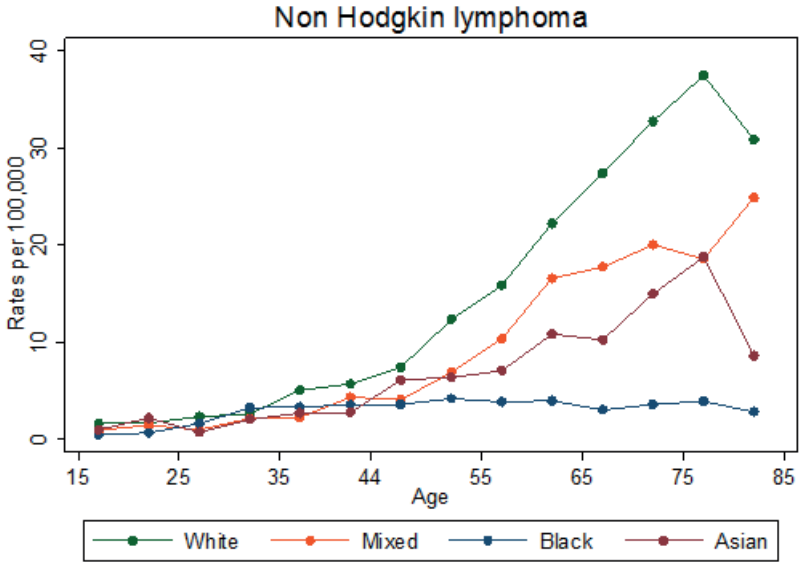
4c


Hodgkin lymphoma
Rates per 100,000
0
1
2
3
4
15
25
35
44
55
65
75
85
Age
White
Mixed
Black
Asian

4d


Non Hodgkin lymphoma
Rates per 100,000
0
10
20
30
40
15
25
35
44
55
65
75
85
Age
White
Mixed
Black
Asian

Article III

Survival from childhood acute lymphoblastic leukaemia in West Germany: Does socio-demographic background matter?

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Contribution statement: Jointly, JS, ER, TR and FE developed the study concept and design. PK, JS and FE contributed to the data collection. FE conducted the statistical data analyses. FE, JS, TL, HZ, ER and PK participated in the interpretation of the results. FE with support from JS prepared the first draft of the manuscript. FE, JS, HZ, TL and ER revised it critically for intellectual content. All authors read and approved the final version of the manuscript.

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Survival from childhood acute lymphoblastic leukaemia in West Germany: Does socio-demographic background matter?

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KEYWORDS
Paediatric acute lymphoblastic leukaemia
Survival
Socio-economic status
Demographic factors

Abstract ***Background:*** Sex, age, immunophenotype and white blood cell count at diagnosis are well accepted predictors of survival from acute lymphoblastic leukaemia (ALL) in children. Less is known about the relationship between socio-economic determinants and survival from paediatric ALL, studied here for the first time in German children.
Methods: ALL cases were diagnosed between 1992 and 1994 and their parents interviewed during a previous nationwide case-control study. Children were followed-up for 10 years after diagnosis by the German Childhood Cancer Registry. Cox proportional hazards models estimating hazard ratios (HRs) were calculated to assess the impact of selected socio-demographic characteristics on overall and event-free survival.
Results: Overall survival was 82.5%, with a higher proportion of girls than boys surviving (85% versus 81%). We found a non-linear relationship between age at diagnosis and survival, with poorer survival in infants and children aged >5 years. There was no association between socio-economic factors and survival or risk of relapse. For five levels of increasing family income, all HRs were close to one. No relationship was seen with parental educational level.
Conclusion: Socio-economic determinants did not affect ALL survival in West German children, in contrast to studies from some other countries. Dissimilarities in social welfare

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systems, including access to health care, lifestyle and differences in treatment may contribute to these differences in findings. Our observation of no social inequalities in paediatric ALL survival is reassuring, but needs continued monitoring to assess the potential impact of evolvement of treatment options and changes in paediatric health service.

1. Introduction

With an annual incidence of 43 per million, acute lymphoblastic leukaemia (ALL) is the most common single malignancy in children (0–14 years) in Germany, accounting for almost a third of all paediatric cancers [1]. Over the last 30 years, advances in treatment have led to considerable improvements in outcome [2–5], with the 5-year survival now exceeding 80% in Germany and other developed countries [1,2,4–7]. The improvement in survival is – besides advances in diagnostic procedures and treatment protocols [8,9] – to a certain extent achieved by identifying determinants predicting poorer survival and high risk groups [9,10]. Sex and age as well as white blood cell count at diagnosis, diagnostic group and response to initial therapy are important predictors for survival [10–13].

As diagnostic procedures and treatment protocols for ALL are generally standardised within developed countries [14,15], the survival rate should be fairly equal across socio-demographic groups in countries where children have equal and free access to health care services. Nonetheless, differences by socio-economic factors have not only been reported for developing regions [16,17], but also for some developed countries [2,14,18–20].

Our aim was to investigate ALL survival in Germany; hence in a country with presumably equal and free access to high quality care for all children and a dense network of specialised paediatric clinics.

2. Materials and methods

2.1. Study population

The study population consists of cases from a former German case-control study, covering all of West Germany [21]. Cases were identified in the nationwide population-based German Childhood Cancer Registry (GCCR). ALL cases were eligible, if diagnosed between October 1992 and September 1994 before the age of 15 years and if the child was living in former West Germany. In total, 788 children were identified. In total, 82% ($N = 647$) participated in the original case-control study. Reasons for non-participation were parents' refusal to participate in the case-control study (74%), physician's preference not to invite the parents to participate (15%), no contact with parents could be made (5%) and late detected violation of eligibility criteria (6%; mainly insufficient language skills). Information on potential risk factors was collected by self-administered questionnaire and a subsequent telephone interview with both parents.

2.2. SES and demographic characteristics

While sex and age are available for all eligible cases, information on socio-economic status (SES) of the family was only available for participants of the former case-control study. During the telephone interview conducted within 2 years after diagnosis, information on parental education, parental occupational training and average monthly family disposable income was collected. Information on monthly family income was compiled in five categories. Levels based on the (internationally unique) German school and educational system can be interpreted hierarchically with '*high degree*' as highest achievable level. The education levels are broadly related to years of school education; a '*low degree*' is associated with at least 9 years mandatory education, an '*intermediate degree*' with at least 10 years and *a* '*high degree*' implies 12–13 years mandatory education, with only the latter allowing later admittance to University or technical college.

2.3. Follow-up

Active vital status follow-up is conducted routinely by the GCCR using information from clinical studies, treating hospitals, families and communities. A set of minimal information for each patient including date of first recurrence or relapse, date and type of secondary neoplasm, vital status, date of death and date of last contact is regularly updated. In the first years after diagnosis (as long as the patient is in contact with the hospital for treatment/follow-up care) the GCCR receives follow-up information from the respective clinical trial or hospital. Almost all ALL patients are entered into clinical trials. At the end of the regular clinical follow-up the GCCR takes over surveillance and contacts the patients or parents directly, if the last follow-up information dates back 5 years or longer [22,23]. Due to this procedure follow-up for 10 years after diagnosis was available for our survival analysis; we censored at 10 years as very few disease-related events occur afterwards.

2.4. Statistical analyses

We defined two primary outcomes for these analyses: overall survival, with death from any cause as the endpoint, and event-free survival, with the first (if any) relapse (defined as >5% lymphoblasts in bone marrow), second malignant neoplasm or death as events. Children were observed for a calendar period of 10 years from the date of diagnosis until the date of event, last date known to be alive or date of 10 years of follow-up, whichever came first.

Initially, for graphical presentation we calculated (unadjusted) survival probabilities stratified by age (grouped into <1, 1–5, 6–9 and 10–14 years), sex, parental school education and monthly family disposable income, using Kaplan–Meier curves. Statistical significance ($P \leqslant 0.05$) of differences in survival probabilities was assessed by log-rank tests [24].

Cox proportional hazards models were used to assess the impact of selected characteristics on overall (Models I and III) and event-free survival (Models II and IV) [25,26]. Results were expressed as adjusted hazard ratios (HRs) along with corresponding 95% confidence intervals (CI). Models including all cases (Models I and II) analyse the association with sex and age at diagnosis, with participation status as a covariate to account for suspected different survival probabilities between study participants and non-participants. Models III and IV were fitted with selected SES indicators but restricted to study participants since SES was only available among respondents to the questionnaire. Two SES proxies were included simultaneously in the main analyses, namely maternal education and monthly family net income. The variables were only weakly correlated (Spearman correlation = 0.27) and reflected both financial resources and educational achievement (Supplement Table S1). Degree of urbanisation was considered as potential confounder and thus also included in these models.

When testing the proportional hazards assumption for the Cox models using the Schoenfeld residuals test [26] it failed for age at diagnosis with the category '<1 year' in one of the models. To test the impact on the hazard ratios, we excluded all cases of this age group ($N = 30$) from the study population and performed separate analyses. However, as the hazard ratios changed only marginally, results in this paper relate to all subjects combined.

Sensitivity analyses were performed: (a) including parental occupational training as SES indicator in various combinations with other SES factors in the Cox models; (b) restricting analysis to B-lineage ALL cases; (c) modelling Cox models assuming that every non-participant as well as item non-responder to the questions on SES indicators had lowest maternal education level (no degree) as well as lowest monthly family income (<2000 DM) and that the distribution of residential area (urban, mixed and rural) in the non-participants is equal to the distribution in the participants.

All statistical analyses were performed using Stata 11 [27].

3. Results

Of the 788 cases, 58.4% were boys and more than 60% were 1–5 years of age at diagnosis (Table 1). Over the follow-up period of 10 years 137 children died, with a higher proportion (28%) in non-participants than participants (15%). In terms of monthly family income and parental education, most of the interviewed parents ranked in the second lowest categories. Missing values were 6.5% for income and 5% for maternal and 10% for paternal school education (Table 1).

The 10-year overall survival of all cases was 82.5%. Twenty-one deaths (18% of all deaths) occurred later than 5 years after diagnosis. Within the first 5 years, only 11 (1.4%) of the 788 ALL-cases were lost to follow-up (Supplement Table S2).

Survival was generally better in girls (85% versus 81%), with differences emerging about 1 year after diagnosis; the sex difference however was statistically significant only in the event-free analyses (Figs. 1a and b). Survival curves by age group and sex show the lowest survival among infant boys, most pronounced in the first 2 years after diagnosis, while among girls survival was also lowest in infants but better compared to boys (Figs. 2a and b).

The multivariate analyses confirm diverse survival probabilities by sex and age (Table 2). We found a non-linear relationship between age at diagnosis and survival ($p < 0.001$); infants had almost a sixfold increased risk of dying and fourfold increased risk of any event, compared to 1–5 year old children. Older children also had an increased HR (both 6–9 year-olds and 10–14 year-olds) compared to the reference group, the magnitude varying around 2.5-fold (overall survival). The greater sex disparity seen in event-free survival was caused by a higher proportion of relapse in boys than in girls (23% versus 15%; *data not shown*). Non-participants had an almost twofold increased HR in overall survival compared to participants (Table 2).

No relationship between socio-economic factors and survival was observed, in both in the univariate as well as the multivariate analyses (Figs. 3a–c and Table 3). Both maternal education and family income did not show any trend or significant impact on survival from ALL (Table 3). For income, all HRs were close to 1. For maternal education, the HR was somewhat elevated, although not significantly, in the small group of mothers having no school degree in the event-free analysis (HR 1.80; CI 0.47; 2.56). Associations seen with sex and age were confirmed in this subset of participants compared to the full dataset.

Table 1
Characteristics of the acute lymphoblastic leukaemia (ALL) cases by diagnosis, deaths and observed person-years.

	ALL-cases	Deaths	% Deaths	Person-years
Total	788	137	17.4	6732
Participants	647 (82.1%)	98 (71.5%)	15.2	5663
Non-participants	141 (17.9%)	39 (28.5%)	27.7	1069
Sex				
Boys	460 (58.4%)	88 (64.2%)	19.1	3854
Girls	328 (41.6%)	49 (35.8%)	14.9	2878
Age at diagnosis (years)				
<1	30 (3.8%)	13 (9.5%)	43.3	175
1–5	491 (62.3%)	54 (39.4%)	11.0	4477
6–9	155 (19.7%)	39 (28.5%)	25.2	1241
10–14	112 (14.2%)	31 (22.6%)	27.7	840
The following characteristics are just available for those who participated in the case-control study				
ALL subtype				
B-cell[a]	571 (88.3%)	75 (76.5%)	13.1	5108
T-cell	58 (9.0%)	19 (19.4%)	32.8	423
Unknown subtype	18 (2.8%)	4 (4.1%)	22.2	132
Family income[b]				
<2000 DM	51 (7.9%)	10 (10.2%)	19.6	429
2000–4000 DM	341 (52.7%)	52 (53.1%)	15.3	3000
4000–6000 DM	162 (25.0%)	19 (19.4%)	11.7	1429
6000–8000 DM	29 (4.5%)	6 (6.1%)	20.7	238
>8000 DM	22 (3.4%)	4 (4.1%)	18.2	193
Missing	42 (6.5%)	7 (7.1%)	16.7	364
Parental education[c]				
Mother				
No degree	22 (3.4%)	4 (4.1%)	18.2	190
Low degree	248 (38.3%)	40 (40.8%)	16.1	2144
Intermediate degree	203 (31.4%)	23 (23.5%)	11.3	1857
High degree	134 (20.7%)	23 (23.5%)	17.2	1137
Others	6 (0.9%)	0 (0%)	0	60
Missing	34 (5.3%)	8 (8.2%)	23.5	276
Father				
No degree	18 (2.8%)	2 (2.0%)	11.1	170
Low degree	277 (42.8%)	36 (36.7%)	13.0	2469
Intermediate degree	118 (18.2%)	19 (19.4%)	16.1	1022
High degree	162 (25.0%)	26 (26.5%)	16.1	1394
Others	6 (0.9%)	1 (1.0%)	16.7	55
Missing	66 (10.2%)	14 (14.3%)	21.2	552
Residential area				
Urban	276 (42.7%)	44 (44.9%)	15.9	2377
Mixed	201 (31.1%)	34 (34.7%)	16.9	1734
Rural	170 (26.3%)	20 (20.4%)	11.8	1552

[a] Common ALL, mature-B ALL, pre-B ALL and pro-B ALL combined.
[b] Average monthly family disposable income stated in *Deutsche Mark* – Currency in Germany before implementation of the Euro in 2002 with an exchange value of 1 DM = 0.51 €.
[c] The education categories should be interpreted hierarchically with '*high degree*' as highest achievable degree. The education levels are related to years of school education; a '*low degree*' is associated with at least 9 years mandatory education, an '*intermediate degree*' with at least 10 years and *a* '*high degree*' comes along with 12–13 years mandatory education (only the latter allows admittance to university or technical college). The original categories used in the German questionnaire are '*kein Schulabschluss*' (*no degree*), '*Hauptschulabschluss*' (*low degree*), '*Mittlere Reife*' (*intermediate degree*) and '*Fachhochschulreife/Abitur*' (*high degree*).

Sensitivity analyses using other SES indicators as well as restricting the analyses only to B-lineage leukaemia did not alter the overall results (Supplements Tables S3 and S4). Calculating models assuming that every non-participant had lowest maternal education level and lowest family income did not show any trend between SES and ALL survival either (*data not shown*).

4. Discussion

4.1. Main findings

We have studied the effect of sex, age and socio-economics on long-term survival in paediatric ALL cases diagnosed in the early 1990s in Germany. No trend

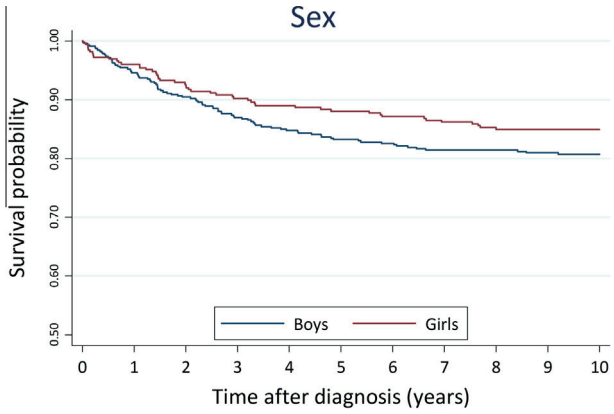

Fig. 1a. Kaplan–Meier estimates of overall survival for all acute lymphoblastic leukaemia (ALL)-cases by sex. Log-rank test of heterogeneity: $\chi^2 = 2.34$, $p = 0.13$.

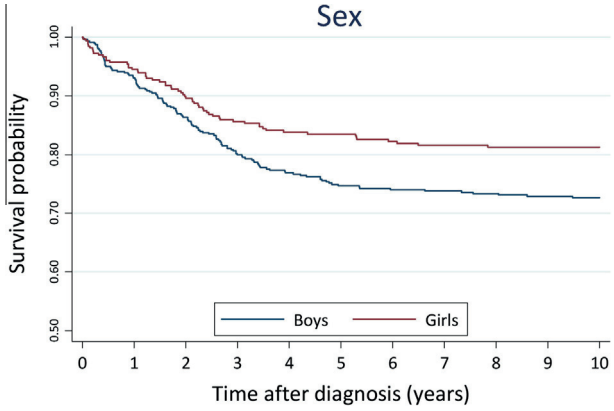

Fig. 1b. Kaplan–Meier estimates of event-free survival for all ALL-cases by sex. Log-rank test of heterogeneity: $\chi^2 = 7.35$, $p = 0.0067$.

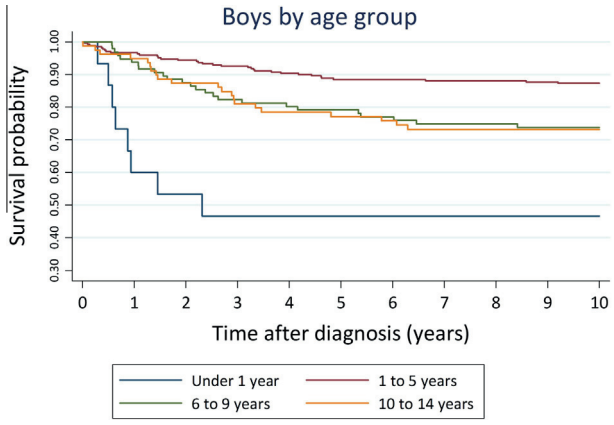

Fig. 2a. Kaplan–Meier estimates of overall survival for boys diagnosed with acute lymphoblastic leukaemia (ALL) by age group. Log-rank test of heterogeneity: $\chi^2 = 32.46$, $p = 0.00$.

or statistically significant associations between socio-economic factors and survival probability or risk of relapse were found. With respect to age and sex, our results are consistent with those described elsewhere [2,13,28]. Boys – known to have a higher ALL incidence

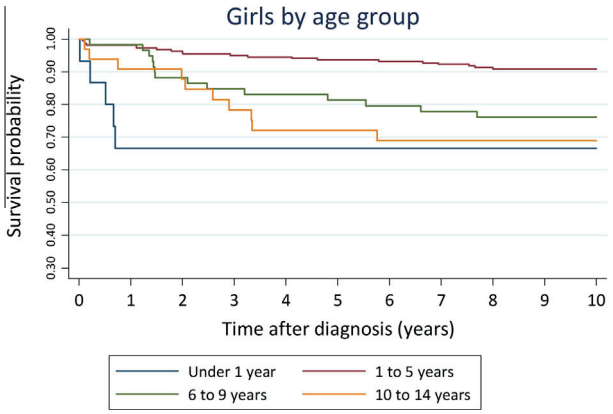

Fig. 2b. Kaplan–Meier estimates of overall survival for girls diagnosed with ALL by age group. Log-rank test of heterogeneity: $\chi^2 = 22.75$, $p = 0.00$.

than girls – showed also worse survival [1,29], noting that boys and girls with ALL were treated identically, both with respect to the intensity and to the length of treatment during the time period 1992–94 [30,31].

Our main finding that socio-economic factors were not related to ALL survival in German children appears plausible in light of the fact that irrespective of coverage by private or statutory health insurance (Germany has a universal multi-payer health care system with two main types of health insurance: private insurance and statutory health insurance (SHI) called sickness funds) and of social background, all German children and adolescents have free access to health care [32].

4.2. Treatment of ALL-cases

The German Health care system allows for a direct consultation of sick children and adolescents with a paediatrician without having to pass through a General Practitioner before. This access is not specific to social groups and may contribute to an explanation of our main finding. Importantly, more than 90% of all paediatric oncology patients are included in clinical trials of therapy optimisation studies in Germany [22]. Almost all paediatric ALL cases are treated according to the treatment schemes developed by the two collaborative study groups ALL-BFM (Berlin–Frankfurt–Münster) and COALL (cooperative study group for childhood acute lymphoblastic leukaemia). Cases included in our study were treated according to the protocol of the ALL-BFM 90 [30] or COALL 92 trial [33]: in these trials, 10-year overall survival as well as event-free survival was reported to be generally better in patients treated by the BFM-90 protocol compared to the COALL-92 protocol (overall survival: 85% versus 81%; event-free survival: 76% versus 73%), whereas the COALL-92 shows better survival considering only T-lineage patients [15,33]. However, we have no reason to assume that treatment by a certain protocol was related to families'

Table 2
Prognostic factors of overall and event-free survival for all cases of acute lymphoblastic leukaemia followed-up for 10 years from date of diagnosis.

	Overall survival (Model I)[a,b]		Event-free survival (Model II)[b,c]	
	Hazard ratio	[95% CI][d]	Hazard ratio	[95% CI][d]
Sex				
Boys	1.30	[0.91; 1.85]	1.50	[1.10; 2.05]
Girls	1.0	Reference	1.0	Reference
Age at diagnosis (year)				
<1	5.80	[3.16; 10.63]	4.12	[2.34; 7.26]
1–5	1.0	Reference	1.0	Reference
6–9	2.35	[1.56; 3.55]	1.79	[1.25; 2.56]
10–14	2.62	[1.67; 4.09]	2.17	[1.49; 3.17]
Participation				
Yes	1.0	Reference	1.0	Reference
No	1.95	[1.34; 2.83]	1.53	[1.08; 2.15]

[a] End-point of overall survival was defined as death from all causes or date of 10 years observation. 788 subjects (137 deaths) are included in the Cox regression model.
[b] Mutually adjusted for each other.
[c] Event of event-free survival was determined as relapse, second malignant neoplasm and death from all causes. 788 subjects (186 events) are included in the Cox regression model.
[d] Corresponding 95% confidence interval.

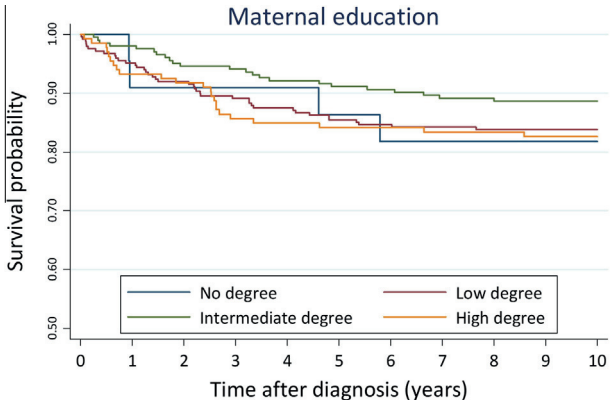

Fig. 3a. Kaplan–Meier estimates of overall survival for all acute lymphoblastic leukaemia (ALL)-cases by maternal school education. Log-rank test of heterogeneity: $\chi^2 = 3.33$, $p = 0.34$.

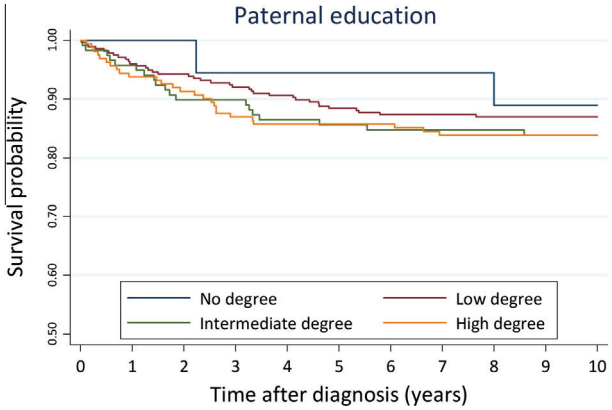

Fig. 3b. Kaplan–Meier estimates of overall survival for all ALL-cases by paternal school education. Log-rank test of heterogeneity: $\chi^2 = 1.37$, $p = 0.71$.

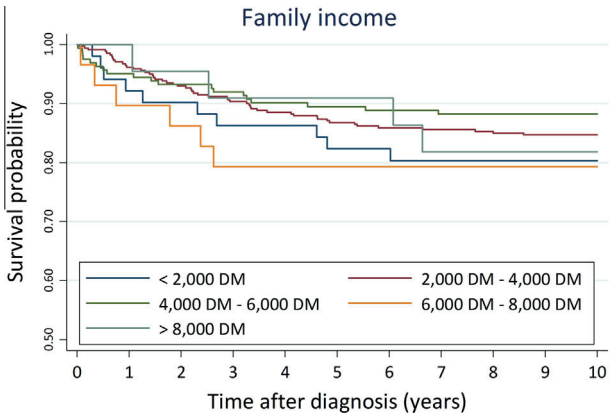

Fig. 3c. Kaplan–Meier estimates of overall survival for all ALL-cases by average monthly family net income. Log-rank test of heterogeneity: $\chi^2 = 3.11$, $p = 0.54$.

social circumstances and it is therefore very unlikely that treatment introduced any bias in our study.

4.3. International comparison

Our finding is consistent with another German study indicating that Turkish and non-Turkish children in Germany do not differ with regard to childhood leukaemia survival [34]. As Turkish migration background is frequently linked with a lower socio-economic status in Germany [35], this study also suggests no differences by socio-economic background.

Nonetheless, in contrast to our findings and besides for developing countries [16,17], a socio-economic impact on childhood leukaemia survival was reported for some economically developed European populations including The Netherlands [20], United Kingdom (UK)

Table 3
Prognostic factors of overall and event-free survival for children with acute lymphoblastic leukaemia followed-up for 10 years from date of diagnosis, in those with data on SES indicators.

	Overall survival (Model III)[a,b]		Event-free survival (Model IV)[b,c]	
	Hazard ratio	[95% CI][d]	Hazard ratio	[95% CI][d]
Sex				
Boys	1.52	[0.96; 2.40]	1.55	[1.06; 2.26]
Girls	1.0	Reference	1.0	Reference
Age at diagnosis (years)				
<1	7.66	[3.87; 15.18]	4.35	[2.28; 8.28]
1–5	1.0	Reference	1.0	Reference
6–9	2.35	[1.40; 3.95]	1.78	[1.15; 2.77]
10–14	2.24	[1.24; 4.05]	2.06	[1.28; 3.33]
Family income				
<2000 DM	1.21	[0.60; 2.44]	1.15	[0.64; 2.06]
2000–4000 DM	1.0	Reference	1.0	Reference
4000–6000 DM	0.80	[0.47; 1.38]	0.79	[0.51; 1.24]
6000–8000 DM	1.27	[0.52; 3.06]	1.24	[0.59; 2.65]
>8000 DM	1.11	[0.37; 3.29]	0.84	[0.32; 2.19]
Maternal education				
No degree	1.07	[0.38; 3.04]	1.80	[0.47; 2.56]
Low degree	1.0	Reference	1.0	Reference
Intermediate degree	0.69	[0.41; 1.17]	0.65	[0.41; 1.01]
High degree	0.92	[0.52; 1.62]	1.05	[0.66; 1.67]
Residential area				
Urban	1.0	Reference	1.0	Reference
Mixed	1.16	[0.71; 1.91]	0.97	[0.64; 1.48]
Rural	0.88	[0.50; 1.55]	0.92	[0.59; 1.43]

[a] End-point of overall survival was defined as death from all causes or date of 10 years observation. 595 subjects (90 deaths) are included in the Cox regression model.
[b] Mutually adjusted for each other.
[c] Event of event-free survival was determined as relapse, second malignant neoplasm and death from all causes. 595 subjects (130 events) are included in the Cox regression model.
[d] Corresponding 95% confidence interval.

[2,36], Greece [18] and Norway [14]. Hence, social disadvantage might influence survival from ALL in other ways than just being an indicator for social inequality in quality of medical treatment and follow-up care. Reasons may include differences in 'host factors', i.e. a poorer health status, health behaviour at the time of diagnosis among socially deprived, as well as socio-economic differences in treatment refusal, abandonment and compliance with the prescribed treatment plan. The most likely reason may be socio-economic variations in the abilities of families to comply with the recommendations for follow-up assessment and treatment. Findings from the UK support this idea, as divergence by SES became more remarkable when treatment management moved from hospital to home [2]. Potentially, also the impact of maternal education on survival found in Norway [14] might be related to follow-up care. Thus, diverse findings for a social impact on leukaemia survival even within European countries may rather result from varying procedure in terms of out-patient care (e.g. frequency of contact to clinical care team) than differences in treatment protocols.

Findings from Australia show that survival was generally poorer for children living in more isolated parts of the countries [37]. Living in more rural, and thus possibly poorer areas was also associated with less favourable prognosis in a recent multi-national study (including Greece, Bulgaria, Izmir, Antalya and Moscow) [38]. However, looking just at Greece, whereas an earlier study found indications for a trend of poorer survival with increasing remoteness, this was not confirmed in more recent years, which was suggested to be linked to improvements in motorway infrastructure [18].

All in all, dissimilarities in social welfare systems, including access to health care, distance to treatment facilities, lifestyle, as well as differences in socio-economic status definitions make international comparisons challenging.

4.4. Strengths and weaknesses

This is the first study in Germany on this topic, and one of few from Europe. Among the strengths are the nationwide coverage of cases of former West Germany and the long and complete follow-up period of 10 years. Multiple indicators of socio-economic status of the family were available on an individual level. Confirmation of known associations by sex and age underline the

validity of our findings as well as poorer survival of T-cell compared with B-cell types [13,39,40] (*data not shown*).

Our study has also limitations. With respect to socio-economic status, we had 18% missing data due to non-participation in the original case-control study, 6.5% of the participating families did not specify their monthly family income and 5.3% did not provide information on maternal education. We observed poorer survival in non-participants. As refusing participation in epidemiological studies is possibly associated with lower socio-economic status, our results might theoretically be biased. However, sensitivity analyses assuming the worst case scenario that every non-participant had lowest maternal education level and lowest family income also yielded no association between socio-economic factors and ALL survival. Information about socio-economic status was collected by an interviewer-administered questionnaire via phone. Therefore, reporting bias cannot entirely be excluded, especially for income that is not very openly discussed in German culture. Bias should be minor for education with easy-to-recall and straightforward categories, assuming that maternal education sufficiently reflects the socio-economic status of a family in Germany in the beginning of the 1990s.

Another limitation is that survival studies are by default historical by the time they are published. Survival probabilities observed in this study have improved in the meantime [1]. As a consequence of the demographic change in Germany and associated financial pressure, the German health care system went through a series of reforms since the cases of our study were treated. However, reimbursement for diagnosis and treatment of paediatric cancer is not known to have been changed by these reforms. Nevertheless, the relationship between SES and ALL survival might have changed since then.

5. Conclusions

In conclusion, socio-economic background did not influence ALL survival in Germany. This contrasts somewhat to some other national studies, but dissimilarities in social welfare systems, including access to health care, remoteness to medical facilities as well as differences in lifestyle may explain diverse findings. Our observation of no social inequalities in paediatric ALL survival in Germany is reassuring. Nevertheless, further research with high completeness as well as high validity of SES indicators is needed. This study may be particularly valuable in longitudinal national comparisons.

Conflict of interest statement

None declared.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2014.01.028.

References

[1] Kaatsch P, Spix J. German Childhood Cancer Registry – annual report 2011 (1980–2010). Mainz: Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI) at the University Medical Center of the Johannes Gutenberg University; 2012.

[2] Lightfoot T, Johnston W, Simpson J, Smith A, Ansell P, Crouch S, et al. Survival from childhood acute lymphoblastic leukaemia: the impact of social inequality in the United Kingdom. Eur J Cancer 2012;48(2):263–9.

[3] Magnani C, Pastore G, Coebergh JW, Viscomi S, Spix C, Steliarova-Foucher E. Trends in survival after childhood cancer in Europe, 1978–1997: report from the Automated Childhood Cancer Information System project (ACCIS). Eur J Cancer 2006;42(13):1981–2005.

[4] Basta NO, James PW, Gomez-Pozo B, Craft AW, McNally RJQ. Survival from childhood cancer in northern England, 1968–2005. Br J Cancer 2011;105(9):1402–8.

[5] Baade PD, Youlden DR, Valery PC, Hassall T, Ward L, Green AC, et al. Population-based survival estimates for childhood cancer in Australia during the period 1997–2006. Br J Cancer 2010;103(11):1663–70.

[6] Pritchard-Jones K, Kaatsch P, Steliarova-Foucher E, Stiller CA, Coebergh JWW. Cancer in children and adolescents in Europe: developments over 20 years and future challenges. Eur J Cancer 2006;42(13):2183–90.

[7] Smith MA, Seibel NL, Altekruse SF, Ries LAG, Melbert DL, O'Leary M, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. J Clin Oncol 2010;28(15):2625–34.

[8] O'Leary M, Krailo M, Anderson JR, Reaman GH. Progress in childhood cancer: 50 years of research collaboration, a report from the Children's Oncology Group. Semin Oncol 2008;35(5):484–93.

[9] Stanulla M, Schrappe M. Treatment of childhood acute lymphoblastic leukemia. Semin Hematol 2009;46(1):52–63.

[10] Inaba H, Greaves M, Mullighan CG. Acute lymphoblastic leukaemia. Lancet 2013;381(9881):1943–55.

[11] Vaitkevičienė G, Forestier E, Hellebostad M, Heyman M, Jonsson OG, Lähteenmäki PM, et al. High white blood cell count at diagnosis of childhood acute lymphoblastic leukaemia: biological background and prognostic impact. Results from the NOPHO ALL-92 and ALL-2000 studies. Eur J Haematol 2011;86(1):38–46.

[12] Pui CH, Carroll WL, Meshinchi S, Arceci RJ. Biology, risk stratification, and therapy of pediatric acute leukemias: an update. J Clin Oncol 2011;29(5):551–65.

[13] Donadieu J, Auclerc M, Baruchel A, Perel Y, Bordigoni P, Landman-Parker J, et al. Prognostic study of continuous variables (white blood cell count, peripheral blast cell count, haemoglobin level, platelet count and age) in childhood acute lymphoblastic leukaemia. Analysis of a population of 1545 children treated by the French Acute Lymphoblastic Leukaemia Group (FRALLE). Br J Cancer 2000;83(12):1617–22.
[14] Syse A, Lyngstad TH, Kravdal O. Is mortality after childhood cancer dependent on social or economic resources of parents? A population-based study. Int J Cancer 2012;130(8):1870–8.
[15] Möricke A, Zimmermann M, Reiter A, Henze G, Schrauder A, Gadner H, et al. Long-term results of five consecutive trials in childhood acute lymphoblastic leukemia performed by the ALL-BFM study group from 1981 to 2000. Leukemia 2010;24(2):265–84.
[16] Mostert S, Sitaresmi MN, Gundy CM, Janes V, Sutaryo, Veerman AJP. Comparing childhood leukaemia treatment before and after the introduction of a parental education programme in Indonesia. Arch Dis Child 2009;95(1):20–5.
[17] Viana M, Fernandes R, de Oliveira B, Murao M, de Andrade Paes C, Duarte A. Nutritional and socio-economic status in the prognosis of childhood acute lymphoblastic leukemia. Haematologica 2001;86(2):113–20.
[18] Sergentanis T, Dessypris N, Kanavidis P, Skalkidis I, Baka M, Polychronopoulou S, et al. Socioeconomic status, area remoteness, and survival from childhood leukemia. Eur J Cancer Prev 2012:1.
[19] Kent E, Sender L, Largent J, Anton-Culver H. Leukemia survival in children, adolescents, and young adults: influence of socioeconomic status and other demographic factors. Cancer Causes Control 2009;20(8):1409–20.
[20] Coebergh JW, van der Does-van den Berg A, Hop W, van Weerden F, Rammeloo J, van Steensel H, et al. Small influence of parental educational level on the survival of children with leukaemia in The Netherlands between 1973 and 1979. Eur J Cancer 1996;32A(2):286–9.
[21] Schüz J, Grigat J, Brinkmann K, Michaelis J. Residential magnetic fields as a risk factor for childhood acute leukaemia: results from a German population-based case-control study. Int J Cancer 2001;91(5):728–35.
[22] Grabow D, Spix C, Blettner M, Kaatsch P. Strategy for long-term surveillance at the German Childhood Cancer Registry – an update. Klin Padiatr 2011;223(03):159–64.
[23] Debling D, Spix C, Blettner M, Michaelis J, Kaatsch P. The cohort of long-term survivors at the German Childhood Cancer Registry. Klin Padiatr 2008;220(06):371–7.
[24] Clark TG, Bradburn MJ, Love SB, Altman DG. Survival analysis part I: basic concepts and first analyses. Br J Cancer 2003;89(2):232–8.
[25] Bradburn MJ, Clark TG, Love SB, Altman DG. Survival analysis part II: multivariate data analysis – an introduction to concepts and methods. Br J Cancer 2003;89(3):431–6.
[26] Bradburn MJ, Clark TG, Love SB, Altman DG. Survival analysis part III: multivariate data analysis – choosing a model and assessing its adequacy and fit. Br J Cancer 2003;89(4):605–11.
[27] StataCorp. Stata statistical software: release 11. College station ed. TX: StataCorp LP; 2009.
[28] Pui CH, Boyett J, Relling M, Harrison P, Rivera G, Behm F, et al. Sex differences in prognosis for children with acute lymphoblastic leukemia. J Clin Oncol 1999;17(3):818–24.
[29] Savage S, Schüz J. Environmental chemicals and childhood cancer. In: Nriagu J, editor. Encyclopedia of environmental health. Elsevier Science & Technology; 2011. p. 336–47.
[30] Schrappe M, Reiter A, Ludwig WD, Harbott J, Zimmermann M, Hiddemann W, et al. Improved outcome in childhood acute lymphoblastic leukemia despite reduced use of anthracyclines and cranial radiotherapy – results of trial ALL-BFM 90. German–Austrian–Swiss ALL-BFM Study Group. Blood 2000;95(11):3310–22.
[31] Harms DO, Gobel U, Spaar HJ, Graubner UB, Jorch N, Gutjahr P, et al. Thioguanine offers no advantage over mercaptopurine in maintenance treatment of childhood ALL: results of the randomized trial COALL-92. Blood 2003;102(8):2736–40.
[32] Busse R, Riesberg A. Health care systems in transition: Germany. Copenhagen: WHO Regional Office for Europe on behalf of the European Observatory on Health Systems and Policies; 2004.
[33] Escherich G, Horstmann MA, Zimmermann M, Janka-Schaub GE. Cooperative study group for childhood acute lymphoblastic leukaemia (COALL): long-term results of trials 82, 85, 89, 92 and 97. Leukemia 2010;24(2):298–308.
[34] Spix C, Spallek J, Kaatsch P, Razum O, Zeeb H. Cancer survival among children of Turkish descent in Germany 1980–2005: a registry-based analysis. BMC Cancer 2008;8(1):355.
[35] Bender S, Seifert W. Zur beruflichen und sozialen Integration der in Deutschland lebenden Ausländer. In: Alba R, Schmidt P, Wasmer M, editors. Deutsche und Ausländer Freunde, Fremde oder Feinde? Empirische Befunde und theoretische Erklärungen, (Blickpunkt Gesellschaft, 05). Opladen: Westdeutscher Verlag; 2000. p. 55–91.
[36] Njoku K, Basta N, Mann KD, McNally RJ, Pearce MS. Socioeconomic variation in survival from childhood leukaemia in northern England, 1968–2010. Br J Cancer 2013;108(11):2339–45 [PubMed PMID: 23652301. Pubmed Central PMCID: 3681006].
[37] Youlden DR, Baade PD, Valery PC, Ward LJ, Green AC, Aitken JF. Differentials in survival for childhood cancer in Australia by remoteness of residence and area disadvantage. Cancer Epidemiol Biomark Prev 2011;20(8):1649–56.
[38] Petridou ET, Dimitrova N, Eser S, Kachanov D, Karakilinc H, Varfolomeeva S, et al. Childhood leukemia and lymphoma: time trends and factors affecting survival in five Southern and Eastern European Cancer Registries. Cancer Causes Control 2013;24(6):1111–8.
[39] Goldberg JM. Childhood T-cell acute lymphoblastic leukemia: the Dana-Farber Cancer Institute acute lymphoblastic leukemia consortium experience. J Clin Oncol 2003;21(19):3616–22.
[40] Pui C, Boyett J, Relling M, Harrison P, Rivera G, Behm F, et al. Sex differences in prognosis for children with acute lymphoblastic leukemia. J Clin Oncol 1999;17(3):818–24.

Supplementary Table S1: Collinearity of available SES indicators [a]

	Paternal occupational training	Maternal occupational training	Family income	Paternal education	Maternal education
Paternal occupational training	1.00				
Maternal occupational training	0.48	1.00			
Family income	0.41	0.31	1.00		
Paternal education	0.66	0.42	0.41	1.00	
Maternal education	0.45	0.52	0.27	0.53	1.00

[a] Spearman correlation

Supplementary Table S2: Deaths, losses to follow-up and survival by year of observation and sex

Year of follow-up	Total	Deaths	Losses	Survival	[95%-Confidence Interval][a]
Boys					
1.	460	25	0	0.95	[0.92 0.96]
2.	435	19	0	0.90	[0.87 0.93]
3.	416	16	1	0.87	[0.84 0.90]
4.	399	10	2	0.85	[0.81 0.88]
5.	387	7	3	0.83	[0.80 0.86]
6.	377	3	3	0.83	[0.79 0.86]
7.	371	5	3	0.82	[0.78 0.85]
8.	363	0	3	0.82	[0.78 0.85]
9.	360	2	8	0.81	[0.77 0.84]
10.	350	1	10	0.81	[0.77 0.84]
Girls					
1.	328	13	1	0.96	[0.93 0.98]
2.	314	12	1	0.92	[0.89 0.95]
3.	301	7	0	0.90	[0.86 0.93]
4.	294	4	1	0.89	[0.85 0.92]
5.	289	3	2	0.88	[0.84 0.91]
6.	284	3	0	0.87	[0.83 0.90]
7.	281	3	0	0.86	[0.82 0.90]
8.	278	3	1	0.85	[0.81 0.89]
9.	274	1	3	0.85	[0.81 0.88]
10.	270	0	3	0.85	[0.81 0.88]

[a] Corresponding 95% confidence interval.

Supplementary Table S3: Sensitivity analysis: overall and event-free survival restricted to children with B-lineage acute lymphoblastic leukaemia

	OVERALL SURVIVAL[ab]		EVENT-FREE SURVIVAL[bc]	
	HAZARD RATIO	[95% CI][d]	HAZARD RATIO	[95% CI][d]
Sex				
Boys	1.48	[0.89; 2.48]	1.48	[0.98; 2.24]
Girls	1.0	Reference	1.0	Reference
Age at diagnosis (years)				
< 1	6.97	[3.40; 14.28]	4.02	[2.05; 7.88]
1 – 5	1.0	Reference	1.0	Reference
6 – 9	1.39	[0.72; 2.70]	1.27	[0.75; 2.18]
10 – 14	1.73	[0.84; 3.59]	1.84	[1.04; 3.26]
Family income				
< 2,000 DM	1.22	[0.55; 2.67]	1.20	[0.63; 2.27]
2,000 – 4,000 DM	1.0	Reference	1.0	Reference
4,000 – 6,000 DM	0.76	[0.40; 1.45]	0.81	[0.50; 1.34]
6,000 – 8,000 DM	1.26	[0.48; 3.32]	1.20	[0.54; 2.70]
> 8,000 DM	1.51	[0.50; 4.58]	0.87	[0.30; 2.50]
Maternal education				
No degree	1.05	[0.32; 3.50]	1.14	[0.45; 2.90]
Low degree	1.0	Reference	1.0	Reference
Intermediate degree	0.67	[0.36; 1.25]	0.67	[0.40; 1.10]
High degree	1.11	[0.59; 2.10]	1.25	[0.76; 2.08]
Residential area				
Urban	1.0	Reference	1.0	Reference
Mixed	1.39	[0.78; 2.45]	1.13	[0.70; 1.80]
Rural	1.04	[0.54; 2.00]	1.07	[0.65; 1.77]

[a] Endpoint of overall survival was defined as death from all causes or date of 10 years observation. 523 subjects (68 deaths) are included in the Cox regression model.
[b] Mutually adjusted for each other.
[c] Event of event-free survival was determined as relapse, second malignant neoplasm and death from all causes. 523 subjects (104 events) are included in the Cox regression model.
[d] Corresponding 95% confidence interval.

Supplementary Table S4: Sensitivity analysis: overall and event-free survival for children with acute lymphoblastic leukaemia analysing the impact of paternal occupational training and maternal school education

	OVERALL SURVIVAL[ab]		EVENT-FREE SURVIVAL[bc]	
	HAZARD RATIO	[95% CI][d]	HAZARD RATIO	[95% CI][d]
Sex				
Boys	1.54	[0.95; 2.49]	1.66	[1.11; 2.48]
Girls	1.0	Reference	1.0	Reference
Age at diagnosis (years)				
< 1	8.07	[3.95; 16.48]	4.92	[2.51; 9.62]
1 – 5	1.0	Reference	1.0	Reference
6 – 9	2.51	[1.44; 4.37]	1.98	[1.25; 3.14]
10 – 14	2.54	[1.40; 4.60]	2.14	[1.32; 3.49]
Paternal occupational training				
No occupational training	0.38	[0.14; 1.08]	0.84	[0.44; 1.64]
Vocational training	1.0	Reference	1.0	Reference
Higher vocational training (school)	0.95	[0.37; 2.42]	0.94	[0.40; 2.20]
Technical college/ University	1.08	[0.53; 1.98]	1.36	[0.82; 2.27]
Maternal education				
No degree	1.51	[0.53; 4.30]	1.48	[0.63; 3.49]
Low degree	1.0	Reference	1.0	Reference
Intermediate degree	0.67	[0.38; 1.15]	0.66	[0.41; 1.05]
High degree	0.77	[0.39; 1.50]	0.84	[0.48; 1.47]
Residential area				
Urban	1.0	Reference	1.0	Reference
Mixed	1.10	[0.65; 1.85]	0.93	[0.60; 1.45]
Rural	0.72	[0.40; 1.32]	0.79	[0.49; 1.28]

[a] Endpoint of overall survival was defined as death from all causes or date of 10 years observation. 563 subjects (82 deaths) are included in the Cox regression model.
[b] Mutually adjusted for each other.

[c] Event of event-free survival was determined as relapse, second malignant neoplasm and death from all causes. 563 subjects (118 events) are included in the Cox regression model.
[d] Corresponding 95% confidence interval.

Article IV

Family circumstances and survival from childhood acute lymphoblastic leukaemia in West Germany

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Contribution statement: FE and JS developed the study concept and design. PK, JS and FE contributed to the data collection. FE conducted the statistical data analyses. FE and JS participated in the interpretation of the results. FE prepared the first draft of the manuscript. FE, JS and PK revised it critically for intellectual content and approved the final version of the manuscript.

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Family circumstances and survival from childhood acute lymphoblastic leukaemia in West Germany

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ABSTRACT

Background: Little is known about the relationship between family characteristics and survival from childhood acute lymphoblastic leukaemia (ALL), which we studied for the first time in German children.
Methods: ALL cases were diagnosed between 1992 and 1994 and information on family characteristics was collected during a previously conducted nationwide case–control study. Children were followed for 10 years after diagnosis, as few disease-related events occur afterwards. Cox proportional hazards models estimating hazard ratios (HR) were calculated using overall as well as event-free survival methods.
Results: Second born children showed statistically significant better survival compared to first or later born children, with HRs ranging between 0.54 and 0.64 compared to firstborns. Somewhat poorer survival was observed for children having 3 or more siblings. A relationship was found for parental age at child's diagnosis, with poorer survival for children with younger parents (≤25 years of age at child's diagnosis), or with older fathers. The HR was statistically significant for fathers being ≥41years of age (HR of 2.1). No relationship between degree of urbanization of the place of residence at diagnosis and ALL survival was observed.
Conclusion: Family circumstances may have an impact on survival from childhood ALL in Germany. Further research is warranted to elaborate the relationship of specific family characteristics and ALL survival and to investigate possible differential adherence to therapy and interactions with physicians.

1. Introduction

With an annual incidence of 44 per million children, acute lymphoblastic leukaemia (ALL) is the most common malignancy in German children, accounting for over a quarter of all paediatric cancers in Germany [1]. Over the last decades, advances in diagnosis and treatment led to considerable improvements in outcome [2,3], with the five-year survival now exceeding 85% in Germany [1] and most of Europe [4].

Diagnostic procedures and treatment protocols are largely standardized within developed countries [2,3,5–8] including Germany [3,9]. Germany has a dense network of specialized paediatric clinics and health care is free of charge for all children irrespective of the family's social circumstances [10]. Therefore we would expect fairly equal survival rates across social groups and independent of family circumstances and, indeed, a recent study did not observe a relationship between socio-economic background and ALL survival in Germany [11]. However, besides physician's compliance to the treatment protocols, parents' and child's adherence to the treatment and supportive care as well as the interaction between families and physicians may indeed affect survival. Treatment of ALL lasts over several years [3,9], and poor adherence to oral maintenance therapy may have negative impact on cure rates [12]. As soon as the child is discharged from hospital, parents are responsible to comply with the recommendations for continuation of a highly demanding therapy.

From an international perspective, only few studies have investigated the relationship between family and social circumstances and survival from leukaemia, with very diverse observations even within Europe [11,13–20]. As an extension to the study on survival from ALL and the impact of socio-economic background [11] we investigated here for the first time the

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impact of family circumstances on survival from paediatric ALL in Germany.

2. Material and methods

2.1. Study population and follow-up

Paediatric ALL was defined as diagnosed at ages younger than 15 years. The study population consists of cases from a former German case–control study, covering all of former West Germany (details published elsewhere [21]). Briefly, cases were identified in the nationwide German Childhood Cancer Registry (GCCR), and eligible if diagnosed between October 1992 and September 1994 and if the child was living anywhere in former West Germany. 82% of the invited case families ($N = 647$) participated in the former case–control [11] study which served as the study population of this follow-up investigation. Information on all family characteristics used in this study was collected by self-administered questionnaire during the original case–control study. Children with ALL were treated according to the treatment protocol of the ALL-BFM 90 [3] or COALL 92 trial [9] during this diagnostic period.

We defined family circumstances by a range of features including parental age, birth order, number of siblings, as well as degree of urbanization of the place of residence, using the official governmental categorization. All characteristics correspond to the situation at the date of child's diagnosis. Birth order and number of siblings were defined by counting all live-births of the same mother.

Active vital status follow-up is conducted routinely by the GCCR [22]. We censored at 10 years follow-up as very few disease-related events occur afterwards but the incidence of competing risks rises. Further information on the follow-up process of the GCCR as well as on adjustment characteristics (e.g. maternal education as indicator of socio-economic status) are published elsewhere [11,22].

2.2. Statistical analyses

We defined two primary outcomes for these analyses: overall survival, with death from any cause as the endpoint, and event-free survival, with the first (if any) relapse (defined as >5% lymphoblasts in bone marrow), second malignant neoplasm or death as events. Children were observed for 10 years from the date of diagnosis until the date of event, last date known to be alive, or date of 10 years of follow-up, whichever came first.

For graphical illustration we calculated (unadjusted) survival probabilities stratified by birth order, number of siblings and parental age, using Kaplan–Meier curves. Statistical significance ($p \leq 0.05$) of differences in survival probabilities was assessed by the log-rank test [23].

Cox proportional hazards models were used to assess the impact of selected characteristics applying overall (Models I and II) and event-free survival methods (Models III and IV) [24]. The multiple regression models were built up in two steps. Initially, we adjusted for the well–established prognostic factors age at diagnosis [3] (grouped into <1 year, 1–5 years, 6–9 years, 10–14 years) and sex [25] (Model I and Model III). Model II and Model IV were additionally adjusted for the possible mediating effect of other family variables (*adjustment varied between family characteristics*). Results were expressed as adjusted hazard ratios (HRs) with corresponding 95% confidence intervals.

The proportional hazards assumption for the Cox models, tested using the Schoenfeld residuals test [24], failed for the variable child's age at diagnosis in the category "<1 year" ($N = 26$). Nevertheless, as the hazard ratios changed only marginally when excluding the infants from the analyses, results in this manuscript relate to all subjects combined.

All statistical analyses were performed using Stata 13 [26].

3. Results

As expected from German national cancer registry data [1], out of the 647 cases, 60% were boys and almost two thirds were 1–5 years of age at diagnosis (Table 1). Among all cohort members, 334 (52%) were firstborns and 159 (25%) were the only child; almost half of the families of our cohort had two children. With respect to place of residence, most families were living in urban areas, and most parents were aged ≤30 years at diagnosis. Numbers of missing values were very low for the key variables, ranging between 0.5% for maternal age and 1.6% for paternal age.

10-year overall survival was 84.7%, based on 98 deaths. Survival was somewhat better for girls than boys (88% vs. 83%) and age-wise highest for children aged 1–5 years at diagnosis.

Kaplan–Meier curves suggest differences in overall survival from ALL by family characteristics *(although statistically significant only for birth order)* (Fig. 1). Considerably poorer survival is seen for children with 3 or more siblings compared to those with fewer siblings. This dissimilarity appears to emerge about 1.5 years after diagnosis. Regarding birth order, survival was highest for second born children ($p = 0.048$). The relationship of parental age at diagnosis and long-term survival from ALL appears to be U-shaped, with poorer survival for children with younger (*≤25 years*) or older parents (*maternal age ≥36 years, paternal age ≥41 years*) but highest in children of mid-aged parents. This U-shape was particularly pronounced for the associations seen with father's age.

Table 2 displays the results from the multivariate analyses on the impact of family characteristics on overall and event-free survival. The adjusted findings confirm the overall associations observed from the unadjusted survival curves, with also similar patterns found for overall and event-free survival and across models. The group of second born children had a statistically significant better survival compared to first or later born children, with HRs ranging between 0.54 and 0.64 compared to firstborns, depending on the model. The risk of dying of children with 3 or more siblings increased with additional adjustment (*Models II* and *IV*), resulting in a non-significant HR of about 1.6 in the fully adjusted model. Children with one or two siblings showed slightly better survival than their counterparts from single child families. A sensitivity analysis mutually adjusting for birth order and number of siblings pointed towards an even stronger relationship between number of siblings and ALL survival, with increasing HRs with increasing number of siblings in a family. HRs for children with 3 and more siblings exceeded 2.4 (*overall survival*) and 2.7 respectively (*event-free survival*) in the fully adjusted models.

The non-linear relationship of parental age at diagnosis and survival persists in the adjusted analyses. Children with a father aged 41 years or older showed a statistically significant increased HR of 2.1 (95% CI 1.04; 4.20). Likewise, children with a father aged 25 years or younger at child's diagnosis had poorer survival (HR 1.65; 95% CI 0.97; 2.81), although not statistically significant. The relationship was weaker for maternal age and persisted in the fully adjusted models mainly for young mothers (HR 1.33; 95% CI 0.81; 2.19).

A sensitivity analysis distinguishing between having either a young mother or a young father and having two young parents (both ≤25 years) indicated that particularly the latter was related to poorer survival. Elevated HRs of up to 1.76 were found for having both a young mother and a young father.

No relationship between degree of urbanization of place of residence at diagnosis and survival was observed, although HRs for living in a rural area were somewhat lower than 1.

Table 1
Characteristics of childhood acute lymphoblastic leukaemia (ALL) cases diagnosed 1992–1994 in former West Germany by deaths, 10-year survival and person-years under risk.

	All cases (column %)		Deaths (row %)[a]		10-Year survival[b]	Person-years
Total	647		98	(15.2%)	84.7%	5663
Sex						
Boys	389	(60.1%)	66	(17.0%)	82.9%	3330
Girls	258	(39.9%)	32	(12.4%)	87.5%	2333
Age at diagnosis (years)						
<1	26	(4.0%)	12	(46.1%)	53.9%	148
1–5	412	(63.7%)	40	(9.7%)	90.2%	3803
6–9	122	(18.9%)	27	(22.1%)	77.5%	1011
10–14	87	(13.5%)	19	(21.8%)	78.1%	701
Birth order						
1st born	334	(51.6%)	56	(16.8%)	83.1%	2870
2nd born	207	(32.0%)	21	(10.1%)	89.8%	1910
3rd born and later	101	(15.6%)	19	(18.8%)	81.1%	847
Missing	5	(0.8%)	2	(40.0%)	60.0%	37
Number of siblings						
Only child	159	(24.6%)	25	(15.7%)	84.2%	1372
1 sibling	311	(48.1%)	39	(12.5%)	87.4%	2787
2 siblings	123	(19.0%)	20	(16.3%)	83.6%	1076
3 and more siblings	50	(7.7%)	12	(24.0%)	75.7%	401
Missing	4	(0.6%)	2	(50.0%)	50.0%	27
Place of residence at diagnosis						
Urban	276	(42.7%)	44	15.9%	83.9%	2377
Mixed	201	(31.1%)	34	16.9%	83.0%	1734
Rural	170	(26.3%)	20	11.8%	88.2%	1552
Mother's age at diagnosis						
≤25	236	(36.5%)	39	(16.5%)	83.3%	2042
26–30	258	(39.9%)	36	(14.0%)	85.9%	2280
31–35	108	(16.7%)	14	(13.0%)	87.0%	955
≥36	42	(6.5%)	8	(19.1%)	80.9%	360
Missing	3	(0.5%)	1	(33.3%)	66.7%	27
Father's age at diagnosis						
≤25	125	(19.3%)	26	(20.8%)	78.9%	1031
26–30	218	(33.7%)	29	(13.3%)	86.5%	1931
31–35	174	(26.9%)	20	(11.5%)	88.5%	1569
36–40	75	(11.6%)	10	(13.3%)	86.7%	676
≥41	45	(7.0%)	11	(24.4%)	75.6%	363
Missing	10	(1.6%)	2	(20.0%)	80.0%	93

[a] Proportion of death from all acute lymphoblastic leukaemia cases by covariates.
[b] Overall survival, with death from any cause or date of 10 years follow-up as endpoint.

4. Discussion

4.1. Main findings

The role of family circumstances on long-term survival in childhood acute lymphoblastic leukaemia cases has not been studied before in Germany. The findings shown here indicate that family circumstances may affect survival from paediatric ALL, although most associations were suggestive rather than statistically significant. Poorer survival was observed for children having 3 or more siblings. Highest survival was seen for second born children. A non-linear relationship was found for parental age at diagnosis, with poorer survival for children with younger fathers and mothers, and most distinct for children with older fathers.

Treatment of ALL lasts over several years, with the maintenance therapy being very much the responsibility of the family to administer [3,9]. As soon as the child is discharged from hospital, parents are responsible to comply with the recommendations for continuation of a highly demanding therapy, including daily drug administration and frequent medical outpatient appointments. Findings from the UK suggest that dissimilarities in ALL survival by socio-economic status emerged about the time when treatment management required parental/child's adherence, i.e. from the time of oral treatment in the outpatient setting and hypothesized that this may due to treatment compliance [14]. In our study, children from families with 4 or more children showed poorer survival and these dissimilarities emerged about 1.5 years after diagnosis, a time by which treatment management has usually moved from hospital to home [3,9]. Smaller families may be able to devote more time to assisting the child and may be better at coping with the cancer experience as well as managing the complex therapy [27,28].

The poorer survival we found for children with young parents might likewise reflect the ability to manage the complex home-base maintenance therapy. Similarly, the capacity to cope with the cancer diagnosis and related circumstances, and may be particularly challenging for young parents [27], with associated effects on adherence to treatment protocols and outpatient appointments.

As an alternative to reasons related to social interactions, the lower survival observed in children with fathers aged 41 years or older might be biological originated. Advanced paternal age has been associated with a higher risk of germ cell sporadic mutations [29] and with genetic aberrations in the offspring. Although the evidence is overall inconsistent, some recent epidemiological studies with large sample sizes suggested an increased risk of childhood leukaemia with increasing paternal age at child's birth

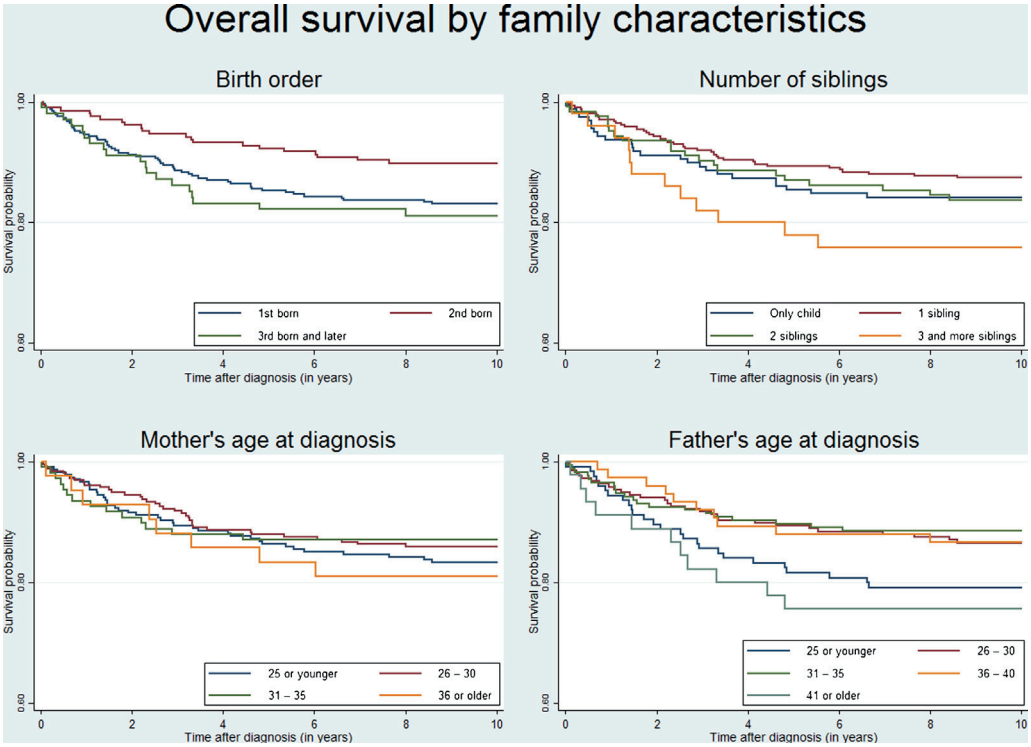

Fig. 1. Overall survival from childhood acute lymphoblastic leukaemia by family characteristics. Kaplan–Meier curves of overall survival by birth order (Log-rank test of heterogeneity: $\chi^2 = 6.09$, $p = 0.048$), number of siblings (Log-rank test of heterogeneity: $\chi^2 = 5.13$, $p = 0.162$), mother's age at the child's diagnosis (Log-rank test of heterogeneity: $\chi^2 = 1.38$, $p = 0.709$), and father's age at the child's diagnosis (Log-rank test of heterogeneity: $\chi^2 = 8.95$, $p = 0.063$).

[30–32]. In addition, there is evidence of oligoclonality in a minority of children with ALL at diagnosis [33,34] and the overall outcome is dependent upon the clone conferring the worst prognosis. It might be hypothesized that relapse is due to surviving clones (or their precursors) present at an undetectable level. These clones are likely to be exposed to the same environmental factors which were present prior to initial diagnosis. Therefore, advanced paternal age might not be only a risk factor for developing ALL but also a prognostic factor for ALL survival.

Similarly, birth order has been used as proxy for exposures that may influence the risk of developing ALL, namely for exposure to infections in early life (perhaps lesser for firstborns) [35] or for exposure to in utero hormone levels (with the mother's first pregnancy endocrinologically differing from later pregnancies [36], and may therefore likewise be related to the risk of relapse. The only environmental factor however for which risk of relapse has been investigated so far is magnetic field exposure, but no association was seen [37]. It is otherwise difficult to come up with plausible explanations for the excellent survival found in second born children; chance may be an option.

Whether children lived in urban or rural areas had no impact on survival; this is plausible as in Germany a dense network of specialized paediatric clinics covers the entire country and treatment is highly standardized [3,9]. Almost all paediatric ALL cases are treated according to the treatment schemes developed by the two collaborative study groups ALL-BFM (Berlin–Frankfurt–Münster) [3] and COALL (cooperative study group for childhood acute lymphoblastic leukemia) [9] (today 99.8% (1)).

4.2. Strength and weakness

This is the first study in Germany on this topic, and one of very few from Europe. Strengths of this study include the nationwide coverage of cases of former West Germany and the long and complete follow-up period of 10 years. Multiple characteristics on family factors were available with almost no missing data.

A limitation of our study is that 18% of the original population-based case families no information on family characteristics was available since they did not participate in the former case–control study, with children of non-participating families having poorer survival [11]. If participation was related to family size or parental age, selection bias could affect our results. An inherent limitation is the sample size with – fortunately for the families – low numbers of deaths in our cohort, being a follow-up investigation of a nationwide case control study on the rare disease outcome ALL in children.

Furthermore, no information on parental marriage and cohabitation status was available which has been hypothesized to be associated with treatment adherence [28].

Survival studies are by default historical by the time they are conducted. As a consequence of the demographic change and the related decrease of financial resources, the German health care system went through a series of reforms [10] since the children of our study were treated. However, financial compensation for diagnosis and treatment of paediatric cancer is not known to have been changed by these reforms. Nevertheless, we cannot exclude that the most recent improvements of treatment may have offset or flatten the relationship between family characteristics and ALL survival found here.

4.3. Comparison with previous research

The observed associations between number of siblings, birth order, and parental age and ALL survival are particularly interesting in the light of the fact that two previously published studies from Germany, focussing on other social factors, did not

Table 2
Cox regression analyses of the association of family characteristics on overall and event-free survival from paediatric acute lymphoblastic leukaemia in Germany, followed-up for 10 years from date of diagnosis.

	Overall survival[a]				Event-free survival[e]			
	Model I[b]		Model II[d]		Model III[b]		Model IV[d]	
	Hazard ratio	[95% CI][c]	Hazard ratio	[95% CI][d]	Hazard ratio	[95% CI][d]	Hazard ratio	[95% CI][d]
Birth order								
1st born	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
2nd born	0.57	[0.34; 0.95]	0.64	[0.37; 1.10]	0.54	[0.36; 0.82]	0.61	[0.39; 0.95]
3rd born and later	1.00	[0.59; 1.69]	1.04	[0.55; 1.95]	0.88	[0.56; 1.37]	1.00	[0.59; 1.71]
Number of siblings								
Only child	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
1 sibling	0.71	[0.43; 1.19]	0.86	[0.48; 1.52]	0.84	[0.55; 1.29]	0.98	[0.61; 1.57]
2 siblings	0.81	[0.44; 1.50]	0.83	[0.42; 1.67]	0.85	[0.51; 1.43]	0.95	[0.53; 1.69]
3 and more siblings	1.27	[0.63; 2.57]	1.58	[0.73; 3.44]	1.20	[0.65; 2.23]	1.65	[0.84; 3.25]
Place of residence at diagnosis								
Urban	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
Mixed	1.10	[0.69; 1.73]	1.12	[0.69; 1.84]	0.92	[0.62; 1.35]	0.92	[0.61; 1.40]
Rural	0.79	[0.46; 1.36]	0.85	[0.49; 1.49]	0.80	[0.52; 1.23]	0.87	[0.56; 1.35]
Mother's age at diagnosis								
≤25	1.16	[0.73; 1.83]	1.33	[0.81; 2.19]	1.15	[0.80; 1.66]	1.38	[0.93; 2.06]
26–30	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
31–35	0.84	[0.45; 1.57]	0.82	[0.42; 1.58]	0.70	[0.41; 1.20]	0.71	[0.41; 1.25]
≥36	1.32	[0.61; 2.84]	1.11	[0.48; 2.55]	0.95	[0.47; 1.91]	0.80	[0.38; 1.72]
Father's age at diagnosis								
≤25	1.65	[0.97; 2.81]	1.65	[0.93; 2.94]	1.46	[0.94; 2.26]	1.46	[0.91; 2.36]
26–30	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
31–35	0.85	[0.48; 1.50]	0.76	[0.42; 1.40]	0.80	[0.51; 1.26]	0.76	[0.47; 1.22]
36–40	1.00	[0.48; 2.05]	0.91	[0.42; 1.96]	0.86	[0.47; 1.57]	0.80	[0.42; 1.50]
≥41	2.09	[1.04; 4.20]	1.89	0.89; 4.01]	1.36	[0.72; 2.58]	1.29	[0.66; 2.52]

[a] Endpoint of overall survival was defined as death from all causes or date of 10 years observation.
[b] Hazard ratios are adjusted for child's age at diagnosis and sex.
[c] Corresponding 95% confidence interval.
[d] Adjustment factors vary by family characteristic. Birth order: hazard ratios are adjusted for child's age at diagnosis, sex, maternal education (as SES indicator) and maternal age at diagnosis. Number of children: hazard ratios are adjusted for child's age at diagnosis, sex, maternal education (as SES indicator) and maternal age at diagnosis. Place of residence: hazard ratios are adjusted for child's age at diagnosis, sex, maternal education (as SES indicator). Mother's age at diagnosis: hazard ratios are adjusted for child's age at diagnosis, sex, maternal education (as SES indicator) and number of children in the family. Father's age at diagnosis: hazard ratios are adjusted for child's age at diagnosis, sex, maternal education (as SES indicator) and number of children in the family.
[e] Events of event-free survival were defined as relapse, second malignant neoplasm or death from all causes.

find a relationship. Neither family's socio-economic conditions [11] as measured by parental education and family income, nor having a Turkish migration background [38] was reported to be associated with survival.

Therefore, in Germany, family obligations and family's social resources (as measured by number of siblings and parental age in the present study), appear to be more relevant than the socio-economic situation whereas for other European countries parental education, income or occupation did matter [13,14,16–18,20]. However, little is known about the role of family circumstances on ALL survival, particularly not their interaction with socio-economic characteristics.

Number of siblings and birth order have been postulated to be related to the occurrence of childhood ALL [39] but have rarely been investigated as prognostic factors for ALL, with inconsistent findings. A large Norwegian study observed for childhood cancers requiring long-term treatment (including ALL) that having no siblings was associated with mortality reductions of approximately 20% [16]. In contrast, in Greece a reduced risk of death was reported for children with siblings and a cancer diagnosed in the late 1990s to early 2000s [18], however, this finding was not confirmed in a recent follow-up study [17]. To our knowledge paternal age at child's diagnosis has not been studied in relation to ALL survival before. Nevertheless, analyses on mother's age at child's birth from Greece and Norway did not suggest a relationship with ALL survival [16,17].

With respect to place of residence, findings from Australia showed that survival was generally poorer for children living in more isolated parts of the countries [40] and living in more rural areas was also associated with less favourable prognosis in a recent multi-national study (including Greece, Bulgaria, Izmir, Antalya and Moscow) [41]. This contrasts with our results but, given the high population density and lack of real remote areas in West Germany, this is not surprising. It should also be kept in mind that changes of residence after diagnosis could not be taken into account.

All in all, dissimilarities in welfare systems, including access to health care and public family support, coverage and distance to specialized treatment facilities, lifestyle, treatment protocols as well as methodical differences between studies make an international comparison challenging. However, a crucial question is to what extent the observed differences across studies are real (reflecting different impact of family conditions due to differences in health care and social stratification, true overall health inequity) or to what extent differences can be explained by features of the studies (including among others differences in study design, data sources, data collection, cancer type, diagnostic period or adjustment factors).

5. Conclusion

In conclusion, despite of the highly specialized and centralized treatment and free access for all children to health care services,

not all children appear to benefit equally from improvements in ALL survival. Our results indicate that some families may need extra supportive care during the extensive and demanding treatment period. Further studies are warranted to confirm our findings and to identify potential underlying mechanisms, particularly with regard to differential adherence to therapy and related interactions of families with paediatric oncologists in Germany and elsewhere. Moreover, studies on the role of social and family factors in survival from other types of childhood cancer are needed.

Conflicts of interest

No potential conflicts of interest were disclosed.

Authorship contribution

FE and JS developed the study concept and design. PK, JS and FE contributed to the data collection. FE conducted the statistical data analyses. FE and JS interpreted the results and drafted the manuscript. FE, JS and PK revised it critically for intellectual content and approved the final version.

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References

[1] Kaatsch P, Spix J. German Childhood Cancer Registry – annual report 2012 (1980–2012). Mainz: Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI) at the University Medical Center of the Johannes Gutenberg University, 2013.
[2] Schmiegelow K, Forestier E, Hellebostad M, Heyman M, Kristinsson J, Soderhall S, et al. Long-term results of NOPHO ALL-92 and ALL-2000 studies of childhood acute lymphoblastic leukemia. Leukemia 2010;24(February (2)):345–54. PMID: 20010622.
[3] Moricke A, Zimmermann M, Reiter A, Henze G, Schrauder A, Gadner H, et al. Long-term results of five consecutive trials in childhood acute lymphoblastic leukemia performed by the ALL-BFM study group from 1981 to 2000. Leukemia 2010;24(February (2)):265–84. PMID: 20010625.
[4] Gatta G, Botta L, Rossi S, Aareleid T, Bielska-Lasota M, Clavel J, et al. Childhood cancer survival in Europe 1999–2007: results of EUROCARE-5—a population-based study. Lancet Oncol 2014;15(1):35–47.
[5] Lie SO, Abrahamsson J, Clausen N, Forestier E, Hasle H, Hovi L, et al. Long-term results in children with AML: NOPHO-AML Study Group – report of three consecutive trials. Leukemia 2005;19(December (12)):2090–100. PMID: 16304571.
[6] Márky I, Björk O, Forestier E, Jónsson ÓG, Perkkiö M, Schmiegelow K, et al. Intensive chemotherapy without radiotherapy gives more than 85% event-free survival for non-Hodgkin lymphoma without central nervous involvement: a 6-year population-based study from the nordic society of pediatric hematology and oncology. J Pediatric Hematol/Oncol 2004;26(9):555–60.
[7] Pui CH, Carroll WL, Meshinchi S, Arceci RJ. Biology, risk stratification, and therapy of pediatric acute leukemias: an update. J Clin Oncol 2011;29(5):551–65.
[8] Mitchell C, Richards S, Harrison CJ, Eden T. Long-term follow-up of the United Kingdom medical research council protocols for childhood acute lymphoblastic leukaemia, 1980–2001. Leukemia 2009;24(2):406–18.
[9] Escherich G, Horstmann MA, Zimmermann M, Janka-Schaub GE. Cooperative study group for childhood acute lymphoblastic leukaemia (COALL): long-term results of trials 82, 85, 89, 92 and 97. Leukemia 2010;24(2):298–308.
[10] Busse R, Riesberg A. Health care systems in transition. Copenhagen, Denmark: WHO Regional Office for Europe on behalf of the European Observatory on Health Systems and Policies, 2004.
[11] Erdmann F, Kaatsch P, Zeeb H, Roman E, Lightfoot T, Schuz J. Survival from childhood acute lymphoblastic leukaemia in West Germany: does socio-demographic background matter? Eur J Cancer 2014;50(May (7)):1345–53. PMID: 24582913.
[12] Bhatia S, Landier W, Shangguan M, Hageman L, Schaible AN, Carter AR, et al. Nonadherence to oral mercaptopurine and risk of relapse in Hispanic and non-Hispanic white children with acute lymphoblastic leukemia: a report from the children's oncology group. J Clin Oncol 2012;30(June (17)):2094–101. PMID: 22564992, PMCID: 3601449.
[13] Coebergh JW, van der Does-van den Berg A, Hop W, van Weerden F, Rammeloo J, van Steensel H, et al. Small influence of parental educational level on the survival of children with leukaemia in The Netherlands between 1973 and 1979. Eur J Cancer 1996;32A(2):286–9.
[14] Lightfoot T, Johnston W, Simpson J, Smith A, Ansell P, Crouch S, et al. Survival from childhood acute lymphoblastic leukaemia: the impact of social inequality in the United Kingdom. Eur J Cancer 2012;48(2):263–9.
[15] Walsh PM, Byrne J, Capra M, Comber H. Childhood cancer survival in Ireland: temporal, regional and deprivation-related patterns. Eur J Cancer 2011;47(12):1852–62.
[16] Syse A, Lyngstad TH, Kravdal O. Is mortality after childhood cancer dependent on social or economic resources of parents? A population-based study. Int J Cancer 2012;130(8):1870–8.
[17] Sergentanis T, Dessypris N, Kanavidis P, Skalkidis I, Baka M, Polychronopoulou S, et al. Socioeconomic status, area remoteness, and survival from childhood leukemia. Eur J Cancer Prev 2012;1.
[18] Charalampopoulou A, Petridou ET, Spyridopoulos T, Dessypris N, Oikonomou A, Athanasiadou-Piperopoulou F, et al. An integrated evaluation of socioeconomic and clinical factors in the survival from childhood acute lymphoblastic leukaemia: a study in Greece. Eur J Cancer Prev 2004;13(5):397–401.
[19] Petridou ET, Kosmidis H, Haidas S, Tong D, Revinthi K, Flytzani V, et al. Survival from childhood leukemia depending on socioeconomic status in Athens. Oncology 1994;51(5):391–5.
[20] Njoku K, Basta N, Mann KD, McNally RJ, Pearce MS. Socioeconomic variation in survival from childhood leukaemia in northern England, 1968–2010. Br J Cancer 2013;108(June (11)):2339–45. PMID: 23652301, PMCID: 3681006.
[21] Schüz J, Kaatsch P, Kaletsch U, Meinert R, Michaelis J. Association of childhood cancer with factors related to pregnancy and birth. Int J Epidemiol 1999;28(4):631–9.
[22] Grabow D, Spix C, Blettner M, Kaatsch P. Strategy for long-term surveillance at the German Childhood Cancer Registry – an update. Klin Padiatr 2011;223(May (3)):159–64. PMID: 21472636.
[23] Clark TG, Bradburn MJ, Love SB, Altman DG. Survival analysis. Part I. Basic concepts and first analyses. Br J Cancer 2003;89(2):232–8.
[24] Bradburn MJ, Clark TG, Love SB, Altman DG. Survival analysis. Part III. Multivariate data analysis – choosing a model and assessing its adequacy and fit. Br J Cancer 2003;89(4):605–11.
[25] Pui C, Boyett J, Relling M, Harrison P, Rivera G, Behm F, et al. Sex differences in prognosis for children with acute lymphoblastic leukemia. J Clin Oncol 1999;17(3):818–24.
[26] StataCorp.. Stata statistical software: release 13. College Station, TX: StataCorp LP, 2013.
[27] Patterson JM, Holm KE, Gurney JG. The impact of childhood cancer on the family: a qualitative analysis of strains, resources, and coping behaviors. Psychooncology 2004;13(June (6)):390–407. PMID: 15188446.
[28] Tebbi C. Treatment compliance in childhood and adolescence. Cancer 1993;71(10 Suppl.):3441–9.
[29] Crow JF. Development. There's something curious about paternal-age effects. Science 2003;301(August (5633)):606–7. PMID: 12893932.
[30] Dockerty J, Draper GJ, Vincent TJ, Rowan S, Bunch K. Case–control study of parental age, parity and socioeconomic level in relation to childhood cancers. Int J Epidemiol 2001;30(6):1428–37.
[31] Johnson KJ, Carozza SE, Chow EJ, Fox EE, Horel S, McLaughlin CC, et al. Parental age and risk of childhood cancer: a pooled analysis. Epidemiology 2009;20(July (4)):475–83. PMID: 19373093, PMCID: 2738598.
[32] Larfors G, Hallbook H, Simonsson B. Parental age, family size, and offspring's risk of childhood and adult acute leukemia. Cancer Epidemiol Biomarkers Prev 2012;21(July (7)):1185–90. PMID: 22539609.
[33] Deane E, Pappas H, Norton J. Immunoglobulin heavy chain gene fingerprinting reveals widespread oligoclonality in B-lineage ALL. Leukemia 1991;5:832–8.
[34] van der Velden VH, Szczepanski T, Wijkhuijs JM, Hart PG, Hoogeveen PG, Hop WC, et al. Age-related patterns of immunoglobulin and T-cell receptor gene rearrangements in precursor-B-ALL: implications for detection of minimal residual disease. Leukemia 2003;17(September (9)):1834–44. PMID: 12970784.
[35] Greaves M. Infection, immune responses and the aetiology of childhood leukaemia. Nat Rev Cancer 2006;6(March (3)):193–203. PMID: 16467884.
[36] Spector LG, Pankratz N, Marcotte EL. Genetic and nongenetic risk factors for childhood cancer. Pediatr Clin North Am 2015;62(February (1)):11–25. PMID: 25435109.

[37] Schuz J, Grell K, Kinsey S, Linet MS, Link MP, Mezei G, et al. Extremely low-frequency magnetic fields and survival from childhood acute lymphoblastic leukemia: an international follow-up study. Blood Cancer J 2012;2:e98. PMID: 23262804, PMCID: 3542478.
[38] Spix C, Spallek J, Kaatsch P, Razum O, Zeeb H. Cancer survival among children of Turkish descent in Germany 1980–2005: a registry-based analysis. BMC Cancer 2008;8(1):355. PMID: 19040749, PMCID: 2628927.
[39] Greaves M. Commentary: birth order and risk of childhood acute lymphoblastic leukaemia (ALL). Int J Epidemiol 2001;1438–9.
[40] Youlden DR, Baade PD, Valery PC, Ward LJ, Green AC, Aitken JF. Differentials in survival for childhood cancer in Australia by remoteness of residence and area disadvantage. Cancer Epidemiol Biomarkers Prev 2011;20(8):1649–56.
[41] Petridou ET, Dimitrova N, Eser S, Kachanov D, Karakilinc H, Varfolomeeva S, et al. Childhood leukemia and lymphoma: time trends and factors affecting survival in five Southern and Eastern European Cancer Registries. Cancer Causes Control 2013;24(June (6)):1111–8. PMID: 23529470.

Article V

Effect of socioeconomic position on survival after childhood cancer in Denmark

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Effect of socioeconomic position on survival after childhood cancer in Denmark

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Abstract

BACKGROUND: Today, 22% of all deaths among children in Europe are due to cancer. If this proportion is to be reduced, studies are needed not only on the biology and treatment of these cancers but also on how social factors affect cure rates. In this Danish nationwide study, we investigated associations between certain socioeconomic characteristics and survival after childhood cancer.

METHODS: We identified the parents and siblings of 3797 children with cancer diagnosed in 1990–2009 before they were 20 years of age; we obtained information on socioeconomic variables and vital status at parental individual level through 2012 by linkage to population-based registries. Hazard ratios (HRs) for dying were estimated in multivariate Cox proportional hazard models.

FINDINGS: Regardless of cancer type, children with cohabiting parents had better survival (HR, 0.82; 95% CI, 0·69–0·99) than children of single parents. Children with siblings had stepwise worse survival (one sibling: HR, 1·12; 95% CI, 0·95–1·31; two or more siblings: HR, 1·26; 1·03–1·53) than children without siblings. Children with non-CNS solid tumours had significantly better survival (HR, 0·66; 95% CI, 0·44–0·99) when their mothers had higher education rather than basic education.

INTERPRETATION: Having cohabiting parents and no siblings was associated with longer survival after any cancer in childhood, and having a mother with higher education was associated with longer survival in children with non-CNS tumours. Further studies of how and why these indicators of social position influence survival, despite a universal health system, are warranted.

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Introduction

All industrialised and most developing countries recognise the special needs of children with cancer and offer what each country regards as the best standard of care during all phases of the treatment trajectory. It is estimated that more than 90% of the 15 000 children in whom cancer is diagnosed annually in the European Union will enter standardised treatment programmes, which usually include participation in randomised trials of the effect of new treatments. Survival might be affected not only by participation in trials but also by the compliance of the treating physician to both standard and experimental protocols, the adherence of parents and patients to guidelines for treatment and supportive care, and the interactions of these factors.

Today, 22% of all deaths among children aged 1–14 years in Europe are due to cancer.[1] If this high proportion of cancer-related deaths is to be reduced, studies must be conducted not only on tumour biology and novel treatment approaches but also on how socioeconomic and social factors influence cure rates.

A number of studies have shown an association between socioeconomic position (SEP) and survival after cancer in adults, with better survival of cancer patients with higher education or high income.[2-4] Few studies, however, have addressed the association between socioeconomic factors and survival after childhood cancer in high-income countries. Most of the available studies included only children with acute lymphoblastic leukaemia (ALL) or haematological cancer in general (n = 714–1559), with inconsistent results for a range of SEP indicators, some finding differences in survival[5–9] and others no differences.[10–12] To our knowledge, only one study included patients with childhood cancers at all sites (N = 6280); that study showed reduced mortality rates from cancers that require lengthy treatment (tumours in the central nervous system [CNS], leukaemias, neuroblastomas, and bone tumours) among children whose mothers had higher education or who had no siblings.[9]

We investigated the association between SEP and survival after childhood cancer overall and separately by diagnostic group in order to determine the extent to which these factors influence survival in a large, population-based, nationwide study, with individual-level information from Danish public administrative registries for all cases. We defined SEP broadly, using parental educational level, income, cohabitation status, and number of siblings as measures of knowledge-related assets, material resources, family social support, and family obligations, thus covering both SEP and the broader social factors that affect resources in a family.

Material and Methods

Study population

We identified 3797 children in whom cancer was diagnosed when they were under the age of 20 years between 1 January 1990 and 31 December 2009 in the Danish Cancer Registry, which contains information on all cancers diagnosed since 1943.[13] We grouped the cancers into 12 diagnostic groups on the basis of the Birch–Marsden classification[14] (also called the International Classification of Childhood Cancer [ICCC]) and defined three main diagnostic groups for our analyses: haematological malignancies (leukaemias and lymphomas; ICCC groups 1 and 2), CNS tumours (ICCC group 3), and non-CNS solid tumours (ICCC groups 4–11).

Identification of families and socioeconomic position

Since 1968, all residents of Denmark have been assigned a unique 10-digit personal identification number by the Danish Civil Registration System, which allows accurate linkage among registries.[15] The System also holds information on first-degree relatives, and > 99% of parents are identifiable for children born in Denmark after 1970.[16] Using the children's

personal identification numbers as the key, we identified all parents (n = 7570) and all full siblings (n = 3250) and half siblings (n = 953) who were under the age of 19 in the year of diagnosis of the cancer. Full siblings have the same mother and father, and half siblings have the same mother or father.

We obtained information on parental socioeconomic factors for the year before diagnosis of the child from registries on education and income kept by Statistics Denmark.[17–19]

Highest attained level of education was categorised into basic education (7–12 years of basic or high school), vocational education (10–12 years), and higher education (≥ 13 years). Individual disposable income after taxation and interest was categorised into quartiles. As the father's income was missing for 9% of cases, the mother's income was used as the measure of material resources. Parental cohabitation status was defined as living with a partner (married or cohabiting) or living without a partner (single, widowed, or divorced). Cohabiting in the absence of marriage was defined as two people of the opposite sex, over the age of 16 years, with a maximum 15 years of age difference, living at the same address with no other adult in residence.

Statistics

Overall survival was our primary outcome. Children were followed-up from the date of cancer diagnosis until the date of death from any cause, emigration, or end of follow-up (31 December 2012), whichever occurred first. For graphical presentation, we calculated unadjusted survival probabilities stratified by mother's education, mother's income, parental cohabitation status, and number of full siblings using Kaplan–Meier curves.

Cox proportional hazards models were used to estimate the hazard ratio (HR) with 95% confidence interval (CI); time since diagnosis was the underlying time scale. We used the statistical software R, version 3.0.2.[20] To assess the impact of socioeconomic factors on

overall survival, we modelled the multivariate analyses in four steps. In the first model, each socioeconomic variable was entered alone (crude HR). In the second model, each socioeconomic variable was adjusted for well-established prognostic factors: child's age at diagnosis (linear), sex, decade of diagnosis, and site of cancer (in the 12 diagnostic groups). In the third model, we further adjusted for the possible mediating effect of parental education, income, and cohabitation status; and, in the fourth model, we adjusted further for mother's age at birth (< 20, 20–29, 30–39, ≥ 40 years) and number of full siblings (none, one, two or more). An overall *p* value for analysis of variance was reported. We performed sub-analyses for the three main diagnostic groups (haematological, CNS, and non-CNS solid tumours) and a separate analysis for ALL in order to compare our results with those of other studies. We conducted separate analyses for non-CNS solid tumours with a favourable prognosis and standardised therapy, including early surgery (Wilms tumour), and for non-CNS solid tumours that frequently require more complex treatment (bone tumours, liver tumours, neuroblastomas, and rhabdomyosarcomas). We repeated all analyses including half siblings. Finally, we calculated rate ratios for death in order to estimate absolute excess risk, with corresponding 95% CIs.

Results

Cancer was diagnosed in 29% of the 3797 children when they were aged 0–4 years and in 33% when they were 15–19 years. The commonest cancers were CNS tumours, followed by leukaemia (Table 1). Almost half the parents had vocational education, and 80% cohabited. About 60% of the childhood cancer patients had one or more full siblings.

Survival after childhood cancer

The median follow-up time was 9.0 years (range, 0–22 years). There were 841 deaths during follow-up, for an overall survival of 78%. Kaplan–Meier curves (Figure 1) indicated better survival with increasing level of maternal education, increasing maternal income, fewer full siblings, and for children of cohabiting parents. The survival curves appeared to diverge within the first year after diagnosis for the association with mother's education and income and after about 2 years for that with cohabitation status and full siblings.

Having both parents with higher education, a mother with higher income, higher maternal age, and cohabiting parents were associated with better survival, as was having no siblings (crude HR), although most estimates did not reach statistical significance (Table 2).

Adjustment for parental education and mother's income only slightly affected the overall results, whereas full adjustment resulted in stronger associations with having parents living alone (HR, 0.82; 95% CI, 0.69–0.99) and having two or more full siblings (HR, 1.26; 1.03–1.53).

The worse survival of children with the youngest mothers appeared to be mediated partly through education, income, cohabitation status, and number of full siblings, the HR decreasing from 1·33 to 1·20, whereas adjustment did not change the better survival of children with the oldest mothers. Addition of half siblings (both all and by the mother only) to the number of full siblings did not change the estimates (data not shown).

Survival by diagnostic group

Children with non-CNS solid tumours who had higher educated mothers (HR_{adj} 0·66; 95% CI, 0·44–0·99; Table 3c) survived significantly longer, whereas the statistically non-significant, unadjusted better survival of children with haematological cancers whose mothers had higher education was not observed in the fully adjusted model (Table 3a), and no association with mothers' educational level was seen in children with CNS tumours (Table 3b).

The cohabitation status of the parents was associated with the survival of children with CNS tumours and non-significantly so for children with non-CNS solid tumours, whereas the number of full siblings was most strongly and statistically significantly associated with the survival of children with non-CNS solid tumours, who had a 45% increase in the risk for dying if they had one sibling (95% CI, 1·11–1·89) and a 29% increase if they had two or more full siblings (95% CI, 0.93–1·79).

In separate analyses for ALL, the risk estimates were closer to null than those for all cancers. Similarly, in separate analyses of subgroups of non-CNS solid tumours that require early surgery or more complex treatment, no difference was found from the results for the combined group of non-CNS solid tumours (data not shown).

Absolute excess risk

Five years after diagnosis, the absolute excess risk for death of the full group of childhood cancer patients was 6 per 1000 person–years for children of single parents when compared with children of cohabiting parents, 6 per 1000 person–years for children with one full sibling and 8 per 1000 person–years for children with two or more full siblings when compared with children with no full siblings (Table 4).

Discussion

In this population-based nationwide study with complete follow-up, we found that having parents with a higher SEP was associated with better survival of children with cancer. The effects of the different indicators of SEP differed, however, by cancer type. For example, the beneficial effect of having a mother with higher education and being an only child was observed only for children with non-CNS solid tumours, whereas the association with having

cohabitating parents was seen mainly for children with CNS tumours, although there were indications of association in all groups.

One explanation of our findings might be delayed diagnosis for some social groups,[21] whereby a more advanced stage of cancer at the time of diagnosis would result in poorer survival. Another explanation might be a greater communication barrier between socioeconomically disadvantaged families and the health sector. Families depend on information and guidance from health personnel, but general health literacy and communication and cognitive skills may differ by level of education, resulting in different understanding by parents who receive the same information. The problem might be exacerbated for children with cancers that require multidisciplinary treatment, like non-CNS solid tumours.[22–25]

The fact that parental cohabitation status is associated with survival implies that living with a partner might facilitate sharing of the prolonged attention and practical work required in caring for a child with cancer and also for coping with the associated mental challenges and anxiety.[9;26–28] Furthermore, cohabitation might enable one parent to reduce his or her working hours to be at the hospital. The finding that having siblings is associated with shorter survival might reflect similar mechanisms: siblings also require time and attention from parents, which could result in less attention to the sick child. The unadjusted survival plots show that differences in survival by cohabitation and number of full siblings begin 1–2 years after diagnosis, which would correspond well to the time of discharge from hospital.

Although the impact of SEP on the chances of survival among children with cancer has drawn attention, the studies published so far have been limited by patient selection (only certain cancer types) or sample size, with limited power. We performed this population-based study with complete follow-up of 3797 children with cancer during a diagnostic period from 1990 to 2009, i.e. when contemporary cancer therapies were used. Some previous studies included

only children with leukemia,[5-8,11], ALL[10] only or lymphomas.[12] In our sub-analyses for all haematological cancers and for ALL, we found no effect of SEP on survival. These results are in line with those of a large study in the USA (subset of children 0-14 year; n = 4158)[11], a smaller ALL study in Germany (n = 788)[10], as well as a Canadian study of lymphomas (n = 692). [12] In contrast, four smaller European studies (n = 714–1559) found associations between various proxies of parental SEP and survival after childhood ALL.[5–8] The associations between better survival and higher maternal education and being an only child were seen mainly for children with non-CNS solid tumours, whereas the association between having cohabiting parents and survival was attributable mainly to a protective effect in children with CNS tumours and less so in children with non-CNS solid tumours. These findings are partly in line with those of a Norwegian study of 6280 children with cancer of all types diagnosed between 1974 and 2007, in which the mother's educational level and the number of siblings were associated with survival after cancers with long-term treatment (CNS tumours, leukaemias, neuroblastomas, and bone tumours).[9] They did not find an association between parental marital status and survival, although their definition did not include cohabiting unmarried parents, which in our study constituted some 19%.

The strengths of this study include the population-based approach, almost complete inclusion of the study population, and virtually no loss to follow-up. Through the Danish Cancer Registry, we included all children with cancer diagnosed in the period 1990–2009 and investigated the impact of a range of SEP indicators on survival from various groups of cancer. We were able to obtain individual information on SEP for both married and cohabiting parents, thus taking into account the joint influence of family and social factors, acknowledging that these factors operate together. We included only cases diagnosed and treated after 1990, when systematic treatment protocols were introduced in Denmark, thus minimising any differences in cancer outcomes due to SEP.

A limitation of the study is the size of the cohort, which, however, was unavoidable, in view of the population of the country. The confidence intervals reflect this small study population, so that several estimates failed to reach statistical significance despite clear patterns of risk by social factors. Disposable household income per person would have been a better proxy than separate information on income for mothers and fathers, but this information was not available.

The potentially preventable fractions of lives depend on SEP factors that are not--and should not be--modifiable, such as the number of siblings. However, the results of our study suggest that it should be an achievable goal to optimize the survival of the worse-off subpopulations among the childhood cancer cases to the level of those patients who are best-off in terms of survival. The absolute number of deaths potentially attributable to these factors is not trivial. Further investigations should be conducted into when and how disparities are introduced in the trajectory of treatment and recovery of these children.

In conclusion, despite highly specialised, centralised treatment and free access for all children to all health services, not all patients benefit equally from improvements in survival.[28] Our results indicate that parents with short education, do not cohabit, and who have more children might need extra support during the treatment and recovery of their child. Further studies are warranted to investigate possible social differences in parent and patient adherence to treatment and follow-up and in interactions with physicians and the specific challenges for single parents and for the parents of more than one child.

Contributors

KSS, KS, SOD conceived and designed the study. KSS, LWL, KKA, JFW and SOD contributed to the collection and assembly of data. KSS, LWL, FE, KKA, JS, JFW, CJ, KS,

SOD participated in analysis and interpretation of the data. All authors contributed to writing the manuscript, and all approved the final version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Table 1. Characteristics of Danish children with cancer diagnosed in 1990–2009, for all childhood cancers combined and for three main diagnostic groups of cancer

	All childhood cancers N (%)	Haematological cancers N (%)	CNS tumours N (%)	Non-CNS solid tumours N (%)
Total	3797	1401 (37)	986 (26)	1353 (36)
Age at diagnosis (years)				
0–4	1118 (29)	489 (35)	252 (26)	360 (27)
5–9	711 (19)	291 (21)	255 (26)	156 (12)
10–14	724 (19)	251 (18)	224 (23)	237 (18)
15–19	1244 (33)	370 (26)	255 (26)	600 (44)
Sex				
Female	1672 (44)	571 (41)	469 (48)	602 (44)
Male	2125 (56)	830 (59)	517 (52)	751 (56)
Decade of diagnosis				
1990–1999	1767 (47)	630 (45)	509 (52)	621 (46)
2000–2009	2030 (53)	771 (55)	477 (48)	732 (54)
Cancer type				
Leukaemia	911 (24)	911 (65)		
Lymphoma				
Hodgkin	255 (7)	255 (18)		
Non-Hodgkin	235 (6)	235 (17)		
Central nervous system tumours	986 (26)		986 (100)	
Sympathetic nervous system tumours	136 (4)			136 (10)
Retinoblastomas	52 (1)			52 (4)
Renal tumours	121 (3)			121 (9)
Hepatic tumours	44 (1)			44 (3)
Malignant bone tumours	184 (5)			184 (14)
Soft-tissue sarcomas	212 (6)			212 (16)
Germ-cell, trophoblastic and other gonadal tumours	243 (6)			243 (18)
Carcinomas and other malignant epithelial neoplasms	361 (10)			361 (27)
Other and unspecified malignant neoplasms	57 (2)			
Mother's income[i]				
1st quartile (lowest)	950 (25)	346 (25)	242 (25)	355 (26)
2nd quartile	949 (25)	335 (24)	267 (27)	334 (25)
3rd quartile	950 (25)	375 (27)	242 (25)	317 (23)
4th quartile (highest)	948 (25)	345 (25)	235 (24)	347 (26)
Mother's education				
Basic	431 (11)	149 (11)	111 (11)	164 (12)
Vocational	2193 (58)	811 (58)	573 (58)	783 (58)
Higher	1104 (29)	419 (30)	284 (29)	379 (28)
Unknown	69 (2)	22 (2)	18 (2)	27 (2)
Father's education				
Basic	517 (14)	179 (13)	137 (14)	189 (14)
Vocational	2202 (58)	828 (59)	571 (58)	777 (57)
Higher	940 (25)	346 (25)	247 (25)	331 (24)
Unknown	138 (4)	48 (3)	31 (3)	56 (4)
Cohabitation status				
Cohabiting	3135 (83)	1161 (83)	817 (83)	1108 (82)
Living without a partner	662 (17)	240 (17)	169 (17)	245 (18)
Mother's age at child's birth (years)				

< 20	108 (3)	32 (2)	33 (3)	40 (3)
20–29	2347 (62)	824 (59)	622 (63)	869 (64)
30–39	1291 (34)	525 (37)	319 (32)	426 (31)
≥ 40	51 (1)	20 (1)	12 (1)	18 (1)
Full siblings < 19 years				
None	1424 (38)	493 (35)	350 (35)	555 (41)
One	1678 (44)	654 (47)	460 (47)	543 (40)
Two or more	695 (18)	254 (18)	176 (18)	255 (19)
Half siblings < 19 years				
None	3224 (85)	1192 (85)	819 (83)	1165 (86)
One	339 (9)	124 (9)	107 (11)	103 (8)
Two or more	234 (6)	85 (6)	60 (6)	85 (6)

[i]1st quartile: < 13 315 €, 2nd quartile: 13 315–17 006 €, 3rd quartile: 17 006–22 016 €, 4th quartile: > 22 016 euro

Table 2. Associations between parental socioeconomic position and survival from childhood cancer

			Overall survival Model 1[i]		Overall survival Model 2[ii]		Overall survival Model 3[iii]		Overall survival Model 4[iv]	
	Deaths (n)	**PY at risk**	**HR**	**95% CI**	**HR_{adj}**	**95% CI**	**HR_{adj}**	**95% CI**	**HR_{adj}**	**95% CI**
Mother's education[v]										*p* = 0·68
Basic	112	4129	1	–	1	–	1	–	1	–
Vocational	501	21892	0·86	0·70–1·05	0·87	0·71–1·07	0·91	0·73–1·12	0·93	0·75–1·15
Higher	222	10021	0·76	0·61–0·96	0·80	0·64–1·01	0·85	0·66–1·08	0·88	0·69–1·13
Unknown	93	3824	1·23	0·93–1·62	1·10	0·84–1·06	1·06	0·74–1·50	1·05	0·74–1·49
Father's education[v]										*p* = 0·60
Basic	132	4995	1	–	1	–	1	–	1	–
Vocational	495	21713	0·88	0·73–1·07	0·87	0·72–1·05	0·90	0·74–1·10	0·90	0·74–1·10
Higher	195	8775	0·81	0·65–1·01	0·83	0·66–1·03	0·89	0·70–1·13	0·89	0·70–1·13
Unknown	106	4384	1·21	0·94–1·57	1·10	0·85–1·42	1·01	0·73–1·40	1·05	0·75–1·46
Mother's income										*p* = 0·47
1st quartile (low)	253	11182	1	–	1	–	1	–	1	–
2nd quartile	241	10220	0·96	0·81–1·15	1·01	0·84–1·20	1·02	0·85–1·22	1·01	0·84–1·21
3rd quartile	195	8344	0·78	0·65–0·95	0·92	0·76–1·13	0·94	0·76–1·15	0·92	0·75–1·14
4th quartile (high)	152	6014	0·63	0·52–0·77	0·83	0·65–1·04	0·85	0·67–1·09	0·84	0·66–1·08
Mother's age (years)										*p* = 0·26
< 20	541	1021	1·33	0·93–1·90	1·34	0·94–1·91	1·22	0·84–1·75	1·20	0·83–1·72
20–29	32	23011	1	–	1	–	1	–	1	–
30–39	262	11255	0·89	0·77–1·04	0·93	0·80–1·08	0·95	0·82–1·11	0·97	0·83–1·13
≥ 40	6	473	0·50	0·22–1·11	0·50	0·22–1·11	0·51	0·23–1·13	0·53	0·24–1·20
Parents' cohabitation status										*p =0·04*
Single parent	164	5935	1	–	1	–	1	–	1	–
Cohabiting	677	29826	0·86	0·72–1·02	0·84	0·71–1·00	0·86	0·72–1·02	0·82	0·69–0·99
Number of full siblings < 19 years										*p* = 0·07
None	295	13699	1	–	1	–	1	–	1	–
One	377	15898	1·10	0·94–1·28	1·07	0·92–1·25	1·13	0·97–1·33	1·12	0·95–1·31
Two or more	169	6163	1·21	1·00–1·46	1·20	0·99–1·45	1·28	1·05–1·55	1·26	1·03–1·53

Multivariable Cox regression analyses

PY, person–years; HR, hazard ratio; CI, confidence interval

[i] Crude analysis

[ii] Adjusted for child's age, sex, decade of diagnosis, site of cancer

[iii] Adjusted for child's age, sex, decade of diagnosis, site of cancer, mother's education, father's education, mother's income and cohabitation status

[iv] Full multivariable model: adjusted for child's age, sex, decade of diagnosis, site of cancer, mother's age and SEP variables (mother's education, father's education, mother's income, cohabitation status and number of full siblings)

[v] Not adjusted for mother's income

Table 3a. Impact of socioeconomic position on overall survival of children with haematological malignancies

			Crude		Full adjusted[i]	
	Deaths (n)	PY at risk	HR	95% CI	HR_{adj}	95% CI
Mother's education[ii]						$p = 0{\cdot}98$
Basic	31	1497	1	–	1	–
Vocational	163	8027	0·98	0·67–1·44	1·05	0·71–1·56
Higher	75	3927	0·87	0·58–1·33	1·10	0·70–1·73
Unknown	35	1330	1·76	1·09–2·88	1·00	0·54–1·86
Father's education[ii]						$p = 0{\cdot}10$
Basic	34	1775	1	–	1	–
Vocational	170	8014	1·11	0·77–1·60	1·14	0·78–1·66
Higher	57	3511	0·85	0·56–1·31	0·95	0·60–1·50
Unknown	43	1482	2·01	1·28–3·16	1·94	1·07–3·49
Mother's income						$p = 0{\cdot}35$
1st quartile (lowest)	80	4307	1	–	1	–
2nd quartile	80	3499	1·12	0·83–1·52	1·17	0·85–1·60
3rd quartile	59	3280	0·68	0·48–0·96	0·81	0·55–1·20
4th quartile (highest)	50	2249	0·65	0·46–0·93	0·82	0·53–1·28
Mother's age (years)						$p = 0{\cdot}17$
< 20	10	299	1·59	0·84–3·01	1·65	0·86–3·14
20–29	167	8139	1	–	1	–
30–39	91	4715	0·86	0·66–1·11	1·03	0·78–1·34
≥ 40	1	180	0·24	0·03–1·70	0·27	0·04–1·92
Parents' cohabitation status						$p = 0{\cdot}65$
Single parent	51	2292	1	–	1	–
Cohabiting	218	11042	0·90	0·67–1·22	0·92	0·66–1·29
Number of full siblings < 19 years						$p = 0{\cdot}66$
None	95	4812	1	–	1	–
One	123	6332	0·98	0·75–1·28	1·08	0·81–1·44
Two or more	51	2190	1·08	0·77–1·52	1·18	0·83–1·69

PY, person–years; HR, hazard ratio; CI, confidence interval

[i] Adjusted for child's age and sex, decade of diagnosis, type of cancer, mother's age and SEP variables (parental education, income, cohabitation status and number of full siblings)

[ii] Not adjusted for mother's income

Table 3b. Impact of socioeconomic position on overall survival of children with CNS tumours

			Crude		Full adjusted[i]	
	Deaths (n)	**PY at risk**	**HR**	**95% CI**	**HR_{adj}**	**95% CI**
Mother's education[ii]						*p* = 0·74
Basic	29	1110	1	–	1	–
Vocational	156	5810	1·04	0·70–1·55	1·20	0·79–1·82
Higher	74	2527	1·02	0·66–1·56	1·17	0·73–1·89
Unknown	23	869	1·28	0·74–2·21	1·42	0·73–2·78
Father's education[ii]						*p* = 0·65
Basic	43	1327	1	–	1	–
Vocational	150	5764	0·81	0·58–1·14	0·82	0·58–1·17
Higher	65	2214	0·84	0·57–1·23	0·89	0·58–1·36
Unknown	24	1012	0·93	0·56–1·53	0·73	0·39–1·36
Mother's income						*p* = 0·74
1st quartile (lowest)	78	2729	1	–	1	–
2nd quartile	75	2961	0·93	0·68–1·28	0·92	0·66–1·28
3rd quartile	61	2154	0·74	0·53–1·05	0·84	0·58–1·22
4th quartile (highest)	48	1471	0·70	0·49–0·99	0·86	0·55–1·34
Mother's age, years						*p* = 0·59
< 20	10	289	1·26	0·67–2·40	1·22	0·63–2·38
20–29	158	6186	1	–	1	–
30–39	91	2763	1·18	0·91–1·53	1·20	0·92–1·58
≥ 40	3	77	1·06	0·34–3·33	1·03	0·33–3·28
Parents' cohabitation status						*p* = 0·04
Single parent	53	1482	1	–	1	–
Cohabiting	209	7834	0·79	0·58–1·06	0·70	0·51–0·97
Number of full siblings < 19 years						*p* = 0·58
None	97	3294	1	–	1	–
One	116	4488	0·90	0·68–1·17	0·89	0·67–1·18
Two or more	49	1533	1·03	0·73–1·45	1·03	0·72–1·48

PY, person–years; HR, hazard ratio; CI, confidence interval

[i] Adjusted for child's age and sex, decade of diagnosis, type of cancer, mother's age and SEP variables (parental education, income, cohabitation status and number of full siblings)

[ii] Not adjusted for mother's income

Table 3c. Impact of socioeconomic position on overall survival in children with non-CNS solid tumours

			Crude		Full adjusted[i]	
	Deaths (n)	**PY at risk**	**HR**	**95% CI**	**HR_{adj}**	**95% CI**
Mother's education[ii]						*p* = 0·26
Basic	49	1494	1	–	1	–
Vocational	178	7874	0·70	0·51–0·96	0·79	0·56–1·11
Higher	71	3410	0·59	0·41–0·85	0·66	0·44–0·99
Unknown	32	1598	0·87	0·56–1·36	0·88	0·48–1·63
Father's education[ii]						*p* = 0·46
Basic	53	1818	1	–	1	–
Vocational	171	7771	0·78	0·58–1·07	0·81	0·59–1·11
Higher	71	2956	0·79	0·55–1·13	0·97	0·65–1·43
Unknown	35	1830	0·89	0·58–1·37	0·87	0·45–1·54
Mother's income						*p* = 0·62
1st quartile (lowest)	94	4114	1	–	1	–
2nd quartile	82	3671	0·88	0·65–1·19	0·88	0·65–1·20
3rd quartile	73	2813	0·94	0·69–1·27	1·11	0·80–1·55
4th quartile (highest)	51	2179	0·56	0·40–0·80	0·81	0·53–1·24
Mother's age, years						*p* = 0·39
< 20	11	412	1·15	0·63–2·12	0·87	0·46–1·65
20–29	209	8473	1	–	1	–
30–39	78	3682	0·76	0·59–0·99	0·81	0·61–1·07
≥ 40	2	211	0·41	0·10–1·67	0·56	0·14–2·28
Parents' cohabitation status						*p* = 0·15
Single parent	57	2105	1	–	1	–
Cohabiting	243	10673	0·90	0·68–1·20	0·80	0·59–1·08
Number of full siblings < 19 years						*p* = 0·02
None						
One	100	5399	1	–	1	–
Two or more	134	5003	1·42	1·09–1·84	1·45	1·11–1·89
	66	2377	1·47	1·08–2·00	1·29	0·93–1·79

PY, person–years; HR, hazard ratio; CI, confidence interval

[i] Adjusted for child's age and sex, decade of diagnosis, type of cancer, mother's age and SEP variables (parental education, income, cohabitation status and number of full siblings)

[ii] Not adjusted for mother's income

Table 4. Absolute excess risk for death after 5 years in children with any paediatric cancer, by parental cohabitation status and number of full siblings

	Death rate per 1000 person years (95% CI)	Deaths prevented if all children had the best rate, per 1000 person–years
Cohabitation status		
Single parents	51 (38–67)	6
Cohabiting parents	45 (33–60)	Reference
Number of full siblings		
None	42 (30–57)	Reference
One	48 (35–64)	6
Two or more	50 (37–66)	8

Figure 1. Kaplan–Meier plot illustrating the probability of survival stratified by mothers' education (A), income (B), parental cohabitation (C) and number of full siblings (D)

Figure 1A

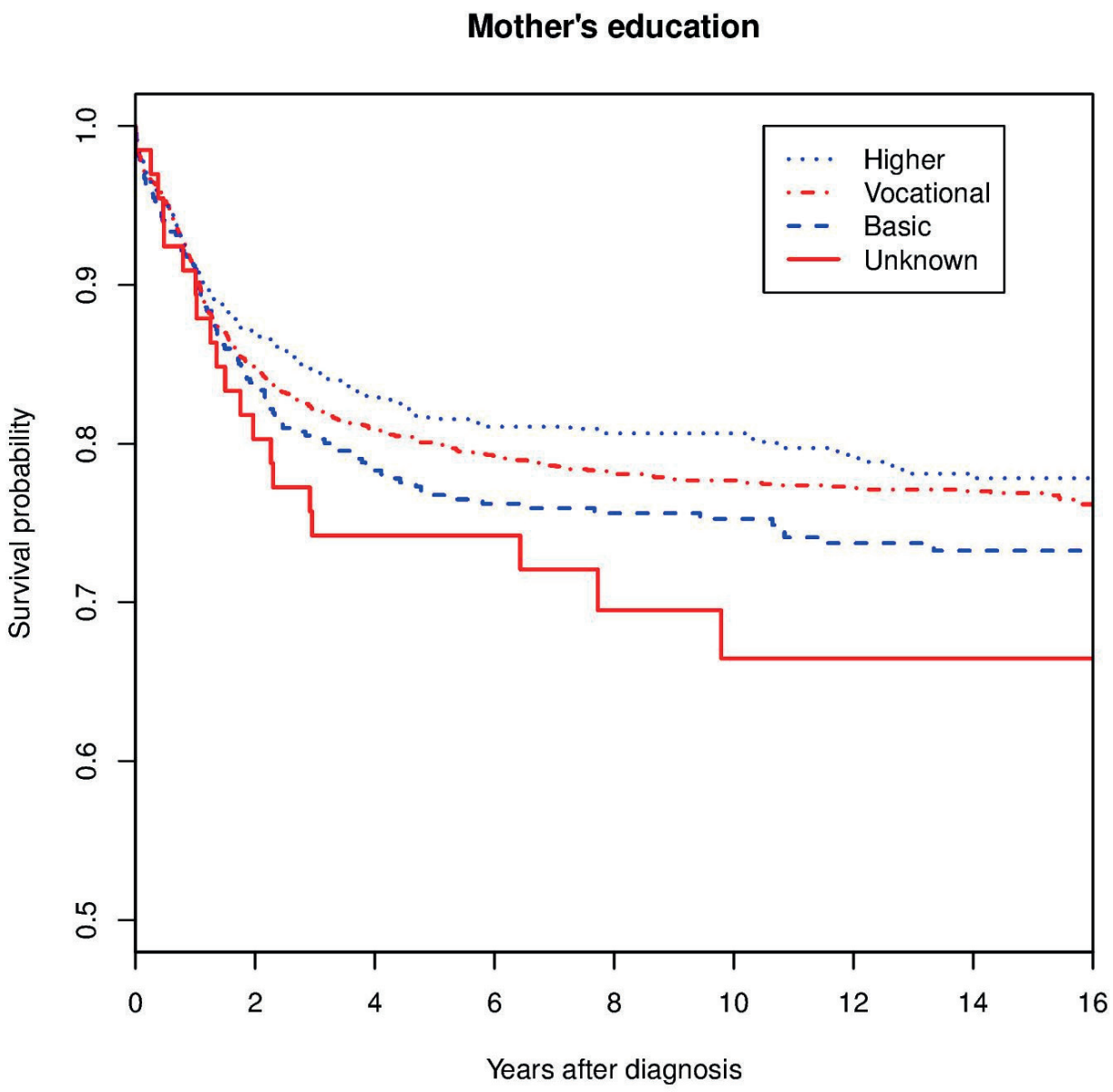


Figure 1B

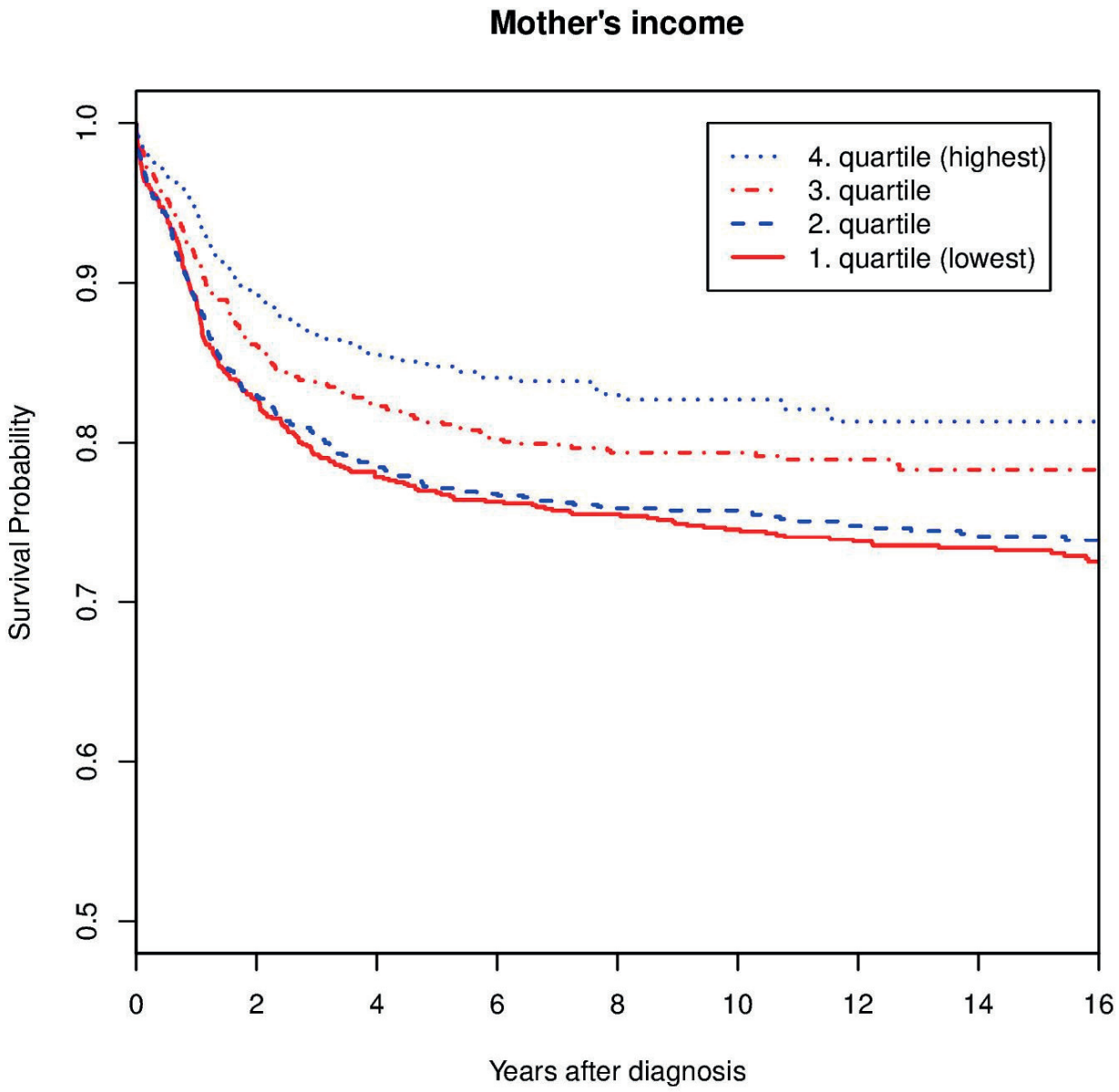

Mother's income
4. quartile (highest)
3. quartile
2. quartile
1. quartile (lowest)
Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0
2
4
6
8
10
12
14
16
Years after diagnosis

Figure 1C

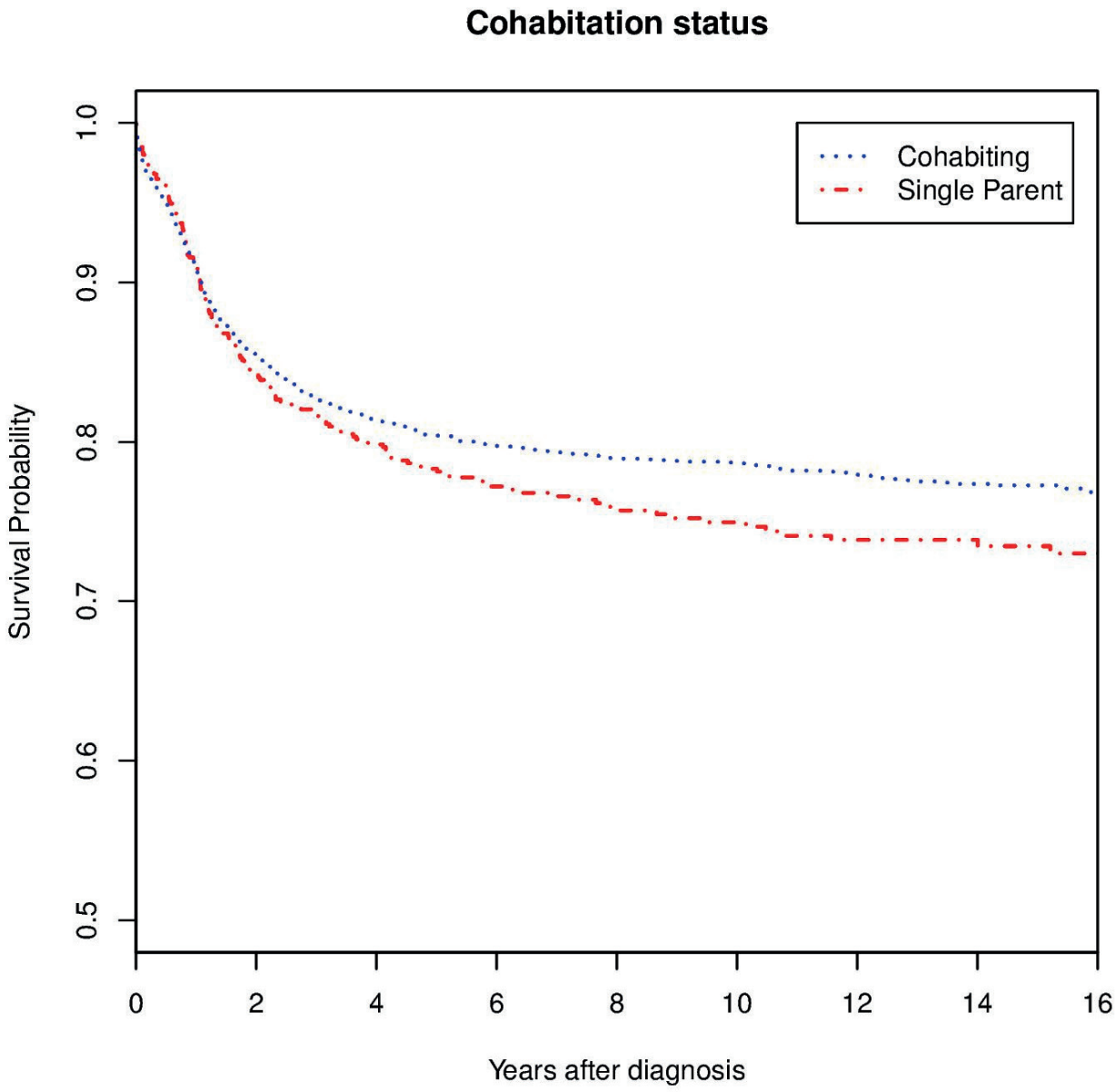
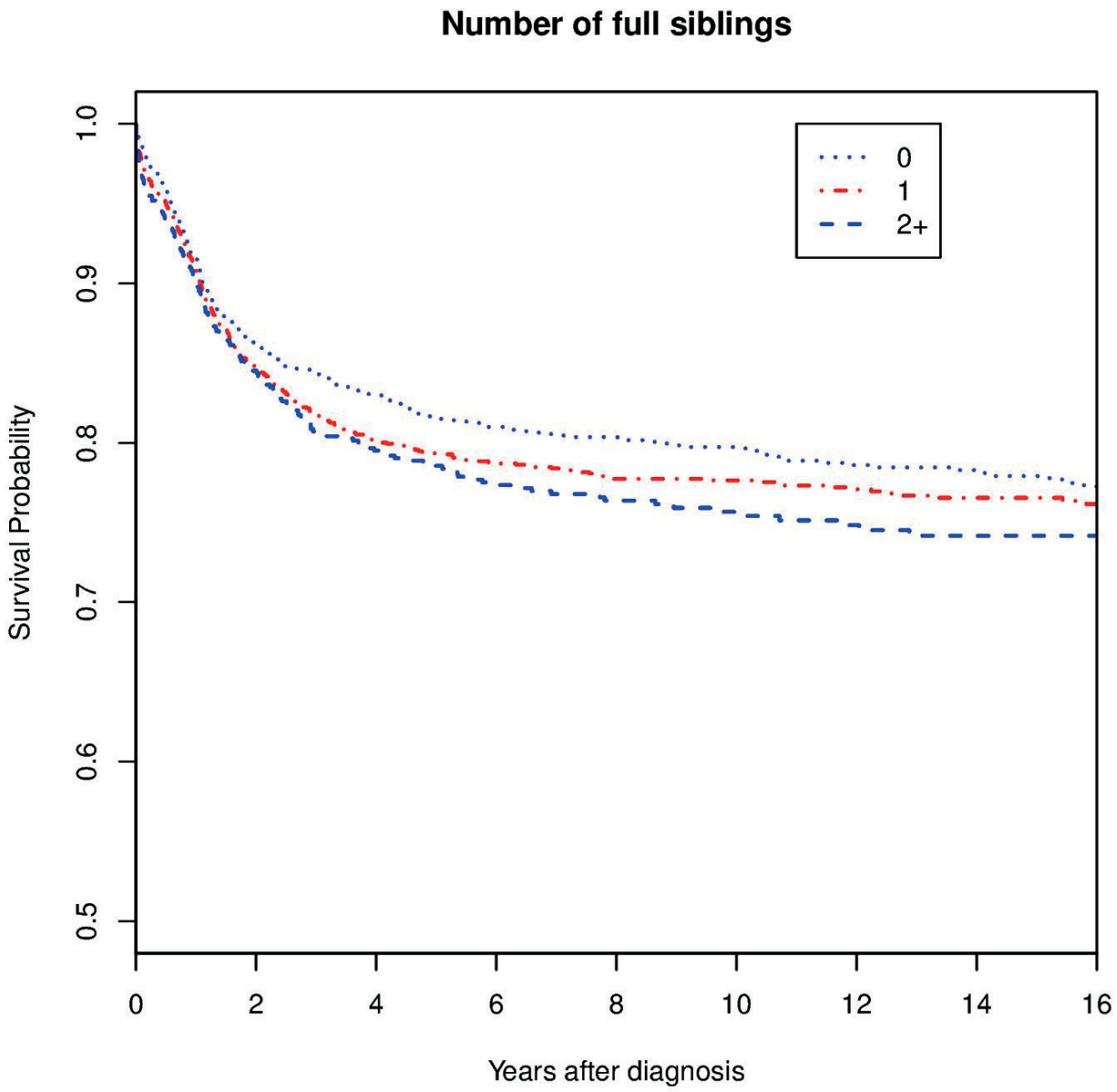

Cohabitation status
Cohabiting
Single Parent
Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0
2
4
6
8
10
12
14
16
Years after diagnosis

Figure 1D


Number of full siblings
Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0
2
4
6
8
10
12
14
16
Years after diagnosis
0
1
2+

References

1 Wolfe I, Thompson M, Gill P, et al. Health services for children in western Europe. *Lancet* 2013; **381**: 1224–34.
2 Rachet B, Woods LM, Mitry E, et al. Cancer survival in England and Wales at the end of the 20th century. *Brit J Cancer* 2008; **99**: S2-10
3 Dalton SO, Schuz J, Engholm G, et al. Social inequality in incidence of and survival from cancer in a population-based study in Denmark, 1994–2003: Summary of findings. *Eur J Cancer* 2008; **44**: 2074–85.
4 Alberto Q, Roberto L, Carlo M, et al. Socio-economic inequalities: A review of methodological issues and the relationships with cancer survival. *Crit Rev Oncol/Hematol* 2013; **85**: 266-77.
5 Coebergh JW, van der Does-van den Berg, Hop WC, et al. Small influence of parental educational level on the survival of children with leukaemia in The Netherlands between 1973 and 1979. *Eur J Cancer* 1996; **32A**: 286–9.
6 Lightfoot TJ, Johnston WT, Simpson J, et al. Survival from childhood acute lymphoblastic leukaemia: the impact of social inequality in the United Kingdom. *Eur J Cancer* 2012; **48**: 263–9.
7 Njoku K, Basta N, Mann KD, McNally RJ, Pearce MS. Socioeconomic variation in survival from childhood leukaemia in northern England, 1968–2010. *Br J Cancer* 2013; **108**: 2339–45.
8 Sergentanis T, Dessypris N, Kanavidis P, et al. Socioeconomic status, area remoteness, and survival from childhood leukemia: results from the Nationwide Registry for Childhood Hematological Malignancies in Greece. *Eur J Cancer Prev* 2013; **22**: 473–9.
9 Syse A, Lyngstad TH, Kravdal O. Is mortality after childhood cancer dependent on social or economic resources of parents? A population-based study. *Int J Cancer* 2012; **130**: 1870–8.
10 Erdmann F, Kaatsch P, Zeeb H, Roman E, Lightfoot T, Schuz J. Survival from childhood acute lymphoblastic leukaemia in West Germany: Does socio-demographic background matter? *Eur J Cancer* 2014; **50**: 1345–53.
11 Kent EE, Sender LS, Largent JA, Anton-Culver H. Leukemia survival in children, adolescents, and young adults: influence of socioeconomic status and other demographic factors. *Cancer Causes Control* 2009; **20**: 1409–20.
12 Darmawikarta D, Pole JD, Gupta S, Nathan PC, Greenberg M. The association between socioeconomic status and survival among children with Hodgkin and non-Hodgkin lymphomas in a universal health care system. *Pediatr Blood Cancer* 2013; **60**: 1171–7.
13 Gjerstorff ML. The Danish Cancer Registry. *Scand J Public Health* 2011; **39**(7 Suppl): 42–5.
14 Birch JM, Marsden HB. A classification scheme for childhood cancer. *Int J Cancer* 1987; **40**: 620–4.
15 Thygesen LC, Daasnes C, Thaulow I, Bronnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. *Scand J Public Health* 2011; **39**(7 Suppl): 12–6.
16 Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006; **53**: 441–9.
17 Baadsgaard M, Quitzau J. Danish registers on personal income and transfer payments. *Scand J Public Health* 2011; **39**(7 Suppl): 103–5.
18 Jensen VM, Rasmussen AW. Danish education registers. *Scand J Public Health* 2011; **39**(7 Suppl): 91–4.
19 Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011; **39**(7 Suppl): 22–5.

20 R Core Team. R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing, 2014 (http://www.R-project.org/).
21 Ahrensberg JM, Schroder H, Hansen RP, Olesen F, Vedsted P. The initial cancer pathway for children--one-fourth wait more than 3 months. *Acta Paediatr* 2012; **101**: 655–62.
22 Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey SG. Indicators of socioeconomic position (part 1). *J Epidemiol Community Health* 2006; **60**: 7–12.
23 Frederiksen BL, Brown PN, Dalton SO, Steding-Jessen M, Osler M. Socioeconomic inequalities in prognostic markers of non-Hodgkin lymphoma: analysis of a national clinical database. *Eur J Cancer* 2011; **47**: 910–7.
24 Dalton SO, Frederiksen BL, Jacobsen E, et al. Socioeconomic position, stage of lung cancer and time between referral and diagnosis in Denmark, 2001–2008. Br J Cancer 2011; **105**: 1042–8.
25 Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey SG. Indicators of socioeconomic position (part 2). *J Epidemiol Community Health* 2006; **60**: 95–101.
26 Patterson JM, Holm KE, Gurney JG. The impact of childhood cancer on the family: a qualitative analysis of strains, resources, and coping behaviors. *Psychooncology* 2004; **13**: 390–407.
27 Botting B. Mortality in childhood. In: Drever F, Whitehead M, editors. *Health Inequalities*. London: Office for National Statistics; 1997; pp. 83–94.
28 Judge K, Benzeval M. Health inequalities: new concerns about the children of single mothers. *Br Med J* 1993; **306**: 677–80.
29 Gatta G, Botta L, Rossi S, et al. Childhood cancer survival in Europe 1999–2007: results of EUROCARE-5--a population-based study. *Lancet Oncol* 2014; **15**: 35–47.

Article VI

Family characteristics and survival from childhood haematological malignancies in Denmark, 1973-2006

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Contribution statement: FE and JS developed the study concept and design. JS, JFW, FE, TL, AB and GF contributed to the data collection and AB and GF helped with the data management. FE conducted the statistical data analyses. FE, JS, JFW, KS, SOD, HZ, ID, TL and KSS participated in the interpretation of the results. FE prepared the first draft of the manuscript. FE, JS, JFW, KS, SOD, HZ, ID, TL and KSS revised it critically for intellectual content. All authors read and approved the final version of the manuscript.

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Family characteristics and survival from childhood haematological malignancies in Denmark, 1973-2006

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Abstract

Little is known about the role of family characteristics on survival from childhood haematological malignancies, which we studied in a nationwide cohort of Danish children. All children with haematological malignancies born and diagnosed between 1973 and 2006 before the age of 20 years (N=1 819) were followed for 10 years. Cox proportional hazards models estimating hazard ratios (HR) and 95% confidence intervals (CI) were calculated. Increasing birth order and having siblings was associated with worse survival from acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML); the associations with AML were stronger and statistically significant. HRs of 1.62 (CI 0.85; 3.09) and of 5.76 (CI 2.01; 16.51) were observed for 4th or later born children with ALL and AML, respectively. Children with older parents showed a tendency of inferior ALL survival, while for AML young maternal age was related to poorer survival. Based on small numbers, NHL survival showed associations with having siblings and with parental age. Overall, results for the full cohort were similar to those diagnosed from 1990 onwards. Family characteristics may have an impact on survival from haematological malignancies in Danish children. Further research should elaborate potential underlying mechanisms, in particular adherence to therapy and physicians-parents interaction.

Introduction

Childhood haematological cancers are a heterogeneous group of malignancies, treated differently and with dissimilar prognosis (1). Over the past decades, advances in tumour biology, risk grouping, and pharmacology have led to substantial improvements in treatment of childhood cancers in particular for acute lymphoblastic leukaemia (ALL) and non-Hodgkin lymphoma (NHL)(1-3). Diagnostic procedures and treatment protocols are nowadays largely standardized within developed countries (3-8). In the Nordic countries treatment of childhood cancers has virtually been identical since the early 1990s (3, 5, 6). Almost all paediatric haematological malignancy patients are treated according to the treatment schemes developed by the collaborative study group NOPHO (Nordic Society of Paediatric Haematology and Oncology) (3, 5, 6) with specific treatment protocols depending on type, prognostic risk group and stage of cancer.

One of the basic principles of the Danish welfare system is equal rights to social security for all citizens, including benefits for families with children as well as tax-funded free health care services.(9) Childhood cancer treatment is centralized to four highly specialized paediatric oncology centres that offer uniform diagnostics and treatment independently of family circumstances or socioeconomic background. Therefore it would be expected that there are fairly equal survival rates across social groups and independent of family circumstances. However, besides physician's compliance to the treatment protocols, parents' and child's adherence to the treatment and supportive care as well as the interaction between families and physicians may affect survival.

For adult cancers in Denmark, it is well established that socioeconomic characteristics influence survival, with cancer patients with higher education or higher income reaching superior survival rates (10). Little is known about the potential role of social conditions and family circumstances on childhood cancer survival. Only one ongoing study addressed survival differences related to socioeconomic position in Danish children(11).

Internationally, only few studies have investigated the relationship between family and social conditions and survival from childhood cancer, mainly focussing on leukaemia survival and with very diverse findings, even within Europe (12-19).

In this nationwide Danish population-based study, we evaluate for the first time whether family circumstances such as birth order, number of siblings, parental age at child's cancer diagnosis and place of residence affect survival from paediatric haematological malignancies, in order to investigate whether Danish children irrespective of family characteristics benefits equally from the improvements in therapy that have been made over the last decades.

Material and Methods

Denmark has a civil registration system with unique personal identification numbers, national population-based administrative registries such as the Danish Cancer Registry or the Danish Medical Birth Registry, and legislation that permits and supports registry-based research (20). Since 1968, all residents of Denmark have been assigned a civil personal registration number (CPR number), which is used in all national registries, enabling accurate linkage of information between registries (21).

Study population

Childhood haematological malignancies were defined as any leukaemia or lymphoma diagnosed in patients up to 19 years of age inclusively. Our study population comprised all children born and diagnosed with any haematological malignancy in Denmark between 1 January 1973 and 31 December 2006.1 819 eligible children with haematological malignancies were identified for the defined time period in the Danish Cancer Registry.

Haematological malignancies were classified according to the International Classification of Childhood Cancer, (ICCC 1st version; i.e., the Birch and Marsden Classification) (22)

until 2003 and ICCC 3rd version (23) thereafter) which classifies haematological malignancies according to the IDC-O-1 or IDC-O-3 nomenclature into the following 2 main diagnostic groups and specific subgroups: I. Leukaemias, myeloproliferative disease and myelodysplastic diseases (Leukaemias), and II. Lymphomas and reticuloendothelial neoplasms (Lymphomas).

Family characteristics

Family circumstances were defined by a range of characteristics including birth order, number of full and half siblings, parental age at diagnosis as well as place of residence. Information on these characteristics for the study subjects was obtained for the date of the cancer diagnosis by data linkage to the Danish Medical Birth Register (24) and the Central Population Registry (CPR). The unique CPR number includes date of birth and sex and allows linkage to first-degree relatives via the Danish Civil Registration System considered to be 100% correct (21).

Linkage of the CPR number of the child with the mother and the father enabled, besides receiving information on parental age at diagnosis (grouped into ≤ 25, 26-30, 31-35, 36-40, 41-45, ≥46 years), the identification of full siblings and half siblings (21). Full siblings were defined as having the same mother and father, and half siblings as having either the same mother or the same father (stillborn children excluded).

From the birth register we obtained data on birth order (24). Birth order was defined by counting all live-births of the same mother (1st born, 2nd born, 3rd born, and 4th born and later). Multiple births were assigned the same birth order to multiples and later births accounted for the real number of siblings, i.e. for twins the next child would be the 3rd born. Information on place of residence at diagnosis was obtained from the Danish Cancer Registry and classified by level of municipality. Provincial cities were defined as those cities with >10,000 inhabitants; rural areas as rural municipalities with <10,000 inhabitants;

and peripheral rural areas as municipalities more than 40 km from a local centre with proper employment possibilities and no shared border with a municipality centre (25).

Statistical methods

We defined overall survival as outcome of our study. Dates of death, disappearance and emigration were obtained until 7 October 2013, collected by the Central Population Registry, and used as follow-up information (21). Children were observed from the date of cancer diagnosis until their death from any cause, emigration, the end of the 10 years follow-up or 7 October 2013, whichever came first. We censored at 10 years follow-up as very few disease-related events occur afterwards, whereas the incidence of competing risks rises.

Cox proportional hazards models were used to assess the impact of family characteristics on overall survival with time since diagnosis as underlying time scale. As the proportional hazard assumptions did not hold when collapsing all haematological malignancies in one group, we analysed the three large subgroups (ALL, AML, NHL) separately, and differing results confirmed this choice. Although Hodgkin lymphoma was another sizable group of clinical relevance, survival (see below) was very high (> 90%), so that the small number of events precluded meaningful survival analyses by subgroups of family circumstances. The multiple regression models were built in two steps. Initially, we adjusted for the following well-established prognostic factors: child's age at diagnosis (3, 5, 6) (grouped into < 1 year, 1-5, 6-9, and 10-14 years, and 15-19 years), sex (5, 26), as well as diagnosis before 1990 *versus* afterwards (3, 5, 21). In a second set of analyses, additional adjustments were made for the possible mediating effects of other family variables (fully adjusted models). The specific adjustment variables varied between family characteristics (see Figure 1). In additional analyses to investigate whether the observations made in the larger cohort of patients diagnosed 1973-2006 held true for the more recent cohort of patients, we restricted the study population to cases of ALL and AML diagnosed from

1990 onwards as treatment has been particularly standardised since then. Results were expressed as adjusted hazard ratios (HRs) with corresponding 95% confidence intervals. Trend tests were also performed, using the same categories as for the main analysis.

To investigate when survival differences emerged we calculated unadjusted survival probabilities for ALL and AML by birth order, number of full siblings and parental ages at diagnosis, using Kaplan-Meier curves and the log-rank test.(27)

Sensitivity analyses were performed to evaluate if (i) adjusting mutually for birth order and number of full siblings as well as number of full and half siblings in the respective multiple Cox models, and if (ii) distinguishing between having either a young/old mother or a young/old father compared to having two young parents (both ≤ 25 years) or having two old parents (both ≥ 46 years) modified the associations.

All statistical analyses were performed using Stata 13 (28).

Results

Of the 1 819 children diagnosed with haematological malignancies between 1973 and 2006, 59% were boys and 40% occurred in 1 to 4 years old children (Table 1). More than half of the cases were diagnosed with ALL (56%), followed by Hodgkin lymphoma compromising 13% of all cases, AML (12%) and NHL (9%). Among all cohort members, 834 (46%) were firstborns and 664 (37%) were second born. 285 (16%) were the only child at date of diagnosis. Most families were living in provincial cities (53%). Mothers and fathers were most frequently aged 31-35 years at diagnosis. Overall 10-years survival was 72.1%, based on 504 deaths. Survival was slightly better for girls than boys (72.7% vs. 71.6%), highest for children aged 1-4 years at diagnosis (76%) and superior for children with Hodgkin lymphoma (91%).

Family characteristics and survival from acute lymphoblastic leukaemia

The Cox regression models suggested dissimilarities in ALL survival by some family characteristics, although most of the associations did not reach statistical significance in either the restricted analysis including children diagnosed with ALL from 1990 onwards (Table 2) or in the analysis including all ALL children diagnosed in the full period 1973-2006 (Figure 1a). Similar results were seen across models (only the fully adjusted models are shown in the figures) and for the full and restricted time periods. Poorer survival was observed for children born as 3rd child or later compared to those with lower birth order, with worst survival for 4th and later born children (non-significant HRs of 1.62; 95% CI 0.85; 3.09 in the fully adjusted model; Figure1a). A tendency of different survival was also noted by number of full or/and half siblings, with best survival for children without any siblings (Figure 1a; Table 2). Mutually adjusting for birth order and number of siblings in one model abolished the association between number of siblings and survival, but did not substantially alter the HRs for the effect of birth order (data not shown).

There was evidence to suggest that children with a mother or father of older age were likely to have a poorer survival with elevated HRs close to 1.5 for children with a mother aged 46 years or older (Figure 1a;Table 2). The trend test for maternal and paternal age reached statistical significance for the diagnostic period since 1990 (maternal age p = 0.04; paternal age p = 0.03). Sensitivity analysis distinguishing between having either an older mother or an older father and having two older parents (both ≥ 46 years) showed that particularly the latter was related to poorer survival (data not shown).

Visual inspection of survival curves did not clearly indicate a time point from which on survival dissimilarities emerged (Figure 2a).

A tendency of poorer survival was observed for children living in peripheral rural areas only among the children diagnosed since 1990 (Table 2).

Family characteristics and survival from acute myeloid leukaemia

Associations between birth order, number of full and/or half siblings and AML survival were more pronounced than for ALL and often statistically significant. Associations were stronger for the diagnostic period 1990 and onwards (Table 2) compared to the full study period (Figure 1b). Particular strong dissimilarities in survival were observed for birth order, with statistically significant increasing HRs by increasing birth order (p for trend ≤ 0.01), resulting in a significant HR of 5.76 (95% CI 2.01; 16.51) for children born 4th or later in the fully adjusted model; among children diagnosed since 1990 the HR was even 7.58, although the confidence interval was wide (95% CI 1.41; 40.74). Sensitivity analyses, mutually adjusting for birth order and number of siblings, showed even higher HRs for the association with birth order, while the associations with number of full/ full and half siblings were entirely eliminated (data not shown).

A linear relationship of mother's age at diagnosis, particularly strong for children diagnosed since 1990 (p for trend ≤ 0.01*)* appeared to affect survival from AML, with poorer survival among children with a young mother (≤ 25 years; HR 1.62; 95% CI 0.81; 3.22 for the entire study period; HR 4.47; 95% CI 1.64; 12.20 for children diagnosed since 1990) and better survival among children with older mothers. The effect of better survival among children with older mothers was driven by the good survival of children having both an older mother and an older father with a HR of 0.55 in the fully adjusted model (95% CI 0.17; 1.80) (data not shown).

Family characteristics and survival from non-Hodgkin lymphoma

Wide confidence intervals reflect the small numbers available for the analyses of NHL survival (Figure 1c). Poorer NHL survival was observed for children with full and/or half siblings compared to only children. Although estimates for most of the categories were not statistically significant, the trend test reached significance (p = 0.02). No clear relationship

was found for number of full siblings. Young parental age might be related to poorer survival, but numbers were small.

Discussion

Main findings

The findings of increasing birth order, numbers of siblings and parental age being associated with poorer survival among childhood haematological cancer patients emphasize the need to include more than just cancer biology and treatment in survival analyses, not least since the impact of these family features might be potentially as strong as that of traditional risk factors (3).

International comparison

Family characteristics such as number of siblings, birth order and parental age have been postulated to be related to the occurrence of childhood cancer (29-36), but evidence on their role as prognostic factors for leukaemia and in particular lymphoma is sparse and with conflicting findings (16-19, 37, 38). In line with our results, a large Norwegian study on children with cancer reported that having no siblings was associated with mortality reductions of almost 20%.(16) In contrast, a study from Greece on children diagnosed with ALL in the late 1990s-early 2000s observed better prognosis for children with increasing number of siblings (18). However, this finding was not confirmed in a recent follow-up study(17). Likewise and in contrast to our findings for Denmark, no relationship between survival from AML and number of siblings was observed there (17).

To our knowledge, so far no investigation has addressed the possible importance of parental age at the child's cancer diagnosis. Nevertheless, analyses of mother's age at child's birth from Norway did not indicate a relationship with childhood cancer survival, whereas the most recent findings from Greece indicated better survival from AML with older maternal age (16, 17), which is basically what we observed for maternal age at child's AML diagnosis.

With respect to place of residence, a study from Australia, a country with vast areas of very low density population, reported better leukaemia survival for children living in major cities compared with those living elsewhere. However, no evidence of geographical variation in survival was observed for children with lymphoma (37). Living in rural areas was also associated with less favourable prognosis in recent multi-national findings from Bulgaria, Turkey and Russia (38). This may likely contrast the small size of Denmark and the lack of real remote areas.

However, dissimilarities in welfare systems, including access to health care and public family support, coverage and distance to treatment facilities, lifestyle and socio-cultural aspects, treatment protocols as well as methodological differences between studies make an international comparison challenging. A crucial question is to what extent the observed differences across studies are real (reflecting different impact of family characteristic due to differences in health care and social stratification, true overall health inequity) or to what extent differences can be explained by features of the studies(including differences in data sources, data collection, cancer type, and diagnostic period).

National context and comparison

Our observed associations are particularly interesting in the context of recent findings about the role of socioeconomic position and childhood cancer survival in Denmark. Whereas parental education and mother's income did not appear to impact on survival from childhood haematological malignancies (11), the demands on families and their social resources (as measured by birth order, number of siblings and parental age at child's diagnosis in the present study) appear to be more relevant than the socioeconomic situation of a family in Denmark, particularly for survival from AML.

The well documented impact of social factors on cancer outcome in adults (10) is associated with differences in the time of diagnosis, in the biological characteristics of the tumour, in the treatments given or in individual factors, such as lifestyle or the presence of comorbidities.(39-41) Nevertheless, dissimilarities in survival from paediatric haematological malignancies would be expected to be less likely related to co-morbidities and children's lifestyle, but might include further reasons such as adherence to treatment recommendations(42). Treatment of lymphoblastic malignancies (ALL and NHL) lasts over several years, and poor adherence to oral maintenance therapy may have negative impact on cure rates (43). As soon as the child is discharged from hospital, parents are responsible to comply with the recommendations for continuation of a highly demanding therapy, including daily drug administration and frequent medical outpatient appointments. Accordingly, findings from the UK indicate that ALL survival dissimilarities by socioeconomic status emerged about the time when treatment management required parental/child's adherence, i.e. from the time of oral treatment in the outpatient setting and hypothesized that this may due to treatment compliance (14). In our study, children with siblings as well as children of higher birth order showed indeed poorer survival. However, the pattern of diverging survival curves after the beginning of home-administered therapy seen in the UK was not reflected in the survival curves for Danish children. Moreover, we observed even stronger effects of number of siblings for AML survival, a disease which is entirely treated in hospital. Thus, the number of siblings might not only be of relevance for the period of the home-administered maintenance therapy for ALL, but for the entire treatment period of AML and ALL. Smaller families may be able to devote more time to assisting the sick child and may better cope with the complex and demanding therapy in general (40). However, the associations seen between number of siblings and leukaemia survival, both ALL and AML, were mainly driven by the effect of birth order. Higher birth order (34) and more social contacts (44) could, according to the adrenal hypothesis (45) suggest that the lymphoblastic malignancies emerged in spite of high glucocorticosteroid exposure and thus were more glucocorticosteroid resistance when diagnosed, a feature

associated with poor prognosis (46). Nevertheless, this explanation would only apply for the observed relationship between birth order and survival from ALL. However, the relationship between survival and birth order noticed for children with AML was even stronger than for ALL and more pronounced for cases diagnosed in the more recent time characterised by a standardised treatment approach (3, 5, 6). Perhaps firstborns might receive more attention from their parents than later born children, possibly positively affecting abilities to cope with the cancer diagnosis, the demanding therapy and related circumstances, but this is speculation.

The poorer survival from AML and NHL reported in this study for children with young mothers (for NHL both mothers and fathers) may possibly also reflect the capacity to cope with the complex therapy, and may be particularly challenging for young parents (47). This might also explain the better survival from AML and NHL among children with older mothers. However, as the parental age-survival relationship seems to be reversed for ALL, interpretation of these findings remains challenging and unclear at present.

Whether children lived in Copenhagen or in more rural areas appeared not to be of high relevance for survival; solely for the very few children living in peripheral rural areas and diagnosed with ALL, poorer survival for the most recent diagnostic period since 1990 was noticed. This overall lack of residential effects is plausible as four specialized paediatric clinics cover the entire country, with relatively short distances to the treating centre from most places in Denmark. Further, treatment is highly standardized,(3, 5, 6) irrespective of the treating hospital.

Strengths and weaknesses

Since this study is a nationwide, population- and register-based cohort study with little risk of bias, the only weakness is the lack of socioeconomic characteristics such as parental education or income as potential confounding factors. Furthermore, no information on

parental marriage and cohabitation status was available which has been hypothesized to be associated with treatment adherence (42). An inherent limitation is the size of our cohort, albeit unavoidable as it reflects the population size of the country. Most of the survival estimates failed to reach statistical significance while there were indications of possibly strong effects.

It is noteworthy that this study is the first investigation on this topic in Denmark and one of very few from Europe. With the national and register-based approach our study virtually covered all cancer cases with a complete follow-up and thus provided a factual reflection of the situation in Denmark.

Conclusion

Despite of the highly specialized treatment of children with cancer and universal healthcare coverage in Denmark, not all children appear to benefit equally from improvements in survival. Our data further suggest that cancer biology and treatment are not the only factors influencing survival. This may in the future call for targeted social interventions and psychological support in order to further improve survival rates and reduce inequity. However, further studies are warranted to elaborate the relationship and underlying mechanism of specific family characteristics and survival, particularly with regard to differential adherence to therapy and related interactions of families with paediatric oncologists in Denmark and elsewhere.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Reference list

1. Gatta G, Botta L, Rossi S, Aareleid T, Bielska-Lasota M, Clavel J, et al. Childhood cancer survival in Europe 1999–2007: results of EUROCARE-5—a population-based study. The Lancet Oncology. 2014;15(1):35-47.
2. de Nully Brown P, Olsen JH, Hertz H, Carstensen B, Bautz A. Trends in survival after childhood cancer in Denmark, 1943-87: a population-based study. Acta Paediatrica. 1995;84(3):316-24.
3. Schmiegelow K, Forestier E, Hellebostad M, Heyman M, Kristinsson J, Soderhall S, et al. Long-term results of NOPHO ALL-92 and ALL-2000 studies of childhood acute lymphoblastic leukemia. Leukemia. 2010 Feb;24(2):345-54. PubMed PMID: 20010622.
4. Moricke A, Zimmermann M, Reiter A, Henze G, Schrauder A, Gadner H, et al. Long-term results of five consecutive trials in childhood acute lymphoblastic leukemia performed by the ALL-BFM study group from 1981 to 2000. Leukemia. 2010 Feb;24(2):265-84. PubMed PMID: 20010625.
5. Lie SO, Abrahamsson J, Clausen N, Forestier E, Hasle H, Hovi L, et al. Long-term results in children with AML: NOPHO-AML Study Group--report of three consecutive trials. Leukemia. 2005 Dec;19(12):2090-100. PubMed PMID: 16304571.
6. Márky I, Björk O, Forestier E, Jónsson ÓG, Perkkiö M, Schmiegelow K, et al. Intensive chemotherapy without radiotherapy gives more than 85% event-free survival for non-Hodgkin lymphoma without central nervous involvement: a 6-year population-based study from the nordic society of pediatric hematology and oncology. Journal of Pediatric Hematology/ Oncology. 2004;26(9):555-60.
7. Pui CH, Carroll WL, Meshinchi S, Arceci RJ. Biology, Risk Stratification, and Therapy of Pediatric Acute Leukemias: An Update. Journal of Clinical Oncology. 2011;29(5):551-65.
8. Mitchell C, Richards S, Harrison CJ, Eden T. Long-term follow-up of the United Kingdom medical research council protocols for childhood acute lymphoblastic leukaemia, 1980–2001. Leukemia. 2009;24(2):406-18.
9. Denmark. DdTowo. Welfare 2014 [27.07.2014]. Available from: www.denmark.dk.
10. Dalton SO, Schüz J, Engholm G, Johansen C, Kjær SK, Steding-Jessen M, et al. Social inequality in incidence of and survival from cancer in a population-based study in Denmark, 1994–2003: Summary of findings. European journal of cancer. 2008;44(14):2074-85.
11. Simony KS, Lund LW, Erdmann F, Andersen KK, Winther JF, Schüz J, et al. Effect of socioeconomic position on survival after childhood cancer in Denmark. *(under preperation)*.
12. Erdmann F, Kaatsch P, Zeeb H, Roman E, Lightfoot T, Schuz J. Survival from childhood acute lymphoblastic leukaemia in West Germany: does socio-demographic background matter? European journal of cancer. 2014 May;50(7):1345-53. PubMed PMID: 24582913.
13. Coebergh JW, van der Does-van den Berg A, Hop W, van Weerden F, Rammeloo J, van Steensel H, et al. Small influence of parental educational level on the

survival of children with leukaemia in The Netherlands between 1973 and 1979. European journal of cancer. 1996;32A(2):286-9.
14. Lightfoot T, Johnston W, Simpson J, Smith A, Ansell P, Crouch S, et al. Survival from childhood acute lymphoblastic leukaemia: the impact of social inequality in the United Kingdom. European journal of cancer. 2012;48(2):263-9.
15. Walsh PM, Byrne J, Capra M, Comber H. Childhood cancer survival in Ireland: Temporal, regional and deprivation-related patterns. European journal of cancer. 2011;47(12):1852-62.
16. Syse A, Lyngstad TH, Kravdal O. Is mortality after childhood cancer dependent on social or economic resources of parents? A population-based study. International Journal of Cancer. 2012;130(8):1870-8.
17. Sergentanis T, Dessypris N, Kanavidis P, Skalkidis I, Baka M, Polychronopoulou S, et al. Socioeconomic status, area remoteness, and survival from childhood leukemia. European Journal of Cancer Prevention. 2012:1.
18. Charalampopoulou A, Petridou ET, Spyridopoulos T, Dessypris N, Oikonomou A, Athanasiadou-Piperopoulou F, et al. An integrated evaluation of socioeconomic and clinical factors in the survival from childhood acute lymphoblastic leukaemia: a study in Greece. European Journal of Cancer Prevention. 2004;13(5):397–401.
19. Petridou ET, Kosmidis H, Haidas S, Tong D, Revinthi K, Flytzani V, et al. Survival from childhood leukemia depending on socioeconomic status in Athens. Oncology. 1994;51(5):391-5.
20. Thygesen LC, Daasnes C, Thaulow I, Bronnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: Structure, access, legislation, and archiving. Scandinavian journal of public health. 2011;39(7 Suppl):12-6.
21. Pedersen CB. The Danish Civil Registration System. Scandinavian journal of public health. 2011 Jul;39(7 Suppl):22-5. PubMed PMID: 21775345.
22. Birch JM, Mardsen HB. Classification scheme for childhood cancer. International Journal of Cancer. 1987;40(15):620-4.
23. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. Cancer. 2005 Apr 1;103(7):1457-67. PubMed PMID: 15712273.
24. Nguyen-Nielsen M, Svensson E, Vogel I, Ehrenstein V, Sunde L. Existing data sources for clinical epidemiology: Danish registries for studies of medical genetic diseases. Clinical epidemiology. 2013;5:249-62. PubMed PMID: 23966801. Pubmed Central PMCID: 3745287.
25. Dalton SO, Steding-Jessen M, Gislum M, Frederiksen K, Engholm G, Schuz J. Social inequality and incidence of and survival from cancer in a population-based study in Denmark, 1994-2003: Background, aims, material and methods. European journal of cancer. 2008 Sep;44(14):1938-49. PubMed PMID: 18684615.
26. Pui C, Boyett J, Relling M, Harrison P, Rivera G, Behm F, et al. Sex differences in prognosis for children with acute lymphoblastic leukemia. Journal of Clinical Oncology. 1999;17(3):818-24.
27. Clark TG, Bradburn MJ, Love SB, Altman DG. Survival analysis part I: basic concepts and first analyses. British journal of cancer. 2003 Jul 21;89(2):232-8. PubMed PMID: 12865907. Pubmed Central PMCID: 2394262.

28. StataCorp. *Stata Statistical Software: Release 13.* College Station, TX. StataCorp LP; 2013.
29. Von Behren J, Spector LG, Mueller BA, Carozza SE, Chow EJ, Fox EE, et al. Birth order and risk of childhood cancer: a pooled analysis from five US States. International journal of cancer Journal international du cancer. 2011 Jun 1;128(11):2709-16. PubMed PMID: 20715170. Pubmed Central PMCID: 3008504.
30. Schmidt LS, Kamper-Jorgensen M, Schmiegelow K, Johansen C, Lahteenmaki P, Trager C, et al. Infectious exposure in the first years of life and risk of central nervous system tumours in children: analysis of birth order, childcare attendance and seasonality of birth. British journal of cancer. 2010 May 25;102(11):1670-5. PubMed PMID: 20461079. Pubmed Central PMCID: 2883153.
31. Schüz J, Kaatsch P, Kaletsch U, Meinert R, Michaelis J. Association of childhood cancer with factors related to pregnancy and birth. International journal of epidemiology. 1999;28(4):631-9.
32. Schuz J, Schmidt LS, Kogner P, Lahteenmaki PM, Pal N, Stokland T, et al. Birth characteristics and Wilms tumors in children in the Nordic countries: a register-based case-control study. International journal of cancer Journal international du cancer. 2011 May 1;128(9):2166-73. PubMed PMID: 20607831.
33. Johnson KJ, Carozza SE, Chow EJ, Fox EE, Horel S, McLaughlin CC, et al. Birth characteristics and childhood carcinomas. British journal of cancer. 2011 Oct 25;105(9):1396-401. PubMed PMID: 21915125. Pubmed Central PMCID: 3241539.
34. Hjalgrim LL, Rostgaard K, Hjalgrim H, Westergaard T, Thomassen H, Forestier E, et al. Birth weight and risk for childhood leukemia in Denmark, Sweden, Norway, and Iceland. Journal of the National Cancer Institute. 2004 Oct 20;96(20):1549-56. PubMed PMID: 15494605.
35. Johnson KJ, Carozza SE, Chow EJ, Fox EE, Horel S, McLaughlin CC, et al. Parental age and risk of childhood cancer: a pooled analysis. Epidemiology. 2009 Jul;20(4):475-83. PubMed PMID: 19373093. Pubmed Central PMCID: 2738598.
36. Larfors G, Hallbook H, Simonsson B. Parental age, family size, and offspring's risk of childhood and adult acute leukemia. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2012 Jul;21(7):1185-90. PubMed PMID: 22539609.
37. Youlden DR, Baade PD, Valery PC, Ward LJ, Green AC, Aitken JF. Differentials in Survival for Childhood Cancer in Australia by Remoteness of Residence and Area Disadvantage. Cancer Epidemiology Biomarkers & Prevention. 2011;20(8):1649-56.
38. Petridou ET, Dimitrova N, Eser S, Kachanov D, Karakilinc H, Varfolomeeva S, et al. Childhood leukemia and lymphoma: time trends and factors affecting survival in five Southern and Eastern European Cancer Registries. Cancer causes & control : CCC. 2013 Jun;24(6):1111-8. PubMed PMID: 23529470.
39. Woods LM, Rachet B, Coleman MP. Origins of socio-economic inequalities in cancer survival: a review. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2006 Jan;17(1):5-19. PubMed PMID: 16143594.
40. Frederiksen BL, Dalton SO, Osler M, Steding-Jessen M, de Nully Brown P. Socioeconomic position, treatment, and survival of non-Hodgkin lymphoma in Denmark--a nationwide study. British journal of cancer. 2012 Feb 28;106(5):988-95. PubMed PMID: 22315055. Pubmed Central PMCID: 3305955.

41. Larsen SB, Olsen A, Lynch J, Christensen J, Overvad K, Tjonneland A, et al. Socioeconomic position and lifestyle in relation to breast cancer incidence among postmenopausal women: a prospective cohort study, Denmark, 1993-2006. Cancer epidemiology. 2011 Oct;35(5):438-41. PubMed PMID: 21227766.
42. Tebbi C. Treatment compliance in childhood and adolescence. Cancer. 1993;71(10 Suppl):3441-9.
43. Bhatia S, Landier W, Shangguan M, Hageman L, Schaible AN, Carter AR, et al. Nonadherence to oral mercaptopurine and risk of relapse in Hispanic and non-Hispanic white children with acute lymphoblastic leukemia: a report from the children's oncology group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012 Jun 10;30(17):2094-101. PubMed PMID: 22564992. Pubmed Central PMCID: 3601449.
44. Kamper-Jorgensen M, Woodward A, Wohlfahrt J, Benn CS, Simonsen J, Hjalgrim H, et al. Childcare in the first 2 years of life reduces the risk of childhood acute lymphoblastic leukemia. Leukemia. 2008 Jan;22(1):189-93. PubMed PMID: 17690702.
45. Schmiegelow K, Vestergaard T, Nielsen SM, Hjalgrim H. Etiology of common childhood acute lymphoblastic leukemia: the adrenal hypothesis. Leukemia. 2008 Dec;22(12):2137-41. PubMed PMID: 18719616.
46. Schmiegelow K, Nyvold C, Seyfarth J, Pieters R, Rottier MM, Knabe N, et al. Post-induction residual leukemia in childhood acute lymphoblastic leukemia quantified by PCR correlates with in vitro prednisolone resistance. Leukemia. 2001;15(7):1066-71.
47. Patterson JM, Holm KE, Gurney JG. The impact of childhood cancer on the family: a qualitative analysis of strains, resources, and coping behaviors. Psycho-oncology. 2004 Jun;13(6):390-407. PubMed PMID: 15188446.

Figure and table legend

Table 1: Children with haematological malignancies diagnosed between 1973-2006, by number of deaths after 10 years of follow-up, 5-year survival and 10-year survival.

Table 2: Analyses of children with acute lymphoblastic leukaemia and acute myeloid leukaemia diagnosed from 1990 onwards: Multivariable Cox regression analyses of the association of family characteristics on childhood leukaemia survival in Denmark, followed-up for 10 years from date of diagnosis.

Figure 1a: Full period multiple Cox regression analyses of the association between family characteristics and 10 year overall survival from childhood haematological malignancies in Denmark. Fully adjusted hazards ratios with 95% confidence intervals for acute lymphoblastic leukaemia (ALL) survival.

* Adjustment variables vary by family characteristic. *Birth order:* hazard ratios are adjusted for child's age at diagnosis, sex, place of residence, and maternal age at diagnosis. *Number of siblings (both full siblings and full and half siblings):* hazard ratios are adjusted for child's age at diagnosis, sex, place of residence, and maternal age at diagnosis. *Place of residence*: hazard ratios are adjusted for child's age at diagnosis, sex, number of full siblings, and mother's age. *Mother's age at diagnosis:* hazard ratios are adjusted for child's age at diagnosis, sex, place of residence, and number of full siblings. *Father's age at diagnosis:* hazard ratios are adjusted for child's age at diagnosis, sex, place of residence, and number of full siblings. 15 cases missed information on place of residence, 6 cases missed information on father's age at diagnosis.

** Hazard ratio with corresponding 95% confidence interval.

Figure 1b: Full period multiple Cox regression analyses of the association between family characteristics and 10 year overall survival from childhood haematological malignancies in Denmark. Fully adjusted hazards ratios with 95% confidence intervals for acute myeloid leukaemia (AML) survival. If upper bound of the confidence intervals exceeded 7, it was trunked in the figure and marked with an *arrow*.

* Adjustment variables vary by family characteristic. *Birth order:* hazard ratios are adjusted for child's age at diagnosis, sex, place of residence, and maternal age at diagnosis. *Number of siblings (both full siblings and full and half siblings):* hazard ratios are adjusted for child's age at diagnosis, sex, place of residence, and maternal age at diagnosis. *Place of residence*: hazard ratios are adjusted for child's age at diagnosis, sex, number of full siblings, and mother's age. *Mother's age at diagnosis:* hazard ratios are adjusted for child's age at diagnosis, sex, place of residence, and number of full siblings. *Father's age at diagnosis:* hazard ratios are adjusted for child's age at diagnosis, sex, place of residence, and number of full siblings. 3 cases missed information on place of residence, 1 case missed information on father's age at diagnosis.

** Hazard ratio with corresponding 95% confidence interval.

Figure 1c: Full period multiple Cox regression analyses of the association between family characteristics and 10 year overall survival from childhood haematological malignancies in Denmark. Fully adjusted hazards ratios with 95% confidence intervals for Non-Hodgkin's lymphoma (NHL) survival. Confidence intervals which exceed a hazard ratio of 7 are trunked in the figure and marked with an arrow.

* Adjustment variables vary by family characteristic. *Birth order:* hazard ratios are adjusted for child's age at diagnosis, sex, place of residence, and maternal age at diagnosis. *Number of siblings (both full siblings and full and half siblings):* hazard ratios are adjusted for child's age at diagnosis, sex, place of residence, and maternal age at diagnosis. *Place of residence*: hazard ratios are adjusted for child's age at diagnosis, sex, number of full siblings, and mother's age. *Mother's age at diagnosis:* hazard ratios are adjusted for child's age at diagnosis, sex, place of residence, and number of full siblings. *Father's age at diagnosis:* hazard ratios are adjusted for child's age at diagnosis, sex, place of residence, and number of full siblings. 3 cases missed information on place of residence.

** Hazard ratio with corresponding 95% confidence interval.

Figure 2a: Overall survival from childhood acute lymphoblastic leukaemia (ALL), by family characteristics. Kaplan-Meier curves of overall survival by birth order (Log-rank test of

heterogeneity: $\chi^2 = 5.79$, $p = 0.12$), number of full siblings (Log-rank test of heterogeneity: $\chi^2 = 3.92$, $p = 0.27$), mother's age at the child's diagnosis (Log-rank test of heterogeneity: $\chi^2 = 19.02$, $p = 0.002$), and father's age at the child's diagnosis (Log-rank test of heterogeneity: $\chi^2 = 10.37$, $p = 0.07$).

Figure 2b: Overall survival from childhood acute myeloid leukaemia (AML), by family characteristics. Kaplan-Meier curves of overall survival by birth order (Log-rank test of heterogeneity: $\chi^2 = 7.64$, $p = 0.05$), number of full siblings (Log-rank test of heterogeneity: $\chi^2 = 1.15$, $p = 0.77$), mother's age at the child's diagnosis (Log-rank test of heterogeneity: $\chi^2 = 10.90$, $p = 0.05$), and father's age at the child's diagnosis (Log-rank test of heterogeneity: $\chi^2 = 13.48$, $p = 0.02$).

Table 1: Children with haematological malignancies diagnosed between 1973-2006, by number of deaths after 10 years of follow-up, 5-year survival and 10-year survival.

	Cases	Deaths (%)[a]	5-year survival	10-year survival
Total	1,819	504 (27.7%)	74.5%	72.1%
Sex				
Boys	1,068 (58.7%)	301 (28.2%)	73.9%	71.6%
Girls	751 (41.3%)	203 (27.0%)	75.4%	72.7%
Age at diagnosis (years)				
< 1	93 (5.1%)	65 (69.9%)	31.2%	30.0%
1 – 4	724 (39.8%)	172 (23.8%)	78.3%	76.1%
5 – 9	404 (22.2%)	114 (28.2%)	73.3%	71.6%
10 – 14	283 (15.6%)	68 (24.0%)	80.2%	75.5%
15 – 19	315 (17.3%)	85 (27.0%)	74.9%	72.8%
Decade of diagnosis				
1973 – 1979	109 (6.0%)	58 (53.2%)	49.5%	46.8%
1980 – 1989	428 (23.5%)	172 (40.2%)	62.9%	59.8%
1990 – 1999	708 (38.9%)	177 (25.0%)	77.5%	75.0%
2000 – 2006	574 (31.6%)	97 (16.9%)	84.2%	82.8%
Decade of birth				
1973 – 1979	481 (26.4%)	194 (40.3%)	63.2%	59.7%
1980 – 1989	718 (39.5%)	207 (28.8%)	73.8%	71.0%
1990 – 1999	485 (26.7%)	80 (16.5%)	84.1%	83.4%
2000 – 2006	135 (7.4%)	23 (17.0%)	83.7%	82.4%
Cancer type [b]				
Leukaemias	1,294 (71.1%)	388 (30.0%)	72.6%	69.8%
• ALL[c]	1,011 (55.6%)	244 (24.1%)	78.7%	75.6%
• AML[d]	213 (11.7%)	110 (51.6%)	49.3%	48.2%
• others[e]	70 (3.9%)	34 (48.6%)	54.3%	51.0%
Lymphomas	525 (28.9%)	116 (22.1%)	79.2%	77.8%
• HL[f]	235 (12.9%)	22 (9.4%)	92.3%	90.5%
• NHL[g]	163 (9.0%)	50 (30.7%)	71.2%	69.2%
• Others[h]	127 (7.0%)	44 (34.7%)	65.4%	65.4%
Birth order				
1st born	834 (45.9%)	211 (25.3%)	76.6%	74.5%
2nd born	664 (36.5%)	189 (28.5%)	74.1%	71.3%
3rd born	240 (13.2%)	77 (32.1%)	70.4%	67.6%
4th born and later	81 (4.5%)	27 (33.3%)	67.9%	66.6%

Siblings				
Full siblings				
0 siblings	476 (26.2%)	128 (26.9%)	76.1%	72.9%
1 sibling	793 (43.6%)	211 (26.6%)	75.3%	73.2%
2 siblings	358 (19.7%)	108 (30.2%)	72.0%	69.5%
3 and more siblings	192 (10.6%)	57 (29.7%)	71.9%	70.1%
Full & half siblings				
Only child	285 (15.7%)	75 (26.3%)	75.8%	73.5%
1 sibling	837 (46.0%)	218 (26.1%)	75.9%	73.8%
2 siblings	433 (23.8%)	135 (31.2%)	71.8%	68.5%
3 and more siblings	264 (14.5%)	76 (28.8%)	73.1%	71.0%
Place of residence at diagnosis[i]				
Greater Copenhagen area	540 (30.3%)	140 (25.9%)	76.3%	73.8%
Provincial cities	949 (53.2%)	271 (28.6%)	73.3%	71.3%
Rural areas	225 (12.6%)	70 (31.1%)	70.7%	68.7%
Peripheral rural areas	71 (4.0%)	17 (23.9%)	83.1%	75.4%
Mother's age at diagnosis (years)				
≤ 25	140 (7.7%)	64 (45.7%)	57.1%	54.2%
26 – 30	348 (19.1%)	94 (27.0%)	75.9%	72.8%
31 – 35	491 (27.0%)	129 (26.3%)	76.0%	73.5%
36 – 40	386 (21.2%)	107 (27.2%)	73.8%	72.1%
41 – 45	268 (14.7%)	72 (26.9%)	75.4%	72.9%
≥46	186 (10.2%)	38 (20.4%)	81.2%	79.3%
Father's age at diagnosis[j] **(years)**				
≤ 25	51 (2.8%)	20 (39.2%)	60.8%	60.8%
26 – 30	239 (13.2%)	84 (35.2%)	67.8%	64.7%
31 – 35	429 (23.7%)	114 (26.6%)	76.2%	73.2%
36 – 40	413 (22.8%)	109 (26.4%)	75.8%	73.4%
41 – 45	338 (18.7%)	96 (28.4%)	73.6%	71.3%
≥46	338 (18.7%)	79 (23.4%)	78.1%	76.4%

[a] Number of and proportion of deaths from all childhood haematological malignancy cases, by characteristics of cases.
[b] Classified by the International Classification of Childhood Cancer, up to 2003 by Birch & Marsden (first edition) and from 2003 onwards by third edition (ICCC-3)
[c] Acute lymphoblastic leukaemia
[d] Acute myeloid leukaemia
[e] Chronic myeloid, other specified and unspecified leukaemia
[f] Hodgkin lymphoma
[g] Non-Hodgkin lymphoma (except Burkitt lymphoma)
[h] Burkitt, other specified and unspecified lymphoma
[i] Grouped at level of the municipality. Provincial cities are those with >10,000 inhabitants; rural areas are rural municipalities with <10,000 inhabitants; peripheral rural areas are

municipalities more than 40 km from a local centre with proper employment possibilities and no shared border with a municipality centre.

[j] No information available on father's age at diagnosis for 11 cases

Table 2: Analyses of children with acute lymphoblastic leukaemia and acute myeloid leukaemia diagnosed from1990 onwards: Multivariable Cox regression analyses of the association of family characteristics on childhood leukaemia survival in Denmark, followed-up for 10 years from date of diagnosis.

	Acute lymphoblastic leukaemia			Acute myeloid leukaemia		
Family characteristic	**Number of Cases**	**Number of deaths**	**HRadj[ab] [95% CI][c]**	**Number of Cases**	**Number of deaths**	**HRadj[ab] [95% CI][c]**
Birth order						
1st born	321	54	1.0 [Ref]	66	23	1.0 [Ref]
2nd born	235	44	1.11 [0.73; 1.68]	59	28	2.84 [1.51; 5.33]
3rd born	79	19	1.24 [0.71; 2.15]	20	9	3.73 [1.49; 9.34]
4th born and later	26	6	1.56 [0.63; 3.88]	5	2	7.58 [1.41; 40.74]
Siblings						
Full siblings						
0 siblings	179	26	1.0 [Ref]	33	11	1.0 [Ref]
1 sibling	290	55	1.18 [0.73; 1.90]	65	30	1.86 [0.86; 4.01]
2 siblings	113	26	1.25 [0.71; 2.19]	40	16	1.63 [0.68; 3.89]
3 and more siblings	79	16	1.09 [0.57; 2.07]	12	5	2.65 [0.72; 9.68]
Full & half siblings						
Only child	105	12	1.0 [Ref]	18	4	1.0 [Ref]
1 sibling	308	57	1.33 [0.69; 2.54]	66	31	4.55 [1.47; 14.07]
2 siblings	150	34	1.33 [0.67; 2.67]	49	19	3.30 [1.00; 10.94]
3 and more siblings	98	20	1.21 [0.57; 2.56]	17	8	6.02 [1.49; 24.24]
Place of residence at diagnosis[d]						
Greater Copenhagen area	205	39	1.0 [Ref]	42	18	1.0 [Ref]
Provincial cities	335	60	0.93 [0.62; 1.41]	85	34	1.02 [0.53; 1.95]
Rural areas	87	17	1.04 [0.58; 1.88]	16	6	0.62 [0.23; 1.65]
Peripheral rural areas	22	6	1.59 [0.67; 3.81]	5	3	1.07 [0.28; 4.16]
Mother's age at diagnosis						
≤ 25	33	4	0.78 [0.26; 2.29]	11	7	4.47 [1.64; 12.20]
26 – 30	129	9	0.46 [0.22; 0.98]	25	12	2.38 [0.98; 5.82]
31 – 35	217	35	1.0 [Ref]	37	12	1.0 [Ref]
36 – 40	149	30	1.02 [0.59; 1.74]	35	17	0.96 [0.39; 2.35]
41 – 45	89	28	1.23 [0.66; 2.29]	22	7	0.38 [0.11; 1.32]
≥46	44	17	1.50 [0.73; 3.07]	20	7	0.42 [0.12; 1.52]

Father's age at diagnosis[e]						
≤ 25	10	0	-- --	4	1	0.73 [0.09; 5.99]
26 – 30	66	5	0.65 [0.25; 1.70]	20	9	1.57 [0.58; 4.27]
31 – 35	189	25	1.0 [Ref]	24	10	1.0 [Ref]
36 – 40	169	31	1.24 [0.71; 2.18]	35	15	0.91 [0.37; 2.22]
41 – 45	125	29	1.19 [0.64; 2.23]	29	16	1.49 [0.56; 4.01]
≥46	96	33	1.75 [0.90; 3.41]	37	11	0.47 [0.15; 1.47]

[a] adjusted Hazard ratio.

[b] Adjustment variables vary by family characteristic. Birth order: hazard ratios are adjusted for child's age at diagnosis, sex, place of residence and maternal age at diagnosis. Number of siblings (both full siblings and full and half siblings): hazard ratios are adjusted for child's age at diagnosis, sex, place of residence and maternal age at diagnosis. Place of residence: hazard ratios are adjusted for child's age at diagnosis, sex, number of full siblings and mother's age. Mother's age at diagnosis: hazard ratios are adjusted for child's age at diagnosis, sex, place of residence and number of full siblings. Father's age at diagnosis: hazard ratios are adjusted for child's age at diagnosis, sex, place of residence and number of full siblings.

[c] Corresponding 95% confidence intervals.

[d] Grouped at level of the municipality. Provincial cities were those with >10,000 inhabitants; rural areas were rural municipalities with <10,000 inhabitants; peripheral rural areas were municipalities more than 40 km from a local centre with proper employment possibilities and no shared border with a municipality centre. Among ALL patients12 cases had missing information on place of residence, among AML 2 cases had no information.

[e] Among ALL patients 6 cases had no information on father's age at diagnosis, among AML cases 1 case had no information.

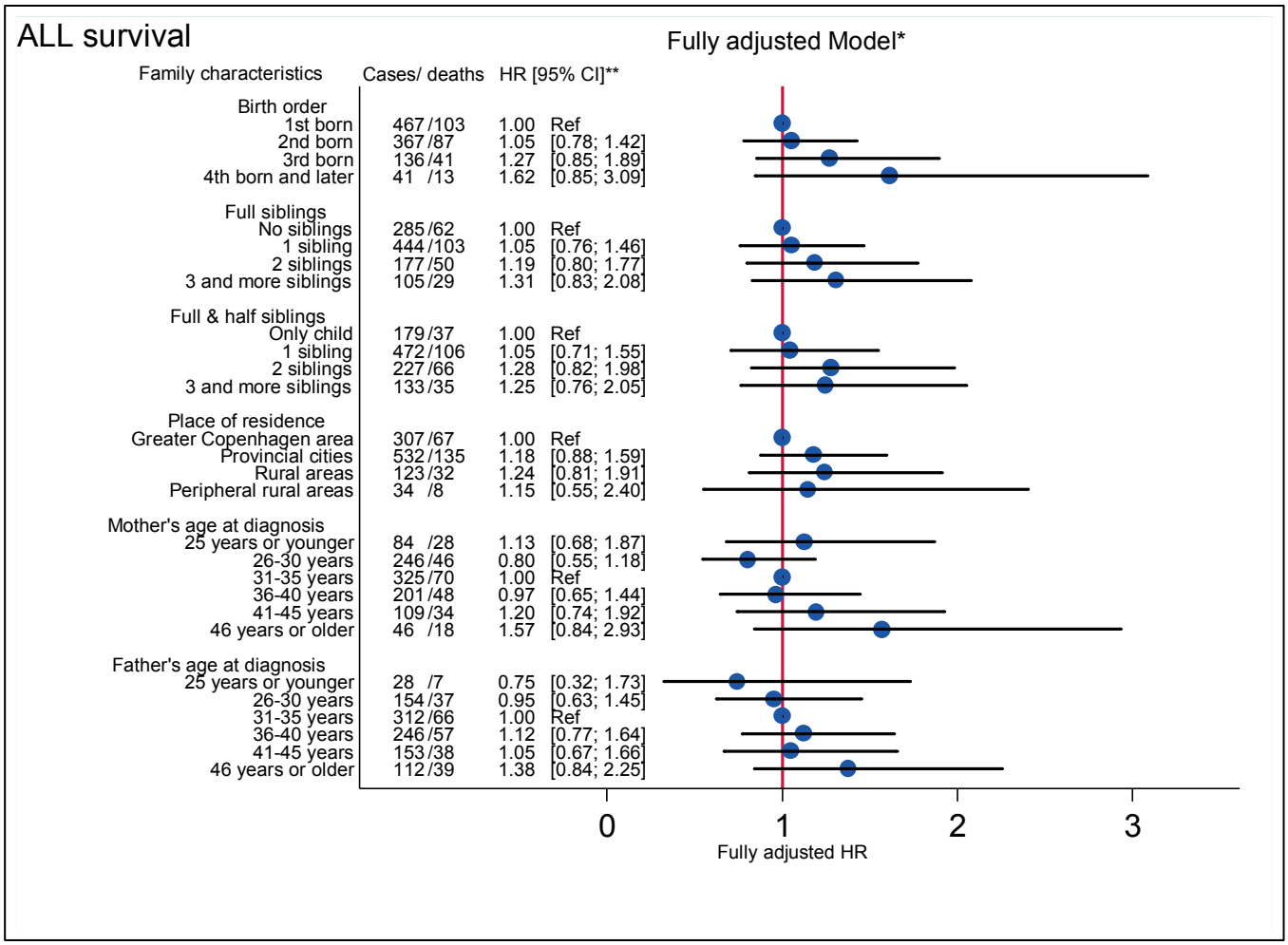


Figure 1a: Full period multiple Cox regression analyses of the association between family characteristics and 10 year overall survival from childhood haematological malignancies in Denmark. Fully adjusted hazards ratios with 95% confidence intervals for acute lymphoblastic leukaemia (ALL) survival.

* Adjustment variables vary by family characteristic. *Birth order:* hazard ratios are adjusted for child's age at diagnosis, sex, place of residence, and maternal age at diagnosis. *Number of siblings (both full siblings and full and half siblings):* hazard ratios are adjusted for child's age at diagnosis, sex, place of residence, and maternal age at diagnosis. *Place of residence*: hazard ratios are adjusted for child's age at diagnosis, sex, number of full siblings, and mother's age. *Mother's age at diagnosis:* hazard ratios are adjusted for child's age at diagnosis, sex, place of residence, and number of full siblings. *Father's age at diagnosis:* hazard ratios are adjusted for child's age at diagnosis, sex, place of residence, and number of full siblings. 15 cases missed information on place of residence, 6 cases missed information on father's age at diagnosis.

** Hazard ratio with corresponding 95% confidence interval.

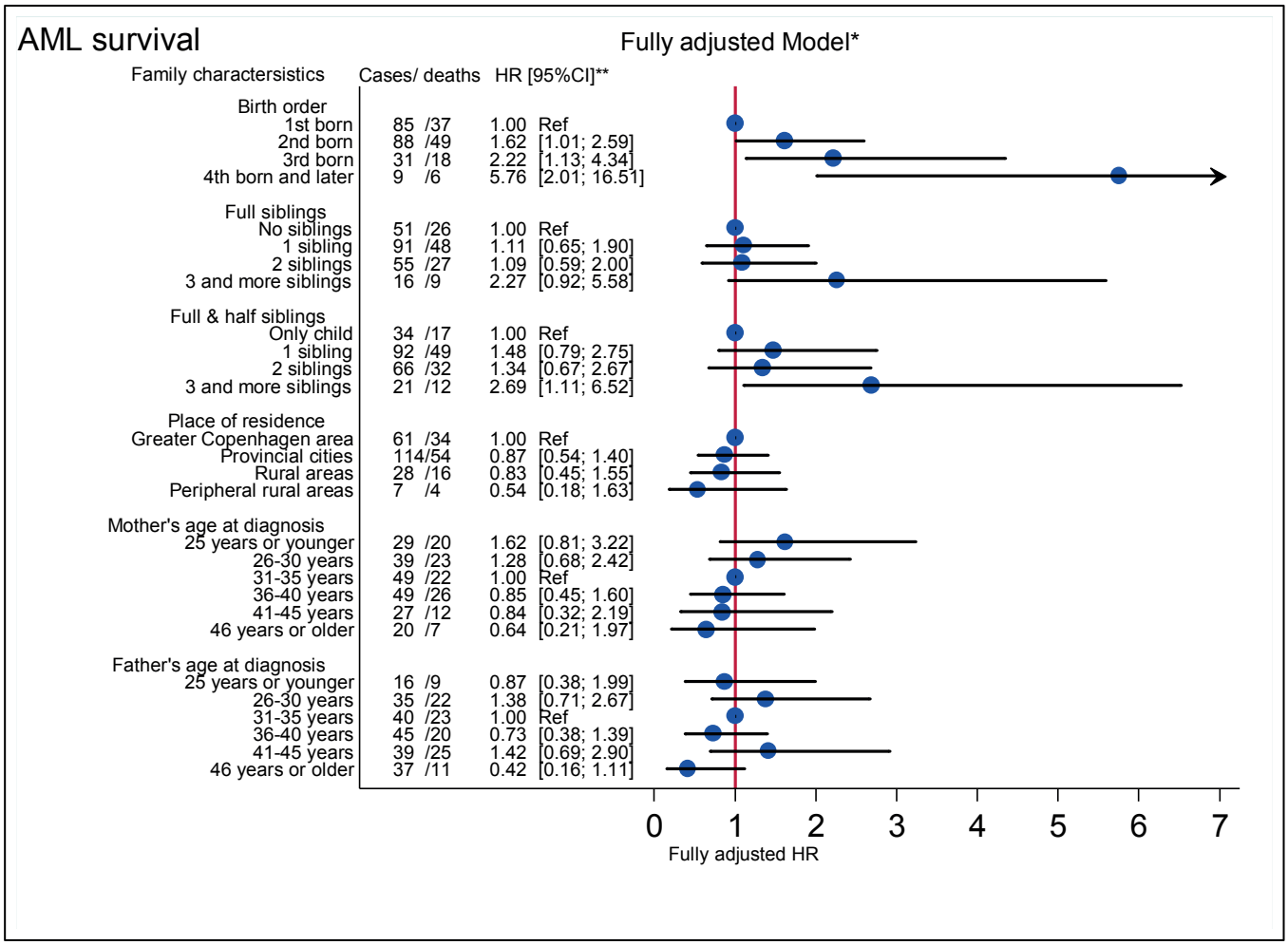


Figure 1b: Full period multiple Cox regression analyses of the association between family characteristics and 10 year overall survival from childhood haematological malignancies in Denmark. Fully adjusted hazards ratios with 95% confidence intervals for acute myeloid leukaemia (AML) survival. If upper bound of the confidence intervals exceeded 7, it was trunked in the figure and marked with an *arrow*.

* Adjustment variables vary by family characteristic. *Birth order:* hazard ratios are adjusted for child's age at diagnosis, sex, place of residence, and maternal age at diagnosis. *Number of siblings (both full siblings and full and half siblings):* hazard ratios are adjusted for child's age at diagnosis, sex, place of residence, and maternal age at diagnosis. *Place of residence*: hazard ratios are adjusted for child's age at diagnosis, sex, number of full siblings, and mother's age. *Mother's age at diagnosis:* hazard ratios are adjusted for child's age at diagnosis, sex, place of residence, and number of full siblings. *Father's age at diagnosis:* hazard ratios are adjusted for child's age at diagnosis, sex, place of residence, and number of full siblings. 3 cases missed information on place of residence, 1 case missed information on father's age at diagnosis.

** Hazard ratio with corresponding 95% confidence interval.

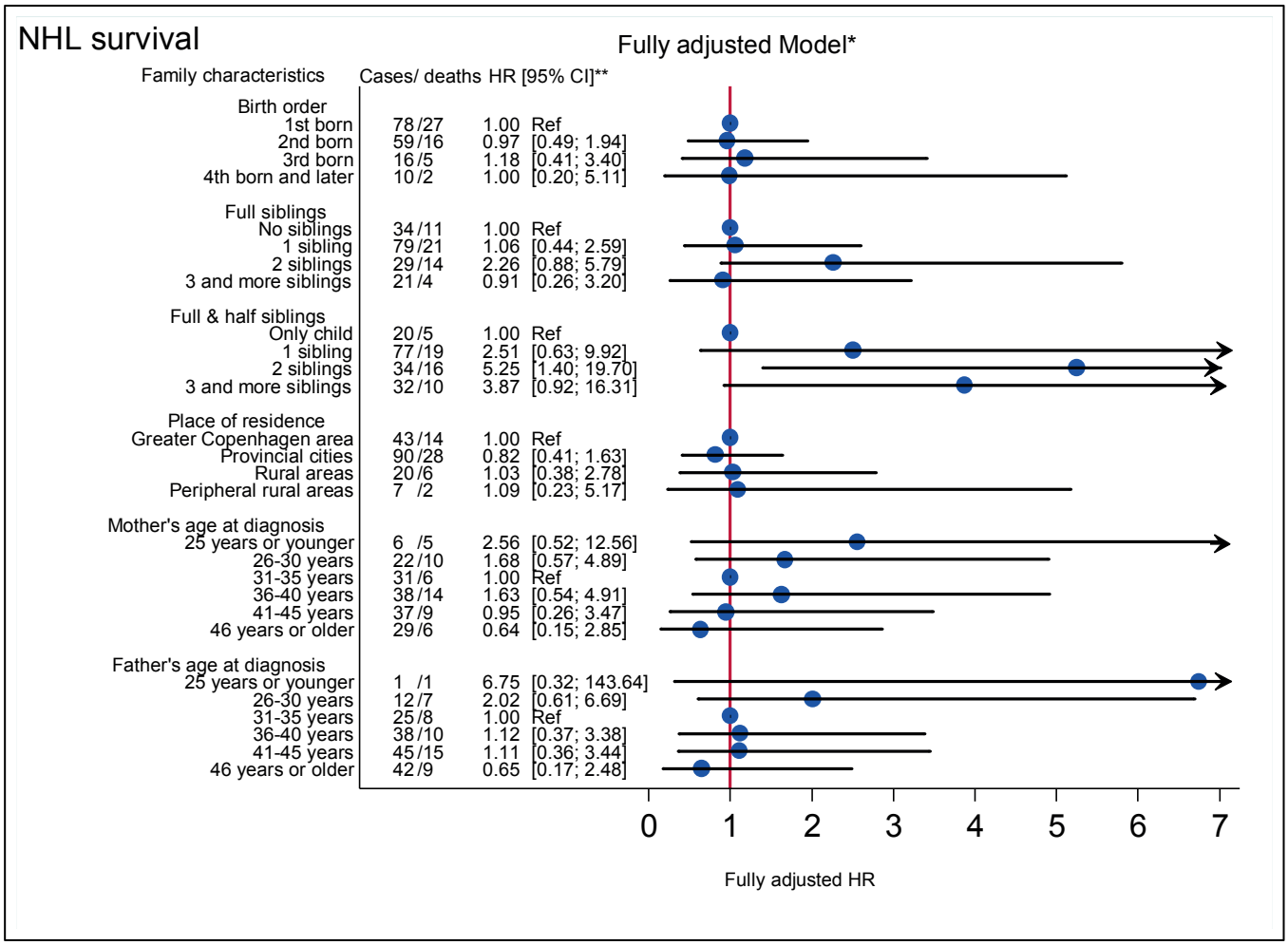
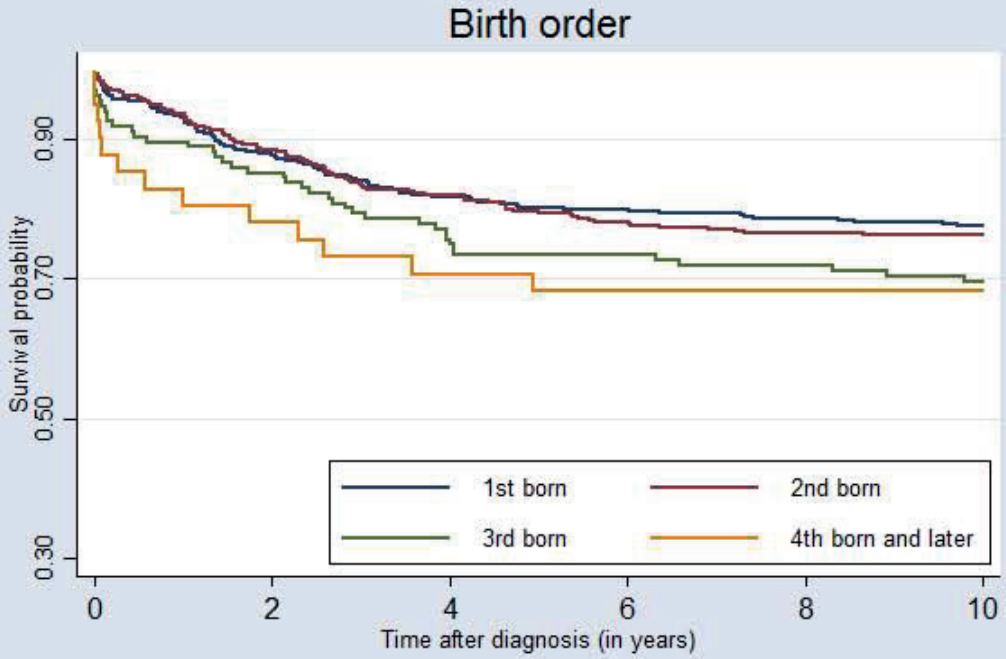


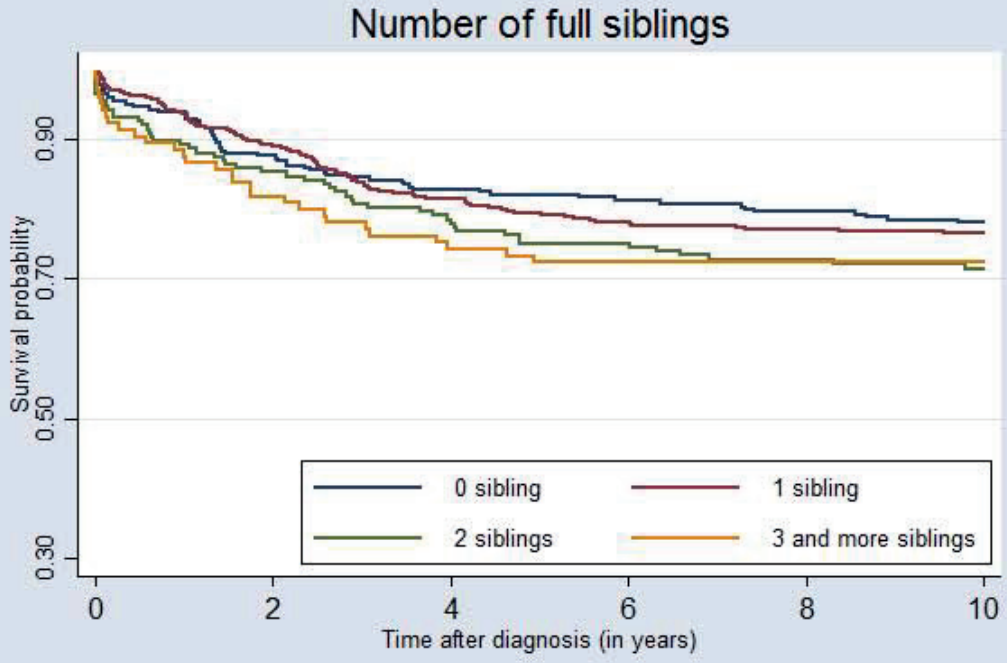
Figure 1c: Full period multiple Cox regression analyses of the association between family characteristics and 10 year overall survival from childhood haematological malignancies in Denmark. Fully adjusted hazards ratios with 95% confidence intervals for Non-Hodgkin's lymphoma (NHL) survival. Confidence intervals which exceed a hazard ratio of 7 are trunked in the figure and marked with an arrow.

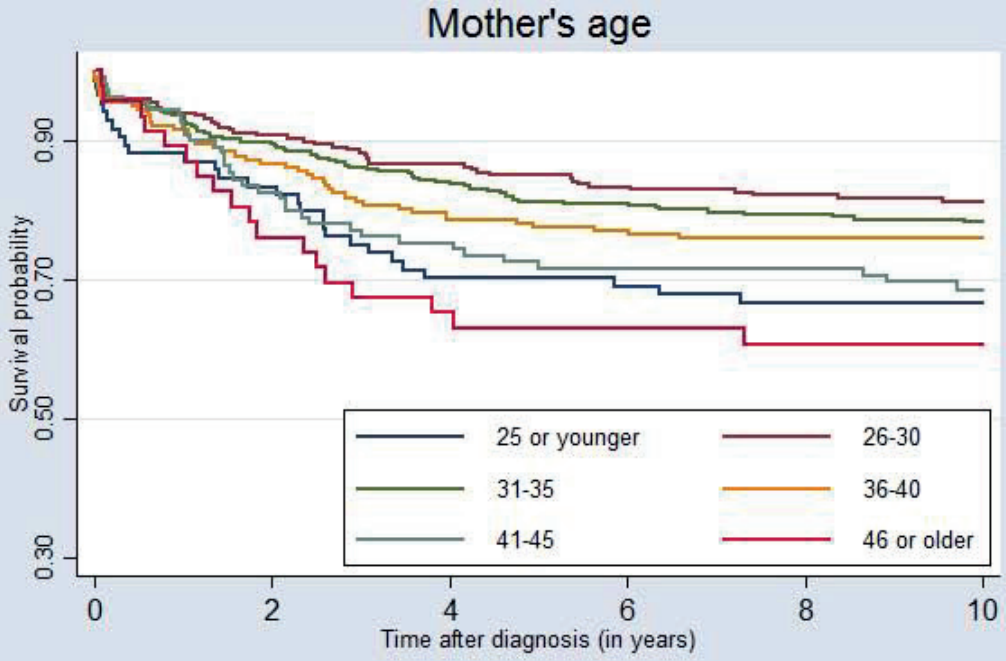
* Adjustment variables vary by family characteristic. *Birth order:* hazard ratios are adjusted for child's age at diagnosis, sex, place of residence, and maternal age at diagnosis. *Number of siblings (both full siblings and full and half siblings):* hazard ratios are adjusted for child's age at diagnosis, sex, place of residence, and maternal age at diagnosis. *Place of residence*: hazard ratios are adjusted for child's age at diagnosis, sex, number of full siblings, and mother's age. *Mother's age at diagnosis:* hazard ratios are adjusted for child's age at diagnosis, sex, place of residence, and number of full siblings. *Father's age at diagnosis:* hazard ratios are adjusted for child's age at diagnosis, sex, place of residence, and number of full siblings. 3 cases missed information on place of residence.

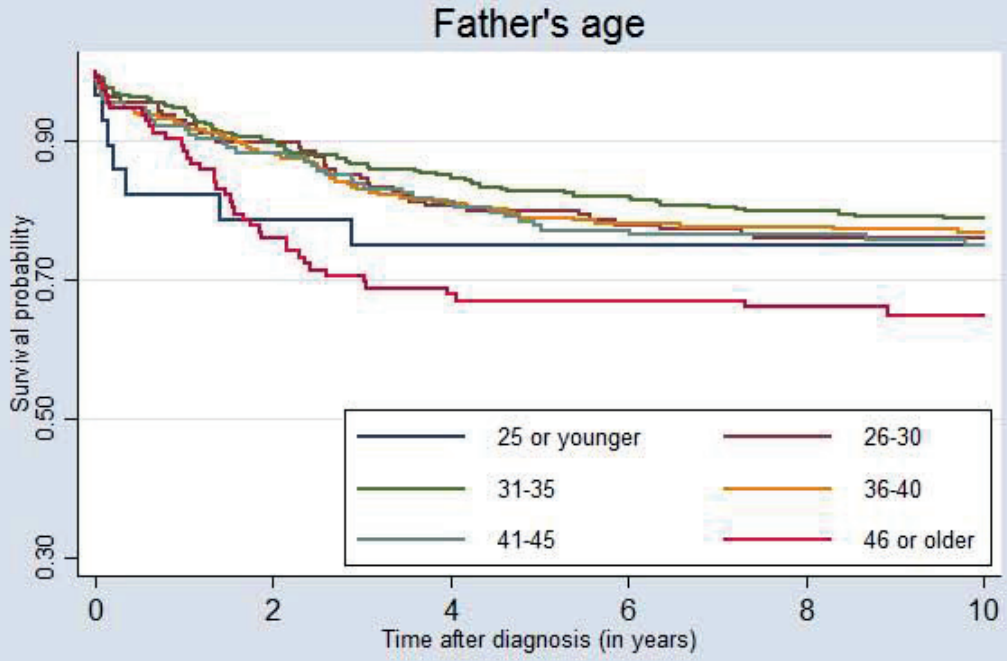
** Hazard ratio with corresponding 95% confidence interval.

Survival from ALL by family characteristics

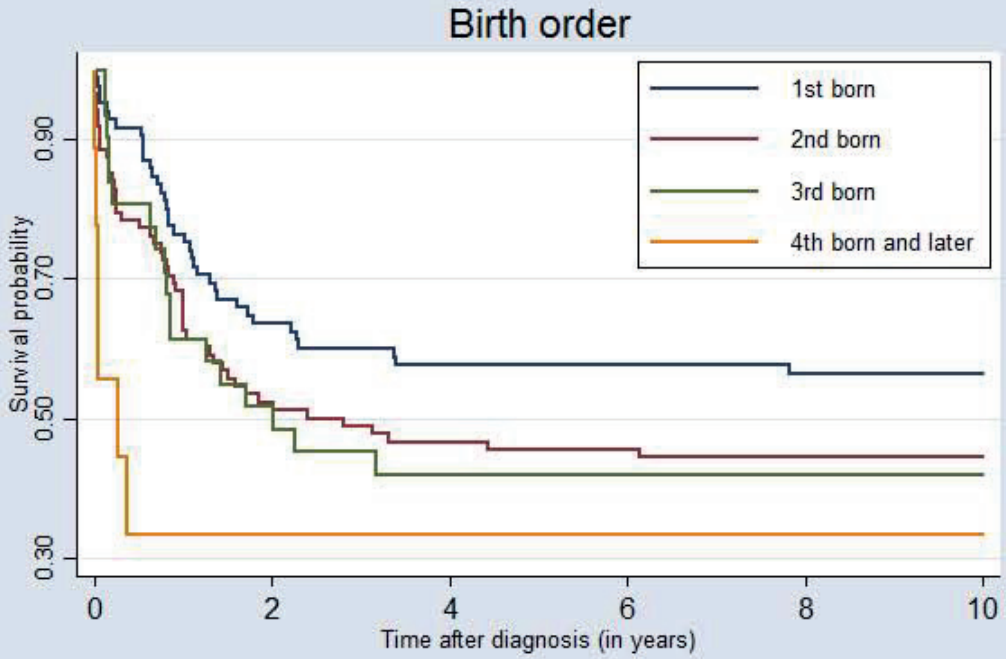


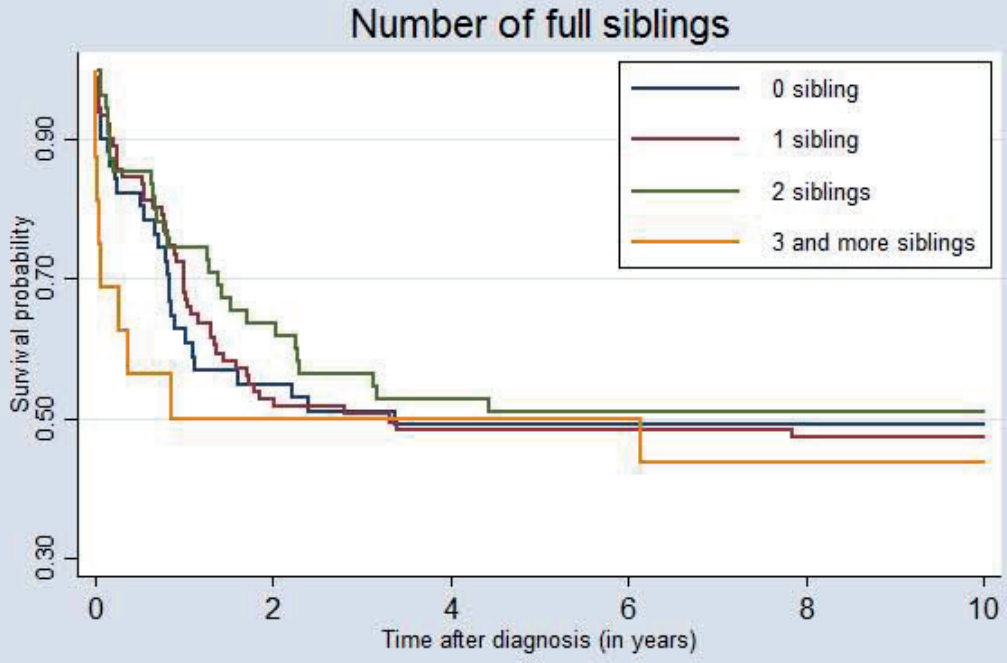


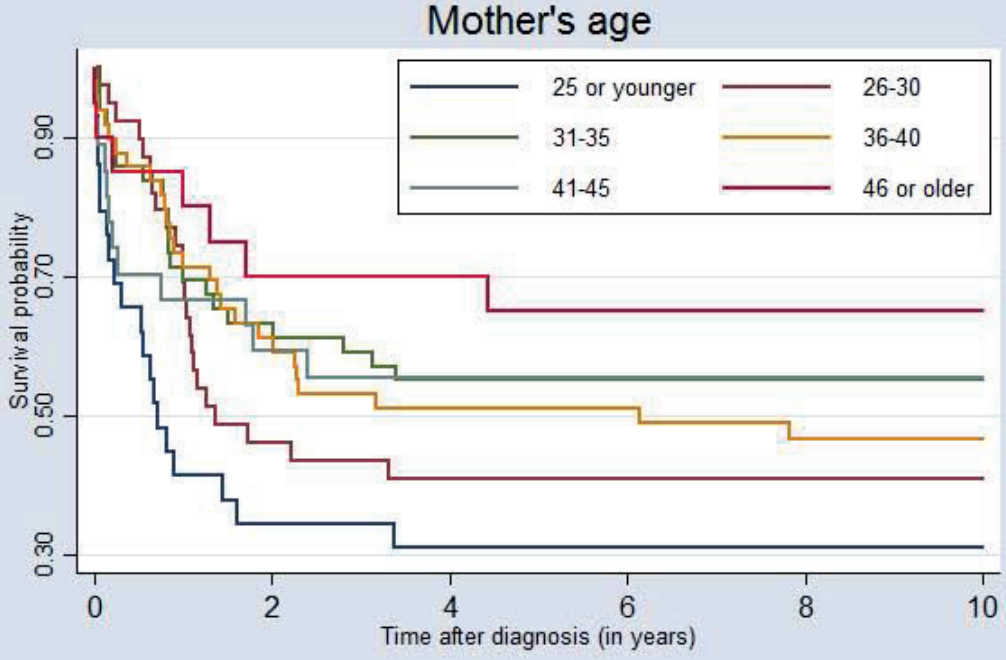


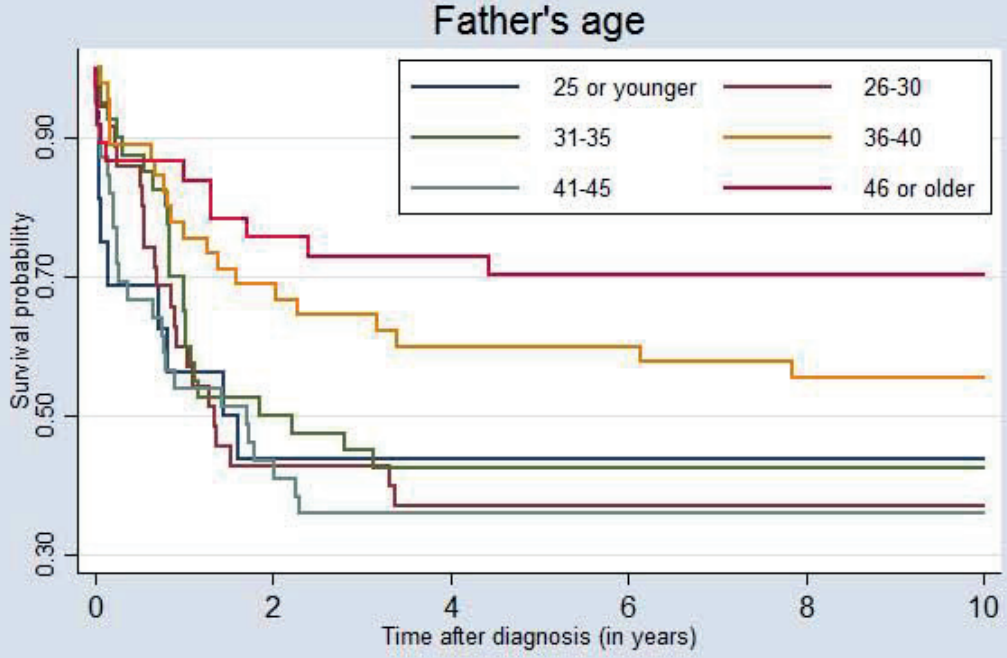


Survival from AML by family characteristics









Article VII

Birth order and risk of childhood cancer in the Danish birth cohort of 1973-2010

First author: Joachim Schüz

Order of authors: Joachim Schüz, George Luta, Friederike Erdmann, Gilles Ferro, Andrea Bautz, Karen Sofie Simony, Susanne Oksbjerg Dalton, Tracy Lightfoot, Jeanette Falck Winther

Contribution statement: JS, TL, FE, and JFW developed the study concept and design. JS, AB, GF, and JFW collected the data and GL, FE, GF, and JS prepared it for analyses. GL conducted the statistical analyses. JS, GL, FE, TL, and JFW participated in the interpretation of the results. JS with support from GL and FE prepared the first draft of the manuscript. All authors have critically revised the manuscript and approved the final version.

Manuscript statistics: 3,397 words (abstract: 188); 2 tables

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TITLE PAGE

Birth order and risk of childhood cancer in the Danish birth cohort of 1973-2010

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ABSTRACT

Many studies have investigated the possible association between birth order and risk of childhood cancer, although the evidence to date has been inconsistent. Birth order has been used as a marker for various in utero or childhood exposures and is relatively straightforward to assess. Data was obtained on all children born in Denmark between 1973 and 2010, involving almost 2.5 million births and about 5,700 newly diagnosed childhood cancers before the age of 20 years. Data were analyzed using Poisson regression models. We failed to observe associations between birth order and risk of any childhood cancer subtype, including acute lymphoblastic leukemia; all rate ratios were close to one. Considering stillbirths and/or controlling for birth weight and parental age in the analyses had no effect on the results. We observed an association between cancer during infancy and being an only child, explained by observing that among firstborn children those who had cancer during infancy had a 1.7-fold statistically significant odds of having subsequent siblings compared to those who did not have cancer. In conclusion, we did not observe an association between birth order and the risk of childhood cancer.

Key words: birth order, childhood cancer, leukemia, risk factors, Denmark

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; CNS, central nervous system; RR, rate ratio; CI, 95% confidence interval

INTRODUCTION

Little is known about the etiology of the heterogeneous group of childhood cancers, but both genetic and environmental factors have been suggested to play a role [1-3]. Many studies have investigated the possible association between birth order and risk of childhood cancer, although the evidence to date has been inconsistent [1, 4-12]. As birth order is relatively straightforward to obtain, either through routine data sources such as birth registries or questionnaire-based studies, where it is generally acknowledged to be well reported [13], it has often been used as a surrogate marker for in utero and/or childhood exposures.

Most notably, birth order has been used as a proxy for examining the role of infectious exposures early in life and the subsequent development of acute lymphoblastic leukemia (ALL), a topic about which there has been much debate, particularly with respect to the "delayed infection" hypothesis [14-16]. According to this hypothesis ALL results from an abnormal reaction to delayed exposure to common infections [17, 18]. It would then be expected that firstborn children would have less contact with infectious agents than children with older siblings and as such have an increased risk of ALL. However, given that data from medical records suggest that children who develop ALL between the ages of 2-5 years have, on average, more infectious illness episodes in the first year of life than those who do not [14, 19-21] it would also be plausible for children with increasing birth order to be at increased risk of ALL.

With respect to in utero exposures, birth order acts as a surrogate for hormone levels, as a mother's first pregnancy differs endocrinologically from later pregnancies [22] with both estrogen and progesterone levels shown to be higher during first pregnancies [23]. Indeed epidemiological studies suggest a decreased risk of testicular cancer with increasing birth order [24]. There is also a well-established positive relationship between maternal parity and

birth weight [25], with high birth weight associated with several different childhood cancer types, including ALL [5, 9, 26, 27]. Furthermore, there is recent evidence to suggest that maternal immune response may also vary with parity [28] and taken together, these two observations may be important for ALL development. One study observed an elevated risk with high birth weight in ALL patients who were first rather than later born, which may or may not reflect the combination of larger fetal size and later exposure to infectious pathogens incurred more frequently in the firstborn child [29]. While birth weight is regarded as a causal factor for several childhood cancers, parental age shows inconsistent evidence [1], but both factors are related to birth order.

In addition to causal mechanisms, alternative explanations cannot be ruled out. One may speculate that having a child with cancer would impact on family planning, for example by not having further children or by delaying having further children. Hence, sampling in case-control studies might increase the chance for controls to be of higher birth order due to larger average numbers of siblings. Lastly, in the case-control studies requiring active participation, family size may be related to willingness to participate introducing selection bias into a study, as it was observed for other family characteristics [30].

The objective of the present study was to investigate the association between birth order and childhood cancer in a nationwide birth cohort over a long time period. For this we obtained data on all children born in Denmark between 1973 and 2010, involving almost 2.5 million births and about 5,700 newly diagnosed childhood cancers before the age of 20 years.

MATERIALS AND METHODS

From the Central Population Register (CPR), we obtained information on all children born in Denmark between January, 1, 1973 (start of the Danish Medical Birth Registry, see below) and December, 31, 2010. Since 1968, all Danish residents receive a unique CPR number, which includes date of birth and sex of the child, and permits accurate record linkage between the different national registries in Denmark [31]. The CPR also includes up to date information on vital status, migration, and first-degree relatives. Through the mother of the index child, all siblings, including their date of birth, were identified in the CPR and all stillbirths in the Danish Medical Birth Register; i.e., information used as the basis for counting of birth order and pregnancy order. The Danish Medical Birth Register was established in 1973 [33] and includes information on parental age at child birth as well as the birth weight of the child.

From the nationwide Danish Cancer Registry established in 1943 [32], we identified all children diagnosed with cancer below the age of 20 years within the defined birth cohort. The cancers were grouped according to the International Childhood Cancer Classification (ICCC; ICCC-1 [Birch Marsden Code; 34] until 2003 and ICCC-3 [35] thereafter). We used the 12 main groups of ICCC, but combined groups XI and XII with group X as "others (X-XII)" because of small numbers and very heterogeneous subtypes. In addition, we subdivided group I into acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and other leukemias. By using only the main groups of ICCC and subgroups for ALL and AML, the potential effect of change in diagnostic classification over time has been minimized.

Our key exposure variable, birth order, was defined in two ways. First, we defined birth order counting all live births of the same mother, in line with the hypothesis that the *number of older siblings* would matter (see above-mentioned delayed infection hypothesis). The group

of firstborn children was subdivided into those without siblings (only children) and those with further siblings with the same mother, to obtain a surrogate measure of even lesser infectious contacts for only children compared to other firstborns, while acknowledging the distinction was only to arise in the future. Second, we defined birth order including stillborn children of the same mother, in line with the hypotheses that the *pregnancy order* would matter. In both definitions, multiple births were treated by assigning the same birth order to multiples and then continuing the counting while accounting for the real number of siblings; for example, for a mother having twins and one further child, the twins would both have a birth order of one while the last child was counted as the third child.

When including birth weight and parental age at the child's birth as other explanatory variables to adjust for potential confounding, maternal age was dichotomized at age 35 years, paternal age at age 40 years, and birth weight was categorized into three categories of < 2.5kg, 2.5-4 kg, and >4 kg. Alternatively, we have also modelled paternal and maternal age using finer categorizations, specifically by categorizing them into 5 year age groups starting with <25 years and ending with >40 years for mothers and >45 years for fathers, respectively. Further sensitivity analyses looked separately at children born between 1973 and 1990, and born between 1991 and 2010, respectively, as day care patterns and birth rates may have changed over time.

Statistical analyses

We used Poisson regression models to evaluate associations between birth order and childhood cancer, estimating the rate ratios (RRs) and corresponding 95% confidence intervals (CIs), with and without controlling for maternal age, paternal age, and birth weight. All children were followed up from date of birth until the age of 20 years, date of death, date of first cancer diagnosis, or end of study period (October, 31, 2013), whichever occurred first.

The firstborn children served as the reference group for the comparisons. Tests for linear trend using Poisson regression models were also performed. The main analysis included all cancers diagnosed up to 20 years of age, but additional analyses were performed restricting to those cases aged 0-14 years at diagnosis for quantitative comparison with previous studies using this age range for their definition of childhood cancer. For the main analyses, birth order excluded stillbirths and RRs were adjusted for maternal age, paternal age, and birth weight. Alternatively using logistic regression models or Cox proportional hazards regression models did not change any of the results (data not shown).

Additional analyses subdividing the group of firstborn children into only children and those with further siblings revealed an association restricted to infants (see Results). As the most likely explanation is reverse causation, we performed an analysis for the firstborn children by modelling the odds of having a subsequent sibling and comparing those who had cancer as infants to those who did not. Here we used a logistic regression model that included infant cancer status, birth year, parental age and birth weight. All analyses were performed using SAS 9.3.

RESULTS

The birth cohort comprised 2,461,283 children, of which 1,262,979 (51.3%) were boys, born between 1973 and 2010 inclusively. Annual numbers of births varied between 52,716 in 1985 and 73,327 in 1975. Among the total cohort, 1,099,058 children were firstborn (44.7%), of which 227,913 (9.3% of total and 20.7% of firstborn) remained only children, with 906,852 (36.8%) second-born, 336,017 (13.7%) third-born, and 119,356 (4.8%) with a birth order of four or higher. When stillbirths were taken into account, there were only slight changes to the

birth order proportions: 1,094,468 (44.5%) firstborn, 905,362 (36.8%) second-born, 339,069 (13.8%) third-born and 122,384 (5.0%) with a birth order of four or higher.

In the study population accruing a total of 38.6 million person-years of follow up, 5,699 childhood cancers were observed, with leukemias and CNS tumors each representing approximately one quarter of cases. Table 1 shows the expected pattern for cancer subtypes with respect to age and sex, with higher proportions of boys being diagnosed with lymphomas, and cancers such as retinoblastoma, neuroblastoma, and hepatic tumors occurring between the ages 1-4 years, and lymphomas occurring in adolescents (15-19 years). Regarding birth order, 45.6% of cancer cases were firstborn, similar to the proportion in the overall cohort.

Table 2 shows the associations between birth order and childhood cancers at ages 0-19 years. No significant associations were observed between birth order and any of the cancer subtypes when using all firstborn children as the reference group; for the majority of cancer types, rate ratios (RRs) were all around one. For acute lymphoblastic leukemia (ALL), all RRs were slightly below one. None of the p values for the tests for linear trend were statistically significant, including for ALL (p=0.10).

When the reference group was stratified into firstborn children with and without siblings (only children), we observed an inverse association with some reduction in RRs for only children, especially for acute myeloid leukemia (AML; RR=0.30; CI 0.13-0.69) and neuroblastoma (RR=0.58, CI 0.34-0.99), and tendencies for CNS tumor (RR=0.85; CI 0.69-1.05), and sarcoma (RR=0.67; CI 0.42-1.07). As these cancers are more likely to be diagnosed at a younger age, a separate post-hoc analysis was conducted combining infants (up to age 1 year) of all cancers: the respective RR for only children was 0.53 (CI 0.35-0.80); reversing the direction of the analysis as the more plausible pathway modeling the odds of

having a subsequent sibling (see Methods) showed a 1.7-fold increased odds (CI 1.13-2.62) among firstborn infants with cancer, based on 28 infants with cancer without subsequent sibling and 193 with subsequent sibling.

Table 2 also shows the same set of results between birth order and different types of cancers among cases aged 0-14 years. Results were similar to the broader age range. None of the p values for the tests for linear trend were statistically significant.

Sensitivity analyses taking into account stillbirths of the same mother in the counting of pregnancy order, had no notable effect as RRs only marginally changed compared to the main analysis (data not shown). Adjustment for parental age and birth weight had little effect, except marginally for all cancers combined and CNS tumors, where non-adjusted RRs were slightly lower than one (but statistically non-significant) and varied around one after adjustment (data not shown), and also the way how paternal and maternal age were modelled (dichotomous or using a finer categorization, see Methods) had no impact. Sensitivity analysis by time period (born between 1973 and 1990, and born between 1991 and 2010, respectively) did not show any consistent patterns, with small deviations most likely due to chance (data not shown).

DISCUSSION

In this large study which included almost 2.5 million children born over a 37 year period and 5,699 cases of childhood cancer, we failed to observe associations between birth order and risk of any of the childhood cancer subtypes. Considering stillbirths and/or controlling for birth weight or parental age in the analyses had no effect on the results. Hence, we didn't find

support for the hypothesis that either the *number of older siblings* or the *pregnancy order* would matter.

Our study has a number of strengths over those previously published. Firstly, we adopted a nationwide approach with complete follow-up and virtually no missing data and thus provide a factual reflection of the situation in Denmark. Furthermore, we had the opportunity to incorporate accurate data on stillbirths into our analyses, as well as on some potential confounding factors, in particular birth weight and parental age – although neither variable impacted the overall results. However, one of the limitations was the lack of socioeconomic characteristics, such as parental education or income, given that previous research has shown that individual social position was not related with the risk of childhood leukemia in Denmark, but children born in low-income municipalities had an increased risk [36].

For ALL, results from epidemiological studies are not very consistent. In a five-state register-based study in the US with 4,699 ALL cases diagnosed 1980-2004, odds ratios were non-significantly lower than one, namely 0.97, 0.96, and 0.94, for children born second, third, or fourth or higher, respectively, compared to firstborn children [4]. In a Californian register-based case-control study of 4,721 ALL cases diagnosed 1988-2008 (overlapping with [4]), the observed odds ratio was 0.97 (CI 0.87-1.08) for higher birth order versus first [6]. Similarly, a Californian record-based case-control study with 3,402 ALL cases aged 0-5 years from 1988-2007 (overlapping with [4, 6]) showed non-significant odds ratios of 1.00, 0.95 and 0.91 for birth orders second, third and fourth or higher, respectively, compared to firstborn children, but indicated some stronger decrease in non-Hispanic whites compared to Hispanic whites [7]. A pooled analysis from the Childhood Leukemia International Consortium (CLIC), using data from 11 questionnaire-based case-control studies from 8 countries with a total of 7,399 ALL cases diagnosed between 1979-2001, showed a pooled odds ratio of 0.94 (CI 0.88-1.00) for later born versus firstborn with no monotonic trend of

decrease with increasing birth order, but with substantial heterogeneity across studies (I^2 of 71%) [8]. Individual-study odds ratios ranged from 0.69 (CI 0.55-0.86; France) to 1.44 (CI 1.15-1.79; Quebec, Canada). A large register-based study combining 1,905 ALL cases from Denmark, Iceland, Norway and Sweden diagnosed 1984-1999 however showed a monotonic trend with decrease in risk of 0.90 (CI 0.84-0.96) per one unit increase in birth order, specifically for B-precursor ALL [5]. This is surprising as there is some overlap of the study with the present study in their Danish cases; design features cannot explain the differences with both studies using an identical setup of registries and it cannot be explained further by the restriction to the subtype, as 86% of ALL were B-precursor ALL in the other study. Reasons are therefore either a stronger effect in the other Scandinavian countries or the restriction to the earlier time period; however, the differences between the two studies were also not marked with clearly overlapping confidence intervals.

Taken together and including our results for ALL, there is a suggestion of an overall, perhaps, 10% decrease in risk in children of second or higher birth order compared to firstborn children with statistical significance depending on the size of study, but also some heterogeneity across studies. This could be due to random variation or because the predictive power of birth order, as a surrogate for an unknown exposure, may depend on the source population of the study. Overall, this finding for birth order does not appear to lend strong support to the delayed infection hypothesis, but neither does it contradict it andother immune-system related factors may matter more [15, 18]. In Denmark social contacts through day care are very common, and the proportion of 0-6 year old children attending day care increased from slightly over 40% in 1980 to 75% in 1999 [37]. Given the UK findings of more frequent infections during infancy in children with ALL, it is surprising the estimated rate ratio does not point in the other direction [19].

Our lack of observation of an association between any of the solid cancers and birth order contrasts with the large US study described above, where reduced risks were restricted to birth order of four and higher compared to firstborn children were observed for CNS tumors (OR 0.77, CI 0.68-0.89), neuroblastomas (OR 0.68, CI 0.55-0.84), and Wilms tumors (OR 0.67, CI 0.54-0.84), leading to an overall decreased odds ratio for their combined 17,672 cancer cases combined of 0.87 (CI 0.81-0.93) [4]. Our respective rate ratio for all cancers combined was 1.00, and no association was seen with any of the three diagnostic subgroups. For later-born children compared to firstborn children, a recent review of neuroblastoma found no clear evidence of an association, although the majority of studies found slightly decreased risks [38]. A large registry-based study in the Nordic countries of 3,983 CNS tumor cases confirmed our finding of no association with birth order, acknowledging some overlap in the Danish cases with our birth cohort [10]. In a similar study in the Nordic countries involving 3,298 cases of Wilms tumor, the odds ratio of later born children compared to firstborn children was 0.98, again consistent with our findings [11]. Overall, there appears to be little evidence of an association between birth order and childhood solid tumor risk. The findings in the US study for high birth order needs attention regarding which underlying exposure may be reflected in the very high birth order in this setting since that might explain the findings being different to the Nordic countries; the US proportion of those born fourth or higher was twice as high as in Denmark (approximately 10% [4] compared to 5%), but we do not know whether this plays any role.

A recent review suggests some evidence of an increased risk of childhood AML with increasing birth order, although the authors suggested this could in part be due to a maternal age effect [39]. We did find a slightly increased risk even after adjustment for maternal age, although stronger for those born second or third than fourth or higher.

An intriguing finding of our study was that there was an inverse association between being an only child and AML and neuroblastoma, and to some extent with CNS tumors and sarcomas; however with the exception of CNS tumors these observations were based on small numbers. A stronger association was observed when combining infants irrespective of type of cancer. Approximately 10% of Danish children were only children. This is explained by the finding that those who have their firstborn child diagnosed with cancer at a very early age decided over-proportionally frequently to later have further children, namely 1.7-fold, which may be the most likely reason for seeing this association. As the association was seen only in infants when all firstborn children were only children and whether they had siblings was only determined in the future, the finding would be difficult to interpret etiologically. Nevertheless, it could be worthwhile to check how these families differ in for instance in social and family factors and occupational exposures. Chance is another option, although both the numbers of affected children and the magnitude of effect are not small and the entire Danish childhood population was included in our study. Notably, this finding is contrary to the initial expectation that families with a child with cancer may have fewer subsequent children; we observed that when the firstborn child has cancer during infancy, it increases the probability of having a subsequent child.

In conclusion, we did not observe an association between birth order and the risk of childhood cancer. From the totality of the literature, there may be a weak protective effect for ALL, although this is still not clear and there is little insight into any causal mechanisms. Among firstborn children, infants with cancer had a higher probability of having subsequent siblings than other infants; this observation needs to be confirmed in other studies.

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References

1. Little J. Epidemiology of childhood cancer. IARC Sci Publ. 149. Lyon: IARC, 1999

2. Savage S, Schüz J. Environmental Chemicals and Childhood Cancer. In: Nriagu J. Encyclopedia of Environmental Healthed.: Elsevier Science & Technology, 2011: 336-47.

3. Buffler P, Kwan M, Reynolds P, Urayama K. Environmental and Genetic Risk Factors for Childhood Leukemia: Appraising the Evidence. Cancer Invest. 2005; 23(1): 60-75.

4. Von Behren J, Spector LG, Mueller BA, Carozza SE, Chow EJ, Fox EE, Horel S, Johnson KJ, McLaughlin C, Puumala SE, Ross JA, Reynolds P. Birth order and risk of childhood cancer: a pooled analysis from five US States. Int J Cancer. 2011; 128(11):2709-16.

5. Hjalgrim LL, Rostgaard K, Hjalgrim H, Westergaard T, Thomassen H, Forestier E, Gustafsson G, Kristinsson J, Melbye M, Schmiegelow K. Birth weight and risk for childhood leukemia in Denmark, Sweden, Norway, and Iceland. J Natl Cancer Inst. 2004; 96(20):1549-56.

6. Oksuzyan S, Crespi CM, Cockburn M, Mezei G, Kheifets L. Birth weight and other perinatal characteristics and childhood leukemia in California. Cancer Epidemiol. 2012; 36(6):e359-65.

7. Marcotte EL, Ritz B, Cockburn M, Yu F, Heck JE. Exposure to Infections and Risk of Leukemia in Young Children. Cancer Epidemiol Biomarkers Prev. 2014 May 3. [Epub ahead of print]

8. Rudant J, Lightfoot T, Urayama KY, Petridou E, Dockerty JD, Magnani C, Milne L, Spector LG, Ashton L, Dessypris N, Kang AY, Miller M, Rondelli R, Simpson J, Stiakaki E, Orsi L, Roman E, Metayer C, Infante-Rivard C, Clavel J. Childhood acute lymphoblastic leukemia and indicators of early immune stimulation: a Childhood Leukemia International Consortium (CLIC). Under review

9. Schüz J, Kaatsch P, Kaletsch U, Meinert R, Michaelis J. Association of childhood cancer with factors related to pregnancy and birth. Int J Epidemiol. 1999; 28(4):631-9.

10. Schmidt LS, Kamper-Jørgensen M, Schmiegelow K, Johansen C, Lähteenmäki P, Träger C, Stokland T, Grell K, Gustafson G, Kogner P, Sehested A, Schüz J. Infectious exposure in the first years of life and risk of central nervous system tumours in children: analysis of birth order, childcare attendance and seasonality of birth. Br J Cancer. 2010; 102(11):1670-5.

11. Schüz J, Schmidt LS, Kogner P, Lähteenmäki PM, Pal N, Stokland T, Schmiegelow K. Birth characteristics and Wilms tumors in children in the Nordic countries: a register-based case-control study. Int J Cancer. 2011; 128(9):2166-73.

12. Johnson KJ, Carozza SE, Chow EJ, Fox EE, Horel S, McLaughlin CC, Mueller BA, Puumala SE, Reynolds P, Von Behren J, Spector LG. Birth characteristics and childhood carcinomas. Br J Cancer. 2011; 105(9):1396-401.

13. Olson JE, Shu XO, Ross JA, Pendergrass T, Robison LL. Medical record validation of maternally reported birth characteristics and pregnancy-related events: a report from the Children's Cancer Group. Am J Epidemiol. 1997; 145(1):58-67.

14. Crouch S, Lightfoot T, Simpson J, Smith A, Ansell P, Roman E. Infectious illness in children subsequently diagnosed with acute lymphoblastic leukemia: modeling the trends from birth to diagnosis. Am J Epidemiol. 2012; 176(5):402-8.

15. Wiemels J. Perspectives on the causes of childhood leukemia. Chem Biol Interact. 2012; 196(3):59-67.

16. Greaves MF. Commentary: Birth order and risk of childhood acute lymphoblastic leukaemia (ALL). Int J Epidemiol. 2001; 30(6):1438-9.

17. Greaves M. Molecular genetics, natural history and the demise of childhood leukaemia. Eur J Cancer. 1999; 35(2):173-85.

18. Greaves M. Infection, immune responses and the aetiology of childhood leukaemia. Nat Rev Cancer. 2006; 6(3):193-203.

19. Roman E, Simpson J, Ansell P, Lightfoot T, Smith A. Infectious proxies and childhood leukaemia: findings from the United Kingdom Childhood Cancer Study (UKCCS). Blood Cells Mol Dis. 2009; 42(2):126-8.

20. Roman E, Simpson J, Ansell P, Kinsey S, Mitchell CD, McKinney PA, Birch JM, Greaves M, Eden T; United Kingdom Childhood Cancer Study Investigators. Childhood acute lymphoblastic leukemia and infections in the first year of life: a report from the United Kingdom Childhood Cancer Study. Am J Epidemiol. 2007; 165(5):496-504

21. Simpson J, Smith A, Ansell P, Roman E. Childhood leukaemia and infectious exposure: a report from the United Kingdom Childhood Cancer Study (UKCCS). Eur J Cancer. 2007; 43(16):2396-403.

22. Bernstein L, Depue RH, Ross RK, Judd HL, Pike MC, Henderson BE. Higher maternal levels of free estradiol in first compared to second pregnancy: early gestational differences. J Natl Cancer Inst. 1986; 76(6):1035-9.

23. Maccoby EE, Doering CH, Jacklin CN, Kraemer H. Concentrations of sex hormones in umbilical-cord blood: their relation to sex and birth order of infants. Child Dev. 1979; 50(3):632-42.

24. Cook MB, Akre O, Forman D, Madigan MP, Richiardi L, McGlynn KA. A systematic review and meta-analysis of perinatal variables in relation to the risk of testicular cancer--experiences of the mother. Int J Epidemiol. 2009; 38(6):1532-42.

25. Juntunen KS, Läärä EM, Kauppila AJ. Grand grand multiparity and birth weight. Obstet Gynecol. 1997; 90:495-9.

26. Harder T, Plagemann A, Harder A. Birth weight and subsequent risk of childhood primary brain tumors: a meta-analysis. Am J Epidemiol. 2008; 168(4):366-73.

27. Harder T, Plagemann A, Harder A. Birth weight and risk of neuroblastoma: a meta-analysis. Int J Epidemiol. 2010; 39(3):746-56.

28. Jones M, Jeal H, Harris JM, Smith JD, Rose ML, Taylor AN, Cullinan P. Association of maternal anti-HLA class II antibodies with protection from allergy in offspring. Allergy. 2013; 68(9):1143-9.

29. Schüz J, Forman MR. Birthweight by gestational age and childhood cancer. Cancer Causes Control. 2007; 18(6):655-63.

30. Schüz J. Non-response bias as a likely cause of the association between young maternal age at the time of delivery and the risk of cancer in the offspring. Paediatr Perinat Epidemiol. 2003; 17(1):106-12.

31. Thygesen LC, Daasnes C, Thaulow I, Bronnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. Scand J Public Health 2011; 39(7 Suppl):12-16.

32. Gjerstorff ML. The Danish Cancer Registry. Scand J Public Health 2011; 39(7 Suppl):42-45.

33. Nguyen-Nielsen M, Svensson E, Vogel I, Ehrenstein V, Sunde L. Existing data sources for clinical epidemiology: Danish registries for studies of medical genetic diseases. Clin Epidemiol. 2013; 5:249-62.

34. Birch JM, Marsden HB. A classification scheme for childhood cancer. Int J Cancer. 1987; 40(5):620-4.

35. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. Cancer. 2005; 103(7):1457-67.

36. Raaschou-Nielsen O, Obel J, Dalton S, Tjønneland A, Hansen J. Socioeconomic status and risk of childhood leukaemia in Denmark. Scand J Public Health. 2004; 32(4):279-86.

37. Petersen AN (editor). Børns levevilkår [Childrens living conditions]. Statistics Denmark 2002; Statistics Denmark Printing, Copenhagen; ISBN 87-501-1286-4

38. Heck JE, Ritz B, Hung RJ, Hashibe M, Boffetta P. The epidemiology of neuroblastoma: a review. Paediatr Perinat Epidemiol. 2009; 23(2):125-43.

39. Puumala SE, Ross JA, Aplenc R, Spector LG. Epidemiology of childhood acute myeloid leukemia. Pediatr Blood Cancer. 2013; 60(5):728-33.

Table 1. Demographic characteristics of childhood cancer cases at ages 0-19 years observed in a cohort of all live-born children born in Denmark between 1973 and 2010, followed up until 31/10/2013, by sex, age group at diagnosis, and birth order, and by cancer type.

	All cancers (I-XII)		Leukemias (I)		ALL[a] (Ia)		AML[b] (Ib)		Lymphomas (II)		CNS Tumors (III)		Neuroblastomas (IV)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	5699	100.0	1464	100.0	1137	100.0	245	100.0	648	100.0	1469	100.0	303	100.0
Sex														
Boys	3150	55.3	817	55.8	656	57.7	117	47.8	422	65.1	771	52.5	168	55.4
Girls	2549	44.7	647	44.2	481	42.3	128	52.2	226	34.9	698	47.5	135	44.6
Age at diagnosis (years)														
< 1	502	8.8	89	6.1	30	2.6	40	16.3	12	1.9	112	7.6	99	32.7
1-4	1734	30.4	735	50.2	618	54.4	90	36.7	71	11.0	365	24.9	147	48.5
5-9	1167	20.5	330	22.5	285	25.1	34	13.9	137	21.1	417	28.4	35	11.5
10-14	956	16.8	173	11.8	130	11.4	34	13.9	164	25.3	300	20.4	16	5.3
15-19	1340	23.5	137	9.4	74	6.5	47	19.2	264	40.7	275	18.7	6	2.0
Birth order														
1st	2595	45.6	658	44.9	523	46.0	96	39.1	304	46.9	683	46.5	134	44.2
2nd	2090	36.7	544	37.2	412	36.2	101	41.2	225	34.7	533	36.3	112	37.0
3rd	750	13.2	200	13.7	153	13.5	37	15.2	82	12.7	185	12.6	47	15.5
4th or higher	264	4.6	62	4.2	49	4.3	11	4.5	37	5.7	68	4.6	10	3.3

(continued)

	Retinoblastomas (V)		Renal tumors (VI)		Hepatic tumors (VII)		Bone Tumors (VIII)		Sarcomas (IX)		Others (X-XII)	
	N	%	N	%	N	%	N	%	N	%	N	%
Total (N)	140	100.0	250	100.0	67	100.0	233	100.0	325	100.0	800	100.0
Sex												
Boys	79	56.4	118	47.2	38	56.7	123	52.8	192	59.1	422	52.8
Girls	61	43.6	132	52.8	29	43.3	110	47.2	133	40.9	378	47.3
Age at diagnosis (years)												
< 1	63	45.0	35	14.0	17	25.4	1	0.4	33	10.2	41	5.1
1-4	71	50.7	146	58.4	27	40.3	13	5.6	93	28.6	66	8.3
5-9	6	4.3	50	20.0	7	10.4	64	27.5	65	20.0	56	7.0
10-14	0	0.0	12	4.8	6	9.0	87	37.3	56	17.2	142	17.7
15-19	0	0.0	7	2.8	10	14.9	68	29.2	78	24.0	495	61.9
Birth order												
1st	61	43.6	110	44.0	28	41.8	109	46.7	147	45.3	361	45.1
2nd	50	35.7	96	38.4	26	38.8	78	33.5	121	37.2	305	38.1
3rd	20	14.3	32	12.8	7	10.4	34	14.6	43	13.2	100	12.5
4th or higher	9	6.4	12	4.8	6	9.0	12	5.2	14	4.3	34	4.3

[a] ALL= acute lymphoblastic leukemia, [b] AML = acute myeloid leukemia

Table 2. Adjusted[a] associations between birth order and childhood cancers at ages 0-19 and in a sub-cohort of those diagnosed at ages 0-14 years, by cancer type, in a cohort of all children live-born in Denmark between 1973 and 2010 , followed up until 31/10/2013.

Ages 0-19 years	All cancers (I-XII)		Leukemias (I)		ALL[b] (Ia)		AML[c] (Ib)		Lymphomas (II)		CNS Tumors (III)		Neuroblastomas (IV)	
	RR[c]	CI	RR[d]	CI	RR	CI	RR	CI	RR	CI	RR	CI	RR	CI
Birth order														
1st	1.00	(ref.)	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
2nd	0.97	0.92-1.03	0.98	0.88-1.11	0.93	0.82-1.06	1.30	0.97-1.73	0.91	0.76-1.07	0.96	0.86-1.08	0.97	0.75-1.25
3rd	0.95	0.87-1.03	0.97	0.82-1.14	0.91	0.75-1.09	1.35	0.91-2.00	0.89	0.69-1.15	0.91	0.77-1.08	1.10	0.78-1.55
4th or higher	0.96	0.84-1.10	0.81	0.61-1.07	0.80	0.58-1.09	1.00	0.49-2.02	1.20	0.83-1.73	1.02	0.78-1.33	0.72	0.37-1.40
p for trend[d]		0.20		0.25		0.10		0.21		0.81		0.48		0.78

Ages 0-19 years	Retinoblastomas (V)		Renal tumors (VI)		Hepatic tumors (VII)		Bone Tumors (VIII)		Sarcomas (IX)		Others (X-XII)	
	RR	CI	RR	CI	RR	CI	RR	CI	RR	CI	RR	CI
Birth order												
1st	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
2nd	0.96	0.65-1.40	1.05	0.79-1.39	1.05	0.61-1.82	0.87	0.65-1.16	0.99	0.78-1.26	1.03	0.88-1.20
3rd	1.04	0.61-1.76	1.01	0.68-1.52	0.72	0.31-1.70	1.05	0.71-1.56	0.97	0.69-1.38	0.91	0.72-1.15
4th or higher	1.48	0.71-3.08	1.18	0.63-2.19	1.02	0.33-3.11	1.12	0.60-2.08	0.79	0.43-1.45	0.91	0.63-1.32
p for trend[d]		0.52		0.69		0.72		0.90		0.59		0.51

(table to be continued)

Ages 0-14 years	All cancers (I-XII)		Leukemias (I)		ALL[a] (Ia)		AML[b] (Ib)		Lymphomas (II)		CNS Tumors (III)		Neuroblastomas (IV)	
	RR[c]	CI[d]	RR	CI	RR	CI	RR	CI	RR	CI	RR	CI	RR	CI
Birth order														
1st	1.00	(ref.)	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
2nd	0.96	0.89-1.02	0.99	0.88-1.12	0.93	0.81-1.07	1.38	0.99-1.89	0.88	0.70-1.10	0.91	0.80-1.03	0.98	0.76-1.27
3rd	0.93	0.84-1.02	0.99	0.84-1.18	0.91	0.75-1.10	1.54	1.01-2.35	0.70	0.49-0.99	0.86	0.71-1.04	1.14	0.80-1.61
4th or higher	0.96	0.83-1.12	0.82	0.61-1.10	0.82	0.60-1.13	0.84	0.36-1.97	0.99	0.61-1.63	0.94	0.70-1.27	0.75	0.39-1.45
p for trend[d]		0.13		0.41		0.14		0.17		0.14		0.13		0.94

Ages 0-14 years	Retinoblastomas (V)		Renal tumors (VI)		Hepatic tumors (VII)		Bone Tumors (VIII)		Sarcomas (IX)		Others (X-XII)	
	RR	CI	RR	CI	RR	CI	RR	CI	RR	CI	RR	CI
Birth order												
1st	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
2nd	0.96	0.66-1.41	1.06	0.79-1.41	1.15	0.64-2.09	0.90	0.63-1.26	0.98	0.74-1.30	0.96	0.74-1.24
3rd	1.05	0.62-1.77	1.06	0.71-1.59	0.80	0.32-2.03	0.95	0.59-1.55	0.91	0.61-1.37	0.89	0.61-1.29
4th or higher	1.50	0.72-3.12	1.25	0.67-2.32	1.40	0.45-4.36	1.29	0.65-2.57	0.93	0.49-1.76	1.16	0.69-1.96
p for trend[d]		0.50		0.52		0.85		0.87		0.67		0.93

[a] Adjusted for parental age and birth weight, [b] ALL= acute lymphoblastic leukemia, [c] AML = acute myeloid leukemia, [d] RR=rate ratio, [e] CI=95% confidence interval, [d] p value for test for linear trend with increasing birth order

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