Birth defects and cancer risk

Nordic population-based studies of cancer risk in children, adolescents, and adults with major birth defects and their siblings

Dagrun Slettebø Daltveit

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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UNIVERSITY OF BERGEN

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List of abbreviations

ALL	Acute lymphatic leukaemia
AML	Acute myeloid leukaemia
ASR	Age-standardized rate
BPA	British Paediatric Association
CI	Confidence interval
CNS	Central nervous system
DAG	Directed acyclic graph
DALY	Disability-adjusted life years
EUROCAT	The European Network of Population-Based Registries for the Epidemiological Surveillance of Congenital Anomalies
HR	Hazard ratio
ICCC	International Classification of Childhood Cancer
ICD	International Classification of Diseases
ICD-O	International Classification of Diseases for Oncology
IVF	*In vitro* fertilization
LMIC	Low- and middle-income countries
OR	Odds ratio

Scientific environment

This work has been carried out at the Section for Epidemiology and Medical Statistics at the Department of Global Public Health and Primary Care (IGS), Faculty of Medicine, University of Bergen (UiB), Norway. The project has been a part of the larger Nordic Countries Linked Birth and Cancer Registries Cohort Project. I have been affiliated with the Centre for Translational Research in Epidemiology (TRACE), the Lifestyle Epidemiology Research Group, the Research School in Public Health and Primary Health Care at UiB, and the National Research School in Population-based Epidemiology (EPINOR). From January 2020 to January 2022, I served as the student representative from UiB on the steering committee of EPINOR.

Main supervisor

Professor Tone Bjørge, Department of Global Public Health and Primary Care, Faculty of Medicine, University of Bergen, and Cancer Registry of Norway, Norwegian Institute of Public Health, Oslo, Norway.

Co-supervisor

Professor Kari Klungsøyr, Department of Global Public Health and Primary Care, Faculty of Medicine, University of Bergen, and Division of Mental and Physical Health, Norwegian Institute of Public Health, Bergen, Norway.

Secondary position

I have held a 20% position at the Norwegian Registry of Cleft Lip and Palate, Surgical Clinic, Haukeland University Hospital, Bergen, Norway.

International exchange

From 17 December 2022 to 16 December 2023, I was enrolled as an Early Career and Visiting Scientist within the International Agency for Research on Cancer (IARC) Research Training and Fellowship Programme, World Health Organization (WHO) in Lyon, France. I was hosted by the Cancer Surveillance Branch (CSU), under the supervision of Dr Isabelle Soerjomataram.

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During my whole PhD period, I have been a member of the research group for *Lifestyle Epidemiology* and have benefited greatly from various multi-disciplinary discussions. Thank you to all members for a friendly working environment which, together with our research group's pianist, have made some of the dark winter (or PhD) days in Bergen feel like a *Sommernatt ved fjorden*. Many thanks also to the members of EPISTAT and TRACE, I have benefited largely from the many research seminars and meetings arranged. Furthermore, I would like to thank the *National Research School in Population-based Epidemiology* (EPINOR) and the *Research School in Public Health and Primary Health Care* at IGS for several interesting and educational courses.

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Dagrun

Bergen, March 2024.

Sammendrag

Bakgrunn Medfødte misdannelser og kreft er begge blant de ti vanligste årsakene til tapte leveår grunnet død eller helsetap for barn mellom 0 og 19 år (ulykker og perinatale sykdommer ekskludert). Årsakene til begge sykdommene er i stor grad ukjente. Alvorlige misdannelser er imidlertid etablert som risikofaktorer for kreft blant barn, noe som kan tyde på en felles etiologi.

Hensikt Vi undersøkte sammenhengen mellom det å ha en alvorlig misdannelse eller å ha et søsken med en alvorlig misdannelse og senere kreftutvikling; blant barn, ungdom og voksne, samt kjønnsforskjeller i denne sammenhengen blant barn.

Metode Vi gjennomførte tre populasjonsbaserte nøstede kasus-kontrollstudier hvor vi kombinerte registerdata fra Danmark, Finland, Norge og Sverige. Personer registrert i fødselsregistrene mellom 1967 og 2014 som utviklet kreft ble definert som kasus. Kontrollene ble matchet på land og fødselsår. Eksponeringene vi undersøkte var alvorlige misdannelser blant individene eller deres søsken. Den relative risikoen for kreft assosiert med eksponeringen ble estimert som oddsratio fra logistiske regresjonsmodeller.

Resultat Den relative risikoen for kreft blant personer med alvorlige misdannelser var 1,7 ganger høyere enn blant personer uten misdannelser. Den økte risikoen vedvarte inn i voksen alder (1,2 ganger høyere), spesielt gjaldt dette voksne med alvorlige misdannelser i hjerte, kjønnsorganer, nervesystemet, skjelettdysplasier og Down syndrom. Sammenhengene mellom alvorlige misdannelser og barnekreft var generelt sterkere blant jenter enn gutter. Blant personer som hadde søsken med alvorlige misdannelser, var risikoen for barnekreft (0 til 19 år) noe økt (1,09 ganger), mens den totale risikoen for kreft blant personer i alderen 0 til 46 år ikke var økt.

Konklusjon Våre resultater stemmer overens med hypotesen om felles bakenforliggende årsaker til alvorlige misdannelser og kreft: genetiske, miljømessige eller en kombinasjon. Arbeidet danner grunnlaget for videre forskning på de biologiske mekanismene som ligger bak begge sykdommene.

Abstract

Background Globally, birth defects and childhood cancer are among the 10 most common causes of childhood disease burden (excluding perinatal diseases and injuries). There are few established risk factors for both diseases, but birth defects have consistently been associated with childhood cancer risk, suggesting a common aetiology. Given the large global public health impact of birth defects and childhood cancer, a broader understanding of the underlying causes is warranted.

Objectives We aimed to explore the associations between having a major birth defect or having a sibling with a major birth defect and cancer among children, adolescents, and adults, and to evaluate if the associations among children differed by sex.

Methods We performed three population-based nested case-control studies where we combined registry data from Denmark, Finland, Norway, and Sweden. Individuals registered in the birth registries between 1967 and 2014 who later developed cancer were defined as cases. Controls were frequency-matched on country and year of birth. The exposure of interest was major birth defects in the individuals or the siblings. The relative risk of cancer associated with the exposure was estimated as odds ratios from logistic regression models.

Results The relative risk of overall cancer in individuals with birth defects compared to individuals without birth defects was 1.7. The increased risk persisted into adulthood (1.2-fold), in particular for individuals with congenital heart defects, genital organ defects, chromosomal anomalies, nervous system defects, and skeletal dysplasia. The birth defect-childhood cancer associations were generally stronger in girls than boys. The risk of childhood cancer (0 to 19 years) was slightly elevated (1.09-fold) in individuals whose siblings had birth defects, but the overall risk of cancer in individuals aged 0 to 46 years was not increased.

Conclusions Our novel findings provide evidence consistent with common aetiologies of birth defects and cancer, such as shared genetic predisposition and environmental factors, and should motivate further research into possible biological mechanisms.

EVIDENCE BEFORE THE STUDY	WHAT THE STUDY ADDS
Paper I	
Having a birth defect is a strong risk factor for childhood cancer.	The increased cancer risk persisted into adulthood.
Risk varies by type of birth defect and childhood cancer and increases by the number of birth defects.	Many structural birth defects were associated with later cancer in the same anatomical location or organ system.
The excess cancer risk is largest in the youngest children but mostly unknown beyond the age of 20.	There was a dose-response relation between the number of birth defects and cancer risk.
Paper II	
Both birth defects and childhood cancer are more common in boys.	We observed sex differences in the birth defect-childhood cancer associations.
The association between birth defects and childhood cancer is well known, but whether the association differs by sex is uncertain.	The birth defect-childhood cancer associations were generally stronger in girls than boys but varied by types of birth defect and childhood cancer.
It has been suggested that birth defects act as mediators in the sex-childhood cancer relationship, explaining up to 40% of the association.	A birth defect was not a strong mediator in the association between sex and childhood cancer, suggesting that other biological pathways are involved.
Paper III	
Birth defects have a recurrence risk in first-degree relatives.	The risk of childhood cancer for individuals whose siblings had birth defects was elevated.
A history of cancer among first-degree relatives is associated with an increased risk of specific childhood cancers.	The overall cancer risk in individuals aged 0 to 46 years was not increased.
Whether the siblings of individuals with birth defects are at increased risk of cancer is not well understood.	Risks differed by type of birth defect, the number of exposed siblings, type of cancer, and age at cancer diagnosis.

List of publications

Paper I

Daltveit, D. S., Klungsøyr, K., Engeland, A., Ekbom, A., Gissler, M., Glimelius, I., Grotmol, T., Madanat-Harjuoja, L., Ording, A. G., Sæther, S. M. M., Sørensen, H. T., Troisi, R., & Bjørge, T. (2020). Cancer risk in individuals with major birth defects: large Nordic population based case-control study among children, adolescents, and adults. *BMJ*, 371, m4060. https://doi.org/10.1136/bmj.m4060

Paper II

Daltveit, D. S., Klungsøyr, K., Engeland, A., Ekbom, A., Gissler, M., Glimelius, I., Grotmol, T., Madanat-Harjuoja, L., Ording, A. G., Sørensen, H. T., Troisi, R., & Bjørge, T. (2023). Sex differences in childhood cancer risk among children with major birth defects: a Nordic population-based nested case-control study. *International journal of epidemiology*, 52(2), 450–465. https://doi.org/10.1093/ije/dyac192

Paper III

Daltveit, D. S., Klungsøyr, K., Engeland, A., Ekbom, A., Gissler, M., Glimelius, I., Grotmol, T., Madanat-Harjuoja, L., Ording, A. G., Sørensen, H. T., Troisi, R., & Bjørge, T. (2023). Cancer risk in the siblings of individuals with major birth defects: a large Nordic population-based case-control study. *International journal of epidemiology*, 52(6), 1826–1835. https://doi.org/10.1093/ije/dyad113

Contents

1. Introduction

Birth defects and childhood cancer both rank among the top ten global causes of childhood disease burden (excluding perinatal diseases and injuries) and were estimated to contribute 51.4 and 11.5 million disability-adjusted life years (DALYs) in 2017, respectively.[1] Annually, 6% of all newborns across the world are estimated to be born with a birth defect.[2] The majority of them are born in low- and middle-income countries (LMICs).[3] Furthermore, in children under the age of five, birth defects were ranked as the 4th most common cause of death in 2019, accounting for 9.4% of all deaths globally.[4] In 2022, more than 270,000 children were estimated to be diagnosed with cancer and more than 100,000 children died of cancer worldwide.[5] The childhood cancer incidence is higher in countries with very high human development index scores, whereas the mortality-to-incidence ratio is higher in less developed regions.[5] Despite significant improvements in childhood cancer diagnostics, pharmacology, and treatment during the last five decades,[6] the global disparities in survival persist with substantially lower survival in resource-limited countries compared to high-income countries.[7]

In 2015, the United Nations announced the 2030 Agenda for Sustainable Development which contains 17 Sustainable Development Goals and associated targets.[8] The third sustainable development goal is to "*Ensure healthy lives and promote well-being for all at all ages*" and it includes the reduction of child mortality (target 3.2) and the reduction of premature mortality from cancer (part of target 3.4). Given the substantial contribution of birth defects and childhood cancer to childhood disease burden, prevention and/or reduction of both are important parts of meeting this goal.

Extensive research to identify causes of birth defects and childhood cancer has been conducted during the last decades.[9-11] Nevertheless, most birth defects and childhood cancers still have unknown aetiologies (~80% and ~90%, respectively) and few consistent risk factors have been identified for both diseases.[10,11] However, being born with a birth defect is one of few established risk factors for childhood cancer,

suggesting a common aetiology.[11-13] The contribution of birth defects to the risk of adult cancer is mostly unknown.[14-17]

1.1 Childhood cancer

Cancer is a large group of diseases that *"manifests itself as either a solid mass or a nonsolid leukemia in the circulatory system"*.[18] The common underlying pathology is characterized by uncontrolled cellular growth and division and can start in almost all cell types and organ systems in the body.[19] Cancer is a genetic disease, meaning that it is caused by genetic and epigenetic changes.[19] Cancer in children (aged 0-19) is rare, accounting for only 1.5% of the total cancer cases globally.[5] Childhood cancer is a heterogeneous group of diseases and is usually biologically different from cancer in adults.[11,20] While adult cancer is commonly classified based on primary site according to the International Classification of Diseases (ICD), childhood cancer is classified by both site and histology based on the International Classification of Diseases for Oncology (ICD-O). The current classification system for childhood cancers is the International Classification of Childhood Cancer, third edition (ICCC-3).[21] There is no clear age cut-off between childhood cancer and cancer in adults, and both 0–14 and 0–19 years are commonly used.[22]

1.1.1 Aetiology

Most childhood cancers have unknown causes and few consistent risk factors have been identified.[11,23] The time window for potential exposure to carcinogens compared to adult cancer is limited, and a major research focus has therefore been on prenatal and early-life exposures.[19] Many childhood cancers are thought to originate *in utero*.[11,19,23] This hypothesis dates back to the 1950s when a modest association between diagnostic radiography *in utero* and childhood cancer was first reported.[24,25] However, a few risk factors have been identified, and some of them are unique to specific cancers (Table 1.1). The research has, however, been performed almost exclusively in high-income countries and may not be generalizable to other regions with different risk profiles.

Table 1.1 Confirmed and suspected risk factors for selected childhood cancers. Adapted from Cancer Epidemiology, Biomarkers & Prevention, Copyright 2020, 29/6, Page 1085, Philip J. Lupo and Logan G. Spector, Cancer Progress and Priorities: Childhood Cancer, with permission from AACR.

	ALL	AML	NB	HB	RB	WT	MB	PNET	Epe.	Ast.	Strength of evidence
Preconception/pregnancy											
Smoking											++
Vitamins											++
Occupational exposures											++
Residental exposures											++
Coffee											+
Alcohol											++
Ionizing radiation											+++
Birth											
Maternal age											++
Paternal age											++
Chromosomal BDs											+++
Non-chromosomal BDs											+++
High birth weight											+++
Low birth weight											+++
C-section											+
Gestational age											+
Childhood											
Breastfeeding											+
Allergies											
Residential chemical											
Passive smoke											+
Irradiation											++

Note: Taken from refs. 25, 30, 31,103-266. For strength of evidence: + epidemiologic evidence with little mechanistic support; ++ can cross placenta or has developmental consequences but epidemiologic evidence is equivocal; +++ strong epidemiologic and mechanistic evidence.
Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; Ast., Astrocytoma; BD, birth defect; Epe., Ependymoma; HB, hepatoblastoma; MB, medulloblastoma; NB, neuroblastoma; PNET, primitive neuroectodermal tumor; RB, retinoblastoma; WT, Wilms tumor.

Legend

Positive, effect estimate <1.5	
Positive, effect estimate ≥1.5	
No association	
Negative, effect estimate >0.67	
Negative, effect estimate ≤0.67	
Inconclusive	

Genetic risk factors

Inherited cancer predisposition syndromes account for approximately 10% of all cancer cases in individuals below the age of 25.[19] For instance, Down syndrome is well known to be associated with an increased risk of leukaemia.[15,26] Several other cancer predisposition syndromes and genes have been identified, including Li-Fraumeni syndrome, neurofibromatosis, and Fanconi anemia.[27] For some of the more common syndromes with a high risk of cancer (~5%), cancer surveillance may be warranted.[28] In addition, genetic predisposition for cancer may also be suspected if i) there is a family history of cancer,[29] ii) the age at diagnosis is younger than usual, iii) the cancer is associated with predisposition syndromes, iv) there are multiple malignancies, v) there are co-occurring birth defects, or vi) there is excessive cancer treatment toxicity.[30]

Environmental risk factors

There is little evidence of environmental risk factors for childhood cancer. The only known environmental cause of childhood cancer is exposure to high-dose ionizing radiation, but this accounts for very few cancer cases.[11] Low-dose radiation, on the other hand, has not been found to be a risk factor for childhood cancer.[31] Other proposed environmental risk factors are air pollution and pesticides, but the evidence of (potential) modest effects is limited.[11] Meta-analyses of maternal alcohol, coffee, and vitamin use, and maternal and paternal smoking have also failed to demonstrate strong associations with childhood cancer.[23,32]

Infections, such as Helicobacter pylori, human papillomavirus and hepatitis B and C virus, are known to cause cancer in adults.[33] Dating back to 1917, exposure to infections, both perinatally and early in life, has also been proposed as a risk factor for childhood cancer, in particular acute lymphatic leukaemia (ALL).[19,23,34-36] For ALL, two specific hypotheses have been proposed: Greaves *delayed infection* hypothesis and Kinlen's *population-mixing* hypothesis, both discussed in Greaves (2018).[34] Both hypotheses postulate that childhood leukaemia could be caused by an abnormal immune response to an infection.[34]

Gestational and perinatal risk factors

Birth weight has consistently been associated with childhood cancer.[11,37] For most cancers, increasing birth weight is associated with increasing risk.[11] One exception is hepatic tumours, for which increasing birth weight is associated with decreasing risk.[38] Higher parental age has been found to increase the risk of many childhood cancers.[11] More specifically, maternal age has been seen to give a 5–10% higher risk per 5 years of age. Birth defects have also been established as a strong risk factor for many childhood cancers.[12,13] Lastly, *in vitro* fertilization (IVF), preeclampsia, gestational diabetes, and maternal obesity are other gestational factors suggested to be associated with increased childhood cancer risk, but so far the evidence is very limited.[11,39,40]

Other risk factors

The risk of childhood cancer varies by age at diagnosis with a U-shaped incidence curve by age. However, the association with age differs strongly by cancer type and different cancers prevail at different ages.[19] Male sex is associated with an approximately 1.2 higher risk of childhood cancer, but the causes of this sex difference are less understood.[41] Finally, differences in risk by ethnicity have been reported in the United States, with higher risk in whites compared to blacks, Asians, and Hispanics.[42]

1.1.2 Descriptive epidemiology

Childhood cancer incidence

According to the GLOBOCAN estimates of cancer incidence in 2022, there were approximately 270,000 new childhood cancer cases worldwide, excluding non-melanoma skin cancer.[5] The majority of cases occurred in Asia (51%) and Africa (22%). The global age-standardized rate (ASR) (world) was 10.5 per 100,000 and ranged from 1.9 in Micronesia to 19.4 in Northern America. There were large variations in incidence between countries, with generally lower rates in Africa and Asia (Figure 1.1). Overall, the incidence was higher in boys compared to girls (ASRs 11.4 versus 9.6, respectively). In 2022, the most common childhood cancers worldwide were leukaemia (28.2%; boys: ASR = 3.5, girls: ASR = 2.6), central nervous system (CNS) tumours (11.2%; boys: ASR = 1.3, girls: ASR = 1.1), and non-Hodgkin lymphoma (8.6%; boys: ASR = 1.1, girls: ASR = 0.7) (Figure 1.2).

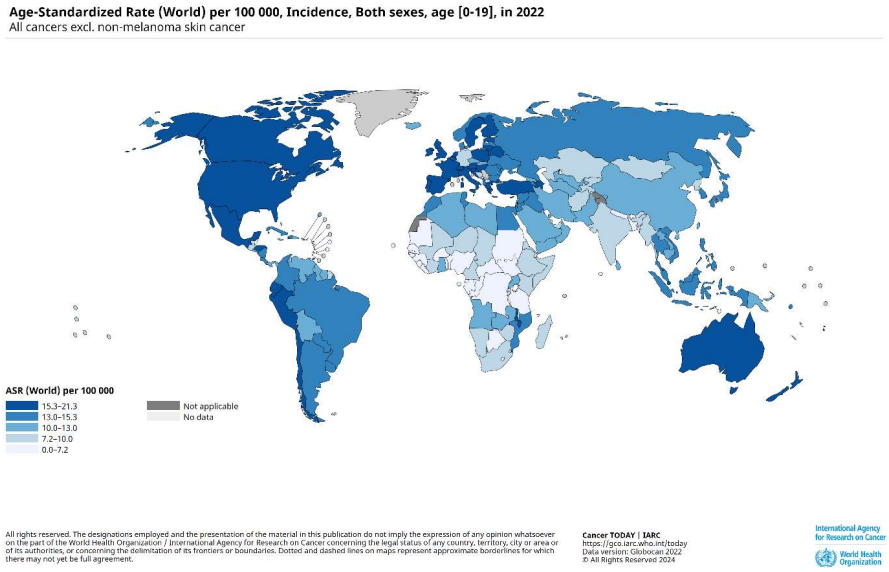

Figure 1.1 Estimated age-standardized incidence rates (world) in 2022, all cancers, both sexes, children (0–19 years). Data source: GLOBOCAN 2022.[5]

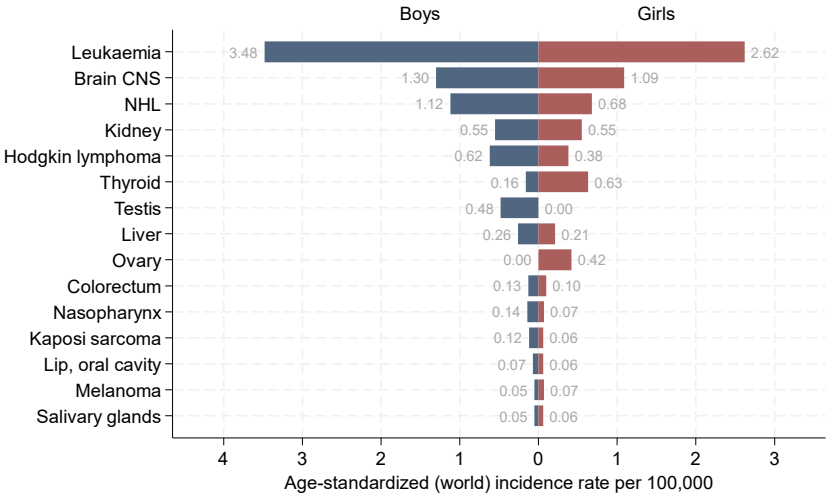

Figure 1.2 Estimated age-standardised rates (world) per 100,000 of the 15 most common childhood cancers (ages 0–19) in 2022 globally, for boys and girls. Ordered by the magnitude of the rate for both sexes combined. Data source: GLOBOCAN 2022.[5]

The male excess in incidence was seen for most childhood cancers with some exceptions (see Figure 1.2). The incidence varied by age at diagnosis, with a global ASR (world) per 100,000 of any cancer, excluding non-melanoma skin cancer, of 11.8 for children aged 0–4 years, 9.3 for children aged 5–9 years, 9.4 for children aged 10–14 years, and 11.8 for children aged 15–19 years.

In the four Nordic countries, around 1000 children are diagnosed with cancer each year.[43] In 2021, the ASRs (world) of childhood cancer in boys and girls were 17.5 and 16.7 per 100,000, respectively. There were some variations between the countries, with rates varying from 15.0 in Sweden to 19.9 in Norway among boys, and from 13.4 in Sweden to 20.2 in Norway among girls. The highest incidence rates were observed for ALL (boys: ASR (world) = 4.4, girls: ASR = 3.6), brain and CNS tumours (boys: ASR = 3.8, girls: ASR = 3.5), Hodgkin lymphoma (boys: ASR = 1.0, girls: ASR = 1.3), and non-Hodgkin lymphoma (boys: ASR=1.6, girls: ASR = 0.6) (Figure 1.3). Different cancer types dominated at different ages, with leukaemia being the most common cancer in the youngest age group (Figure 1.4).

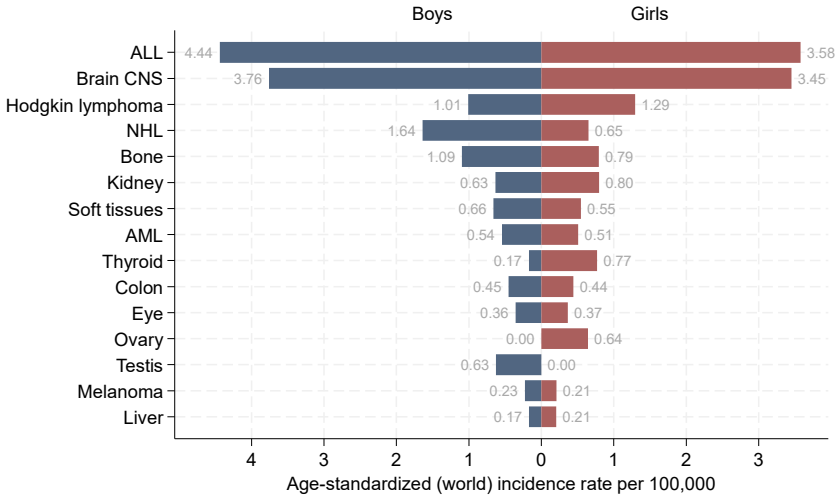

Figure 1.3 Estimated age-standardised rates (world) per 100,000 of the 15 most common childhood cancer cases (ages 0–19) in 2021, for boys and girls in Denmark, Finland, Norway, and Sweden. Ordered by the magnitude of the rate for both sexes combined. Data source: NORDCAN.[43]

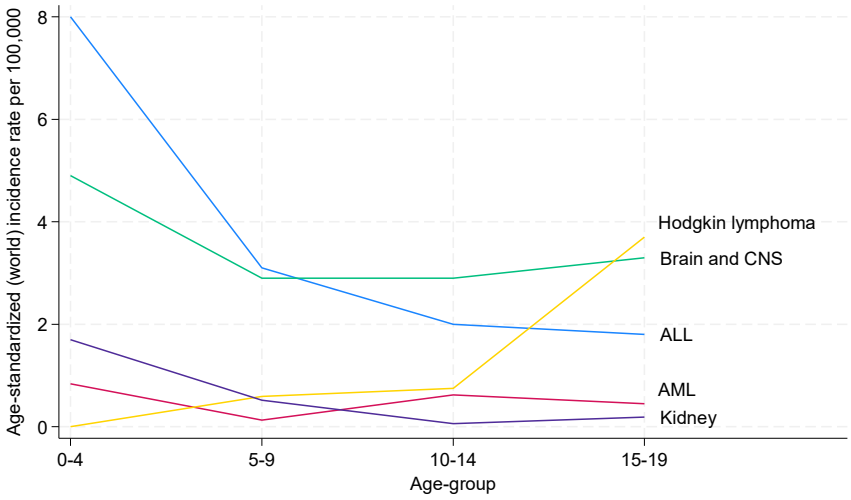

Figure 1.4 Age-specific estimated age-standardised rates (world) per 100,000, both sexes, ages 0–19 years, for selected cancer types in Denmark, Finland, Norway, and Sweden in 2021. Data source: NORDCAN.[43]

Childhood cancer disease burden

The Global Burden of Disease Study estimated the global DALYs due to childhood cancer in 2017 to be 11.5 million years, where 97% of these were due to years of life lost and 3% due to years lived with disability.[1] This puts childhood cancer as the world's ninth leading cause of childhood disease burden.[1]

The mortality of childhood cancer varies substantially across world regions (Figure 1.5).[5] In 2022, the observed mortality was highest in Latin America and the Caribbean (boys: ASR (world) = 5.3 per 100,000, girls: ASR = 4.2), followed by Africa (boys: ASR = 5.1, girls: ASR = 4.2), Asia (boys: ASR = 4.5, girls: ASR = 3.4), Oceania (boys: ASR = 3.6, girls: ASR = 2.5), Europe (boys: ASR = 2.7, girls: ASR = 2.2), and Northern America (boys: ASR = 2.5, girls: ASR = 2.1). Reduction in childhood cancer mortality is mainly achievable through improvements in survival due to the lack of established risk factors for childhood cancer and therefore limited opportunities for cancer prevention. Five-year survival has long been used as an index of successful cancer treatment, and generally, survival of childhood cancer has improved over the last

decades due to improvements in diagnostics and treatment.[6] Overall, children in high-income countries have a 5-year survival rate of 80%.[1] Reliable data on childhood cancer survival in LMICs are scarce, but the global 5-year survival estimate in 2015 was only 37%.[44] In addition, the survival varies greatly by cancer type. Generally, survival is better for ALL, lymphomas, retinoblastoma, and renal tumours and worse for acute myeloid leukaemia (AML) and brain tumours.[45] There are still large disparities in survival across the world regions for most cancers, such as ALL (reliable 5-year survival estimates ranging from 50% in Ecuador to 95% in Finland) and brain tumours (ranging from 29% in Brazil to 80% in Sweden and Denmark).[7] In Europe, the observed overall survival was not different for boys and girls, but the survival of Burkitt's lymphoma was better for boys and the survival of ALL was better for girls.[45]

In the Nordic countries, the overall 5-year survival is above 80%.[45] The highest survival is observed for Hodgkin lymphoma and retinoblastoma (5-year survival of 90%) while the lowest survival is seen for CNS tumours (65%) and osteosarcoma (62%).

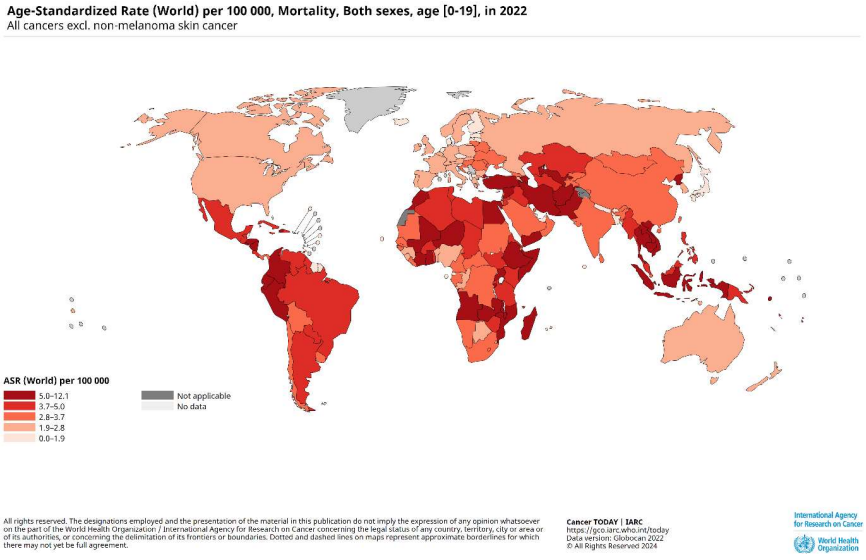

Figure 1.5 Estimated age-standardized mortality rates (world) in 2022, all cancers, both sexes, children (0–19 years). Data source: GLOBOCAN 2022.[5]

1.2 Cancer in adults

The risk of cancer increases drastically with age and it is mostly a disease of the elderly, with slow progression from pre-cancerous lesions to malignant tumours.[46] Multiple risk factors for cancer in adults have been identified, including alcohol consumption[47], tobacco use,[48] UV radiation,[49] obesity,[50] and infections.[33] It is currently estimated that 30–50% of cancers are preventable by avoiding/reducing known risk factors.[46,51] Cancer in adults is usually classified according to the site using the ICD classifications.[52]

In 2022, more than 18 million adults (20+ years) were estimated to be diagnosed with cancer globally.[5] The most common cancers were lung (13%), breast (12%) and prostate cancer (7%). The ASRs (world) of the 15 most common cancers globally are displayed in Figure 1.6. Approximately 9.6 million adults died of cancer in 2022 (global ASR [world] = 149.2 per 100,000), most commonly from lung (19%), liver (8%), and breast cancer (7%). In the Nordic countries, the three most common cancers in 2021 were breast (females: ASR = 148.2), prostate (males: ASR = 135.5), and lung cancer (males: ASR = 39.2, females: ASR = 37.4).[43]

Cancer in adults under the age of 50 is often defined as early-onset cancer, and cancer incidence in this age group is rising in many parts of the world.[53] The clinical, pathological, and molecular characteristics of early-onset cancer are different from cancer at later ages, and early-life exposures are suggested to play an important role.[53] The common early-onset cancers are different from the common cancers in the overall adult population. Globally, the most common early-onset cancers in 2022 were thyroid (10%), liver (8%), and lung cancer (7%) in males, and breast (33%), thyroid (15%), and cervical cancer (13%) in females.[5] In the Nordic countries, the most common early-onset cancers were testicular cancer (ASR (world) = 16.6 per 100,000), melanoma (ASR = 12.4), and brain/CNS tumours (ASR = 7.4) in males, and breast cancer (ASR = 40.6), melanoma (ASR = 16.8), and cervical cancer (ASR = 13.0) in females (Figure 1.7).[43]

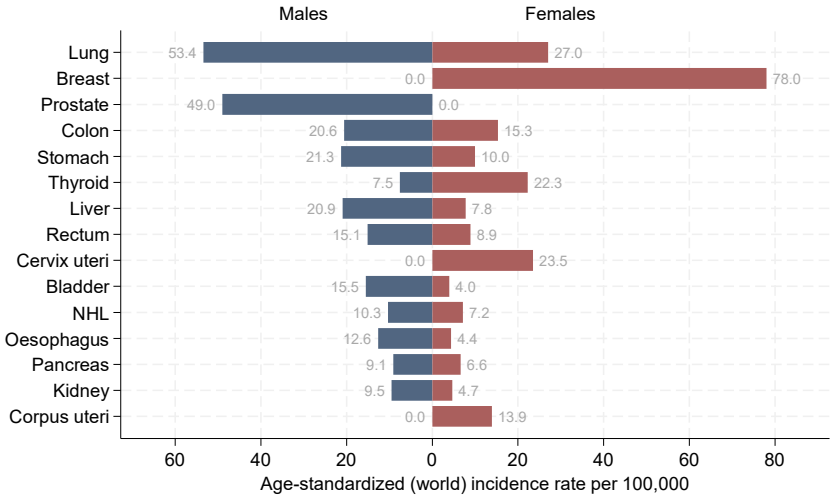

Figure 1.6 Estimated global number of new cancer cases in adults (20+ years), both sexes, in 2022. Ordered by the size of the rate for both sexes combined. Data source: GLOBOCAN 2022.[5]

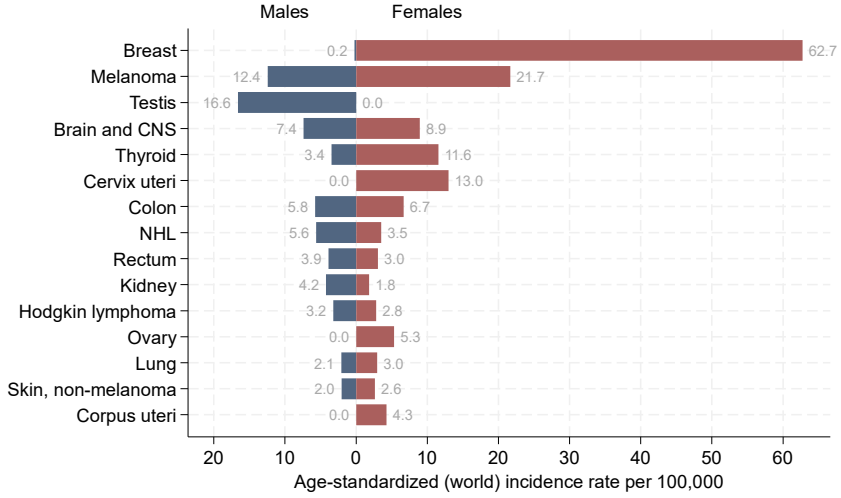

Figure 1.7 Estimated age-standardised rates (world) per 100,000 of the 15 most common cancers (ages 20–49) in 2021, for males and females in Denmark, Finland, Norway, and Sweden. Ordered by the size of the rate for both sexes combined. Data source: NORDCAN.[43]

1.3 Birth defects

Congenital disorders, congenital abnormalities or birth defects can be defined as *"structural or functional anomalies […] that occur during intrauterine life and can be identified prenatally, at birth, or sometimes may only be detected later in infancy, such as hearing defects"*.[3] More than 7000 different birth defects have so far been identified.[54] Structural birth defects are anomalies related to the structure of body parts, and common examples include congenital heart defects and cleft lip and/or palate.[55] Some of the structural birth defects can be corrected with surgery. Functional birth defects are anomalies that affect how body systems function, such as Down syndrome affecting the nervous system. The European Network of Population-Based Registries for the Epidemiological Surveillance of Congenital Anomalies (EUROCAT) issues guides for coding and classification of major birth defects.[56] The most recent version is the EUROCAT Guide 1.5 from 2022,[57] which is a revision of the former Guide 1.4 (2013).[56] In the EUROCAT classification, major birth defects are grouped together based on organ groups or shared aetiology and coded according to ICD-10[58] with the British Paediatric Association (BPA) one-digit extension.[56] In addition, a list of minor and unspecified birth defects for exclusion is provided.

1.3.1 Aetiology

Most birth defects have unknown aetiology, but it is likely that the causes are multifactorial and include combinations or interactions of environmental and genetic factors.[59] In a study on the aetiology of birth defects by Feldkamp *et al*. (2017), they were only able to assign causes for 20% of the birth defects.[10] The majority of the stated causes were chromosomal or genetic conditions (95%), followed by teratogens (4%) and specific twinning abnormalities (acardiac or conjoined twins) (1%). Among the 80% with unknown causes, a family history of birth defects was present for 5%. Toufaily *et al*. (2018) reported similar findings, with 27% of the birth defects in their study having a known cause, where 3.4% were due to environmental factors.[9]

Genetic risk factors

Genetic factors are important in the development of certain birth defects and approximately 20% of all birth defects are suspected to have genetic causes.[60] Many of the syndromic birth defects have known genetic causes.[61] For non-syndromic birth defects, large genome-wide association studies have identified candidate genes and risk loci for specific defects such as congenital heart defects, orofacial clefts, and hypospadias.[62] Also, there is a known recurrence risk of birth defects in first-degree relatives.[63-66]

Environmental risk factors

Environmental risk factors, such as maternal conditions, infections, and drugs, account for approximately 10% of all birth defects.[60] Maternal diabetes has been found to increase the risk of birth defects in the child,[67] and maternal alcohol use can cause foetal alcohol syndrome.[68] Maternal use of folic acid supplements, on the other hand, reduces the risk of neural tube defects and likely also some other birth defects, e.g., orofacial clefts and limb reduction defects.[69-72] Several maternal infections during pregnancy are known to increase the risk of specific birth defects, e.g., Zika virus, rubella, cytomegalovirus, and toxoplasmosis.[73,74] Finally, some maternal medication during pregnancy can increase the risk of birth defects in the offspring, such as the use of thalidomide,[75] diethylstilboestrol,[76] and anti-epileptic drugs.[77-79] Women with epilepsy are recommended high-dose folic acid supplements to mitigate the risk of birth defects, which has recently been suggest to increase the risk of childhood cancer in offspring.[80]

Other risk factors

Advanced maternal age is well known to increase the risk of Down syndrome in the offspring.[81] Also, birth defects are more common in boys compared to girls (~1.2-fold).[82] In the United States, maternal race and ethnicity have also been suggested as risk factors for specific birth defects, such as pyloric stenosis, gastroschisis, and orofacial clefts.[83] The causes behind these associations are not well understood but likely include differences in social, physical, and built environment, and/or genetic factors.[83] Lastly, IVF has also been seen to increase the risk of birth defects.[40]

1.3.2 Descriptive Epidemiology

Birth defect prevalence

In 2019, more than 8.5 million children worldwide were estimated to be born with a birth defect.[84] The majority of these (more than 80%) were born in LMICs. The prevalence varied across regions and countries (Figure 1.8). The most common major birth defects globally were congenital heart defects (~3.1 million), followed by musculoskeletal and limb defects (~2.3 million), and urogenital defects (~1.1 million). In Europe, the prevalence of birth defects has been relatively stable during 2005–2021, with a prevalence of around 350 per 10,000 births in total and around 200 per 10,000 for live births (Figure 1.9).

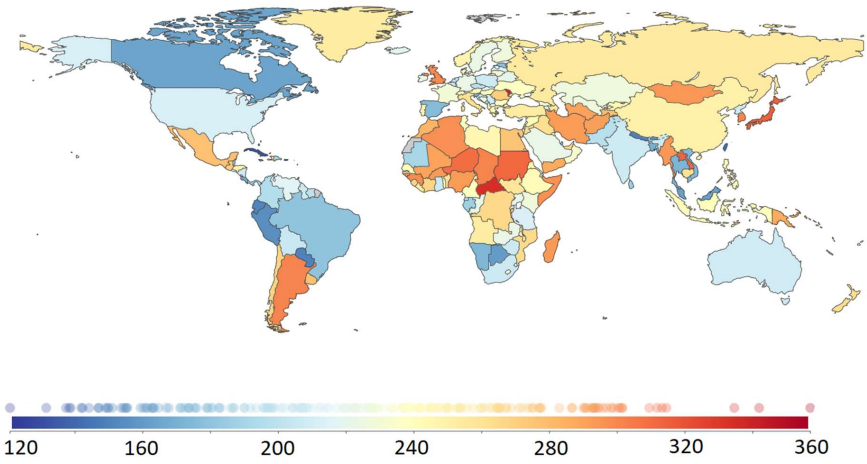

Figure 1.8 Prevalent cases of birth defects per 10,000 children < 5 years of age, in 2019. Not including stillbirths and terminations. Adapted from the Global Burden of Disease Study.[84]

Birth defect disease burden

In 2019, birth defects were the 10th most common cause of global DALYs in all ages, accounting for 2.1% of the total DALYs.[85] An estimated 240,000 deaths within 28 days of birth are attributable to birth defects globally.[86] However, the mortality varies between countries and is substantially higher in LMICs compared to high-income countries, with the estimates in LMICs likely being underestimated.[87] Among children under 5 years, birth defects were the 4th leading cause of mortality accounting for 9.4% of all deaths.[4] In total, there was an estimated 71 deaths per 100,000 in children under the age of five.[84] Estimates by the Global Burden of Disease Study display large variations in mortality across countries (Figure 1.10). However, these estimates only include liveborn children and therefore likely underestimate the total burden of birth defects (including stillbirths and terminations).[88] Also, variability in termination rates across countries could partially explain the differences in mortality for liveborn children between LMICs and high-income countries. The overall perinatal mortality (stillborn + death within the 1st week) associated with birth defects in Europe during 2008–2012, measured by EUROCAT, was 0.92 per 1000 births (Table 1.2). There were some variations in mortality rates across countries, with a perinatal mortality per 1000 births ranging from 0.31 in Portugal and Italy to 3.14 in Malta (in Malta, termination of pregnancy for congenital anomaly is illegal, likely explaining the higher perinatal mortality compared to countries where termination is legal). In Norway and Denmark, the perinatal mortality rates were 0.74 and 0.64 per 1000 births, respectively. The major birth defects contributing most to perinatal mortality were chromosomal defects, congenital heart defects, and nervous system defects (Table 1.2).

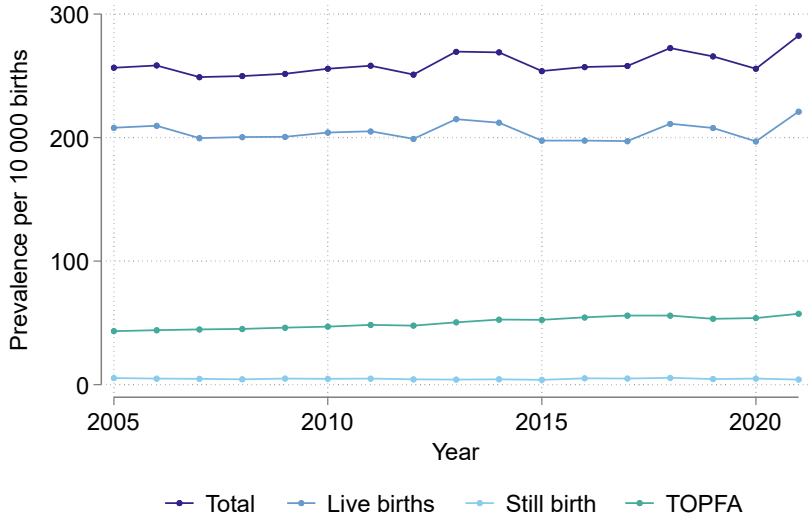

Figure 1.9 Prevalence of birth defects, including genetic conditions, per 10,000 births from 2005 to 2021 in Europe. Abbreviations: TOPFA, termination of pregnancy for congenital anomaly. Data source: EUROCAT, all full registries.[89]

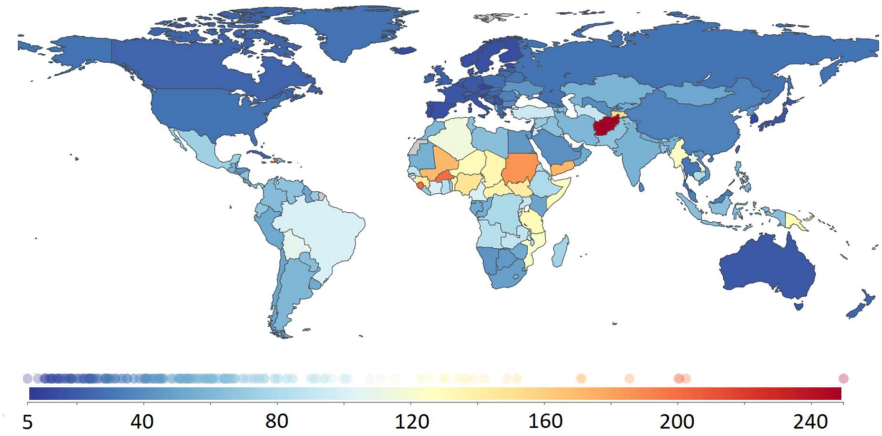

Figure 1.10 Deaths due to birth defects per 100,000 children under the age of five, in 2019. Not including stillbirths and terminations. Adapted from the Global Burden of Disease Study.[84]

Table 1.2 Perinatal mortality associated with congenital anomalies. Including all EUROCAT full member registries (n=29[1]), 2008-2012, by type of anomaly. Adapted from EUROCAT Key Public Health Indicators.[90]

Description[2]	Breakdown by anomaly subgroup (as a % of all FDs)	Breakdown by anomaly subgroup (as a % of all Early Neonatal Deaths)	Prevalence of FD per 1,000 births	Prevalence of Early Neonatal Deaths per 1,000 births	Perinatal Mortality per 1,000 births[3]
All Anomalies	100	100	0.45	0.47	0.92
All excl. chrom.	66.9	85.0	0.30	0.40	0.70
Nervous system	18.3	15.6	0.08	0.07	0.16
NTD	7.9	7.2	0.04	0.03	0.07
Anencephalus[4]	5.4	4.8	0.02	0.02	0.05
CHD	16.6	30.6	0.07	0.14	0.22
Severe CHD	8.2	17.4	0.04	0.08	0.12
VSD	4.6	7.7	0.02	0.04	0.06
HLHS	2.0	6.6	0.01	0.03	0.04
Respiratory	5.4	13.0	0.02	0.06	0.09
Digestive system	6.6	16.5	0.03	0.08	0.11
CDH	1.8	8.5	0.01	0.04	0.05
Urinary	10.1	18.3	0.05	0.09	0.13
Limb	10.2	9.5	0.05	0.04	0.09
Chromosomal	33.1	15.0	0.15	0.07	0.22
Down Syndrome	11.1	2.6	0.05	0.01	0.06
Edward syndrome	10.4	5.8	0.05	0.03	0.07

[1]Saxony Anhalt, Antwerp, Malta, N England, N Netherlands, Norway, Odense, Paris, Mainz, Isle de Reunion, Hungary, Hainaut, Dublin, SE Ireland, Basque Country, Tuscany, Emilia Romagna, Thames Valley, E Mid & S York, Vaud, Wales, Wessex, Valencia Region, Zagreb. [2]Only subgroups contributing to at least 5% of early neonatal deaths or FD are shown. [3]Perinatal mortality is sum of FD + early neonatal deaths. All figures rounded to 2 decimal places. [4]Anencephalus and similar. CDH=Congenital diaphragmatic hernia; CHD=Congenital heart defects; FD=Fetal deaths from 20 weeks; early neonatal deaths=liveborns that died within the 1st week; HLHS=Hypoplastic left heart; NTD=Neural tube defects; VSD=Ventricular septal defect.

1.4 Birth defects and cancer risk

Being born with a birth defect is one of the strongest confirmed risk factors for childhood cancer.[12,13,15,23,91] This association could indicate a common aetiology – environmental, genetic, or a combination of both. One of the first descriptions of the association between birth defects and childhood cancer was by Stewart *et al*. (1958) who reported a higher incidence of Down syndrome among leukaemia cases.[25] Since then, several epidemiologic studies on the association between birth defects and childhood cancer have been conducted.[15,92-100] In 2017, Johnson *et al*. summarized the evidence in a systematic review.[13] Later, Lupo *et al*. (2019) confirmed and reported novel associations between birth defects and childhood cancer. Several specific combinations of birth defect-cancer associations have been identified and increasing

risk estimates by increasing number of birth defects have been reported.[12,13,91] The excess cancer risk is greatest among the youngest children, but few studies have investigated birth defects and cancer risk beyond childhood and adolescence.[13,15]

The underlying biology for the association between birth defects and childhood cancer is not well-established, but genetic and environmental exposures are thought to be involved. Research on the shared genetic origins of the diseases is very limited due to the rarity of both diseases and therefore low power for detecting genetic associations.[101] One hypothesis is that childhood cancer, in particular embryonal tumours, results from foetal developmental errors.[96,102,103]

The relative risks observed in epidemiological studies vary substantially by type of birth defect and type of cancer. Children with chromosomal anomalies have a sharply elevated relative risk of cancer, with more than 11-fold risk of any cancer compared to children without birth defects.[12] Specifically, children with Down syndrome have an approximately 120-fold risk of AML and are also 28 times more likely to be diagnosed with ALL.[12] The relative risk of cancer among children with any non-chromosomal defects is lower (~2.5-fold),[12] but higher for some specific birth defects such as nervous system defects (~5-fold) and eye defects (~4-fold).[12] Many other specific combinations of associations between birth defects and cancers have been identified, including nervous system defects and CNS tumours (~10-fold) and congenital heart defects and germ cell tumours (~5.5-fold).[12]

Research on sex differences in the association between birth defects and childhood cancer is sparse. Both the prevalence of birth defects and the incidence of childhood cancer are higher among males than females (~1.2-fold).[41,82] A relatively recent study by Marcotte *et al*. (2020) suggested that birth defects may act as a strong mediator explaining up to 40% of the established association between sex and childhood cancer.[104]

A common aetiology of birth defects and cancer could also suggest that relatives of individuals with birth defects have an increased risk of cancer. Birth defects have an increased recurrence risk in first-degree relatives and a history of cancer among first-

degree family members is associated with an increased risk of specific childhood cancers.[29,63-66] But, it is not well understood whether the siblings of individuals with birth defects have an increased risk of cancer. Previous studies on the topic are mostly inconclusive and underpowered but suggest that there is a lack of an overall association.[15,105-111] However, there is some evidence for an association between specific combinations of siblings' birth defects and cancer: increased overall cancer risk among siblings of individuals with nervous system defects and ear, face, and neck defects;[105] increased risk of ALL among siblings of individuals with congenital heart defects;[109] and increased risk of CNS tumours among siblings of individuals with any birth defect.[110]

The literature search was completed by March 2024.

2. Objectives

The main objective of this thesis was to examine associations between birth defects and cancer. Specifically, we wanted to:

1) Investigate the associations between major birth defects and cancer in children, adolescents, and adults,
2) Investigate sex differences in childhood cancer risk among children with major birth defects,
3) Investigate cancer risk in siblings of individuals with major birth defects.

Our aim was to contribute new knowledge to the underlying aetiology of both diseases for future prevention and/or mitigation of risk.

3. Material and methods

3.1 Data sources

The four Nordic countries Denmark, Finland, Norway, and Sweden have a total population of more than 27 million inhabitants.[112] Each country has tax-funded universal health care independent of income, and national population-based health and administrative registries.[113] The nationwide health registries are based on compulsory notification within the different countries.[113] All residents have country-specific unique identification numbers, facilitating accurate linkage across registries. Because of the similarities between the Nordic countries, multinational studies combining data from all countries offer unique opportunities to study rare diseases.

In this study, we used information from nationwide population and health registries in Denmark, Finland, Norway, and Sweden from 1967 to 2014 (Figure 3.1). Information on birth defects was retrieved from the medical birth registries and was supplemented with information from the Danish National Patient Registry, the Register of Congenital Malformations in Finland, and the Swedish National Patient Register. Information on cancer was obtained from the cancer registries in the four countries, and information on deaths and emigration was retrieved from the national population registries.

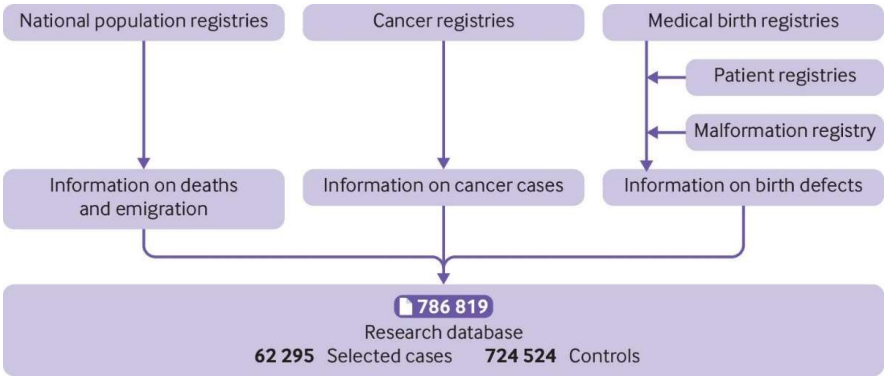

Figure 3.1 The data sources for the total study population in *Paper I* (reprint).[114]

3.1.1 The Medical Birth Registries

The medical birth registries in the Nordic countries contain information on all births in Denmark, Finland, Norway, and Sweden since 1973, 1987, 1967, and 1973, respectively.[115] The registries contain all live births and stillbirths from varying gestational ages and collect data on the mother, offspring, and father (in Denmark and Norway).[115] Data collected by the medical birth registries includes information on the pregnancy, delivery, and maternal and infant characteristics.[113] Data used in the current project is information on birth year, sex, IVF, maternal age, maternal smoking, gestational age, birth weight, and birth defects. Information on IVF was reported from 1990 in Finland, 1984 in Norway, 1995 in Sweden, and was not available in Denmark. Information on maternal smoking was collected from 1991 in Denmark, 1987 in Finland, 1998 in Norway, and 1982 in Sweden.

3.1.2 The National Patient Registries

The national patient registries in Denmark and Sweden are nationwide registries containing information on in-patient hospital care and hospital-based outpatient care.[113,116,117] The Danish National Patient Registry was established in 1977, with nationwide coverage since 1978 and with the inclusion of outpatient care since 1995. The Swedish National Patient Register at the Swedish National Board of Health and Welfare was established in 1964, with nationwide coverage since 1987 and inclusion of outpatient care since 2001.

3.1.3 The Register of Congenital Malformations

The Finnish register of congenital malformation contains information on birth defects in live and stillborn children since 1963.[118] The registry receives data from hospitals, healthcare professionals, genetic laboratories, other health registries, and the cause of death registry.[118] The data are primarily from the child's first year of life, and all diagnoses are validated before entering the registry.[118]

3.1.4 The Cancer Registries

The Nordic cancer registries cover the entire population in Denmark, Finland, Norway, and Sweden since 1943, 1953, 1953, and 1958, respectively.[119] In all countries,

notification of cancer is mandatory with completeness of registrations close to 100%.[119] There are, however, small variations in completeness by cancer type, age at diagnosis, and calendar periods.[119-124] The data sources for incident cancer cases are similar in all countries, ensuring comparability.[119] Data collected by the cancer registries and used in this study include information on age at diagnosis, diagnosis year, and cancer topography and morphology.

3.1.5 The National Population Registries

All Nordic countries have national population registries with information on death and emigration, covering the whole population.[113] Data has been available since 1964 in Norway, since 1968 in Denmark and Sweden, and since 1971 in Finland. These registries contain information on birth, death, and migration with complete follow-up for the entire population in each country.[113]

3.2 Study design and population

We conducted a population-based nested case-control study combining data from the described nationwide registries in Denmark, Finland, Norway, and Sweden in the period 1967–2014. Cases were defined as live-born individuals in the birth registries, with a later cancer diagnosis registered in the cancer registries. Only primary cancer diagnoses were included. Controls were frequency matched on country and year of birth and selected among persons alive, living in the country, and cancer-free at the time of data linkage with a case-control ratio of 1:10. Controls who had case siblings were excluded as controls. The success rate for the matching was 100%. However, in some countries (predominantly Sweden) the data from the cancer registries contained benign cases (for example cervical cancer precursor lesions), which we later excluded from the research database. None of the controls were excluded. Hence, the final case-control ratio in the main database for **paper I** was 1:12.

To construct a childhood cancer database for **paper II**, we extracted all cases aged 0–19 years from the main database and included 10 controls per case (matched on country and year of birth).

In **paper III**, we investigated both cancer overall and childhood cancer using both the main database and the childhood cancer database and excluded cases and controls without siblings or with an incomplete sibling history (i.e. when siblings were born before the birth registries were established). Also, to be able to separate the effect of having a major birth defect from the effect of having a sibling with a major birth defect, we included only individuals without their own birth defects.

3.3 Assessment and classification of exposure

The exposure of interest in **paper I** and **paper II** was having a major birth defect, while in **paper III** the exposure was having a sibling with a major birth defect. Siblings were defined as individuals sharing the same biological mother. Birth defect diagnoses were retrieved from the medical birth registries in all countries and supplemented with diagnoses from the Register of Congenital malformation in Finland, and the national patient registries in Denmark and Sweden. We retrieved ICD diagnoses for inpatients only, due to low validity for outpatient diagnoses.[117] We also restricted the diagnoses to those collected during the first year of life for consistency of exposure across countries.

In Finland, the birth defects were coded according to the ICD-9 Atlanta modification since 1986, and with the retrospective inclusion of the ICD-10 codes since 1996. In Denmark, the birth defects were coded according to ICD-8 throughout 1993 and ICD-10 thereafter. Norway used the ICD-8 from 1967 to 1998, including some internally generated codes, and the ICD-10 including the BPA extension from 1999 onwards. In Sweden, they used Swedish versions of ICD-8 (1973–86), ICD-9 (1987–96), and ICD-10 since 1997.

Birth defects were classified according to the EUROCAT Guide 1.4, and minor anomalies were excluded.[56] Table 3.1 displays the birth defect groups included in the study. The EUROCAT subgroup classification system uses ICD-10 codes with the BPA one-digit extension. However, we did not use the BPA codes since these were not available in all countries (only available in Finland and Norway). Single birth defects,

multiple defects in the same anatomical subgroup, and multiple defects as part of a sequence were defined as *isolated birth defects*. Multiple birth defects from different anatomical subgroups, and not part of a sequence, were defined as *multiple birth defects* using the algorithm from Garne *et al*.[125]

3.4 Assessment and classification of outcome

The outcome of interest in our studies was cancer. Information on cancer diagnoses was retrieved from the national cancer registries. In the total study population in **paper I** and **paper III**, we classified cancer into ICD-10 groups, except for leukaemia and lymphoma, which we classified into ICD-O-3[126] morphology groups (Table 3.2, details are provided in Supplementary Table A in **paper I**). This was done to facilitate comparison across all age groups (children, adolescents, and adults). In **paper II** and **paper III,** we additionally classified childhood cancer according to the childhood cancer specific ICCC-3.

All countries currently provide ICD-10 and ICD-O-3 codes; however, older cancer cases were coded by older ICD versions.[119] For each country, we chose to use the codes that covered most of the study period among those provided. In Norway and Finland, we used ICD-O-3 codes provided by the cancer registries. In Denmark we used ICD-O-3 codes for leukaemia and lymphoma, and ICD-10 codes in combination with ICD-O-3 morphology codes for the remaining cancer sites. In Sweden, we used the ICD-7, combined with morphology diagnosis coded by ICD-O-2/3 or the WHO/HS/CANC/24.1 classification.[127] All non-malignant neoplasms, except for tumours in the urinary tract or central nervous system and other intracranial tumours (other endocrine glands), and cases without verified morphology, except for central nervous system and other intracranial tumours, were excluded from the study. In addition, basal cell carcinomas were excluded. In the childhood cancer database for **paper II** and **paper III**, we excluded non-malignant neoplasms, except for CNS tumours (ICCC-3 site group III) and intracranial and intraspinal germ cell tumours (ICCC-3 site group Xa), cases without verified morphology and cases not classified by the ICCC-3.

Table 3.1 Classification of birth defects based on EUROCAT Guide 1.4.[56]

Birth defect groups	ICD–10
All anomalies	Q-chapter, D215, D821, P350, P351, P371
Minor anomalies for exclusion	Q101, Q102, Q103, Q105, Q135, Q170, Q171, Q172, Q173, Q174, Q175, Q179, Q180, Q181, Q182, Q184, Q185, Q186, Q187, Q189, Q261, Q270, Q31, Q320, Q331, Q381, Q382, Q400, Q401, Q430, Q523, Q525, Q53, Q610, Q627, Q633, Q65, Q662, Q663, Q664, Q665, Q666, Q667, Q668, Q669, Q67, Q680, Q683, Q684, Q685, Q752, Q753, Q765, Q825, Q833, Q845, Q760, Q899, Q95 If GA <37[i]: Q250 and Q256
Nervous system *NTD*	Q00, Q01, Q02, Q03, Q04, Q05, Q06, Q07, *Q00, Q01, Q05*
Eye	Q10 (not Q101–103, 105) Q11, Q12, Q13 (not Q135), Q14, Q15
Ear, face, neck	Q17 (not Q178), Q18 (not Q183, Q188, Q189)
Congenital heart defects	Q20–Q24, Q25 (not Q250 and Q256 If GA<37[i]), Q26 (not Q261)
Respiratory	Q300, Q32 (not Q320), Q33 (not Q331), Q34
Orofacial clefts *CPO* *CL/P*	Q35–Q37 (not if also Q00 or Q042) *Q35* *Q36, Q37*
Digestive	Q38 (not Q381, Q382), Q39, Q40 (not Q400, Q401), Q41–Q42, Q43 (not Q430), Q44–Q45, Q790
Abdominal wall defect	Q792, Q793, Q795
Urinary	Q60, Q61 (not Q610), Q62 (not Q627), Q63 (not Q633), Q64, Q794
Genital	Q50–Q51, Q52 (not Q523, Q525, Q527), Q54, Q55 (not Q552), Q56
Limb	Q66 (not Q662–69), Q68 (not Q680, Q683–85), Q69–Q74
Skeletal dysplasia	Q77, Q78
Genetic syndromes and microdeletions	Q751, Q754, Q87, Q936, D821
Chromosomal anomalies *Down syndrome*	Q90–92, Q93 (not Q936), Q96–99 *Q90*
Other	All major anomalies not included in another subgroup.

[i]If GA is missing or misclassified: exclude if birth weight < 2 standard deviations below average birthweight at 37 weeks (<2285g for male and <2200g for female).
CPO, cleft palate only; CL/P, cleft lip with/without cleft palate; GA, gestational age; NTD; neural tube defect.

Table 3.2 Classification of cancer based on ICD-10.[58]

ICD-10 groups	
1 Lip (C00)	28 Cervix uteri (C53)
2 Tongue (C01–02)	29 Corpus uteri (C54)
3 Mouth, other (C03–06)	30 Uterus, other (C55)
4 Salivary glands (C07–08)	31 Ovary etc. (C56, C57.0–4)
5 Pharynx (C09–14)	32 Placenta (C58)
6 Oesophagus (C15)	33 Prostate (C61)
7 Stomach (C16)	34 Testis (C62)
8 Small intestine (C17)	35 Other male genital (C60, C63)
9 Colon (C18)	36 Kidney (excl. renal pelvis) (C64)
10 Rectum, rectosigmoid (C19–20)	37 Urinary tract (C65–68)
11 Anus (C21)	38 Eye (C69)
12 Liver (C22)	39 Central nervous system (C70–72, D32–33, D42–43)
13 Gallbladder, bile ducts (C23–24)	40 Thyroid gland (C73)
14 Pancreas (C25)	41 Other endocrine glands (C37, C74–75, D35.2–35.4, D44.3–44.5)
15 Other digestive organs (C26)	42 Other or unspecified (C39, C76, C80)
16 Nose, sinuses (C30–31)	43 Hodgkin lymphoma (C81)
17 Larynx, epiglottis (C32)	44 Non-Hodgkin lymphoma (C82–86)
18 Lung, trachea (C33–34)	45 Immunoproliferative disease (C88)
19 Heart, mediastinum and pleura (C38)	46 Multiple myeloma (C90)
20 Bone (C40–41)	47 Acute lymphatic leukaemia (C91.0)
21 Melanoma of the skin (C43)	48 Chronic lymphatic leukaemia (C91.1)
22 Skin, non-melanoma (C44)	49 Other and unspecified lymphatic leukaemia (C91.2–9)
23 Mesothelioma (C45)	50 Acute myeloid leukaemia (C92.0, C93.0, C94.0, C94.2, C94.4–5)
24 Peripheral nerves and autonomic nervous system (C47)	51 Chronic myeloid leukaemia (C92.1, C93.1, C94.1)
25 Soft tissues (C48–49)	52 Other and unspecified myeloid leukaemia (C92.2–9, C93.2–9, C94.3, C94.7)
26 Breast (C50)	53 Leukaemia, cell unspecified (C95)
27 Other female genital (C51–52, C57.7–9)	54 Other hematopoietic diseases (C94.6, D45–47)

3.5 Statistical analysis

3.5.1 Main analysis

In all three papers, we used unconditional logistic regression models to estimate odds ratios (ORs) of cancer comparing exposed individuals with unexposed individuals.[128] In **paper I**, we calculated 99% confidence intervals (CIs) for the estimated ORs, while in **paper II** and **paper III** we estimated 95% CIs. Because the outcome was relatively rare among both the exposed and the unexposed, we interpreted the estimated ORs in all three papers as approximations of relative risks.[129,130]

In **paper I** and **paper II**, we evaluated the following variables as confounders (in addition to the matching variables): sex, IVF, maternal age, and maternal smoking (Figure 3.2). We decided to run the main analyses with minimal adjustments (adjusting for sex [in **paper I** and **paper II**] and the matching variables [country and birth year]), as additional adjustments for maternal age did not impact the estimated ORs. Maternal smoking and IVF were evaluated as confounders in sensitivity analyses since these variables were only available for a subset of the study population. The inclusion of these as confounders did not change the results substantially.

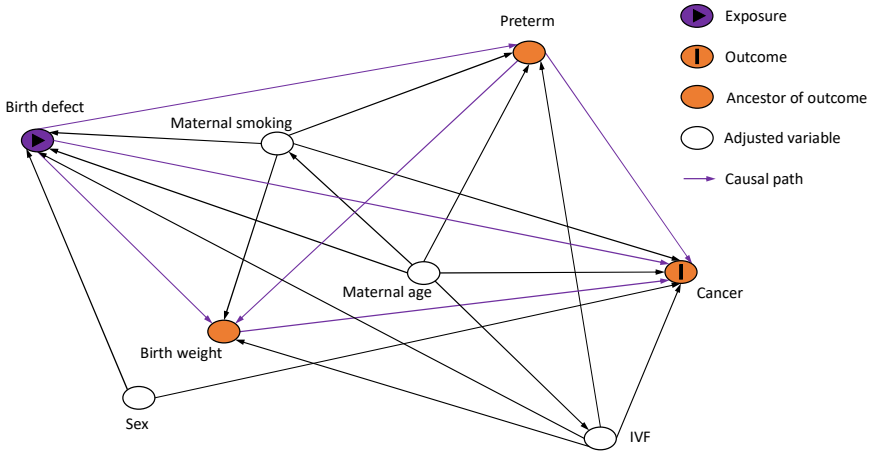

Figure 3.2 Directed acyclic graph (DAG) illustrating confounder selection in paper I and paper II. Adapted from figure A, Supplementary Content, paper I.[114]

When estimating the total effect of birth defects on cancer risk, we did not adjust for intermediate factors (birth weight and being born preterm). In **paper III**, all regression models were adjusted for the matching factors country and birth year (Figure 3.3). Additional adjustments for maternal age and maternal smoking (evaluated in sensitivity analyses) did not change the estimated ORs substantially. In all analyses, missing data was handled using the complete case approach.

In all papers, we investigated chromosomal and non-chromosomal birth defects separately and we performed stratified analyses to assess cancer risk by age at diagnosis. In **paper II,** we evaluated sex differences in the birth defect-cancer association and performed analyses stratified by sex and analyses where we included a sex-birth defect interaction term.

To determine whether there was a dose-response relationship, i.e., increasing levels of exposure associated with increasing risk of the outcome, we investigated cancer risk by number of birth defects / siblings with birth defects. This was assessed by including the number of birth defects (0, 1, 2, 3, or ≥4) / siblings with birth defects (0, 1, ≥1) as a categorical exposure in the logistic regression models and testing for linear trend using orthogonal polynomial contrasts.[131]

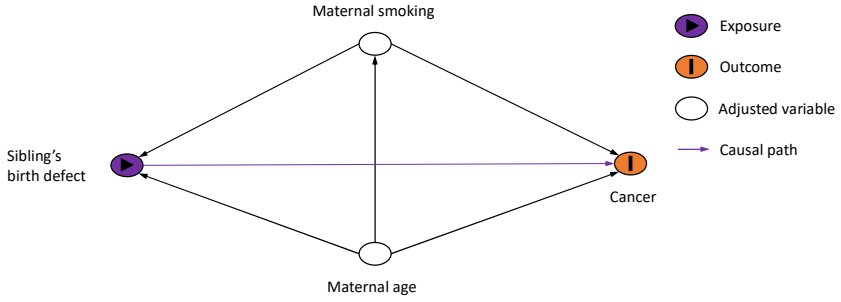

Figure 3.3 Directed acyclic graph (DAG) illustrating confounder selection in paper III.

3.5.2 Mediation analysis

In **paper II**, we investigated cancer risk in children with birth defects by sex and in addition evaluated the role of birth defects as a mediator in the sex-childhood cancer association (Figure 3.4). Mediation analyses can be defined as "*analyses used to assess the relative magnitude of different pathways and mechanisms by which an exposure may affect an outcome*."[132] We conducted a mediation analysis using a counterfactual framework, allowing for exposure-mediator interaction, where we estimated the controlled direct effect, the natural indirect effect, the natural direct effect, and the marginal total effect (i.e., the product of natural direct and indirect effects), as described in Vanderweele (2015).[133] The controlled direct effect is the effect of sex that is not mediated through birth defects (using females as the reference). The natural direct effect compares cancer risk in males to that in females if birth defect status for males was set to what would have been seen had they been females. The natural indirect effect describes the proportion of the sex effect explained by mediation alone. A causal interpretation of the mediation analyses assumes no unmeasured confounding concerning (1) exposure–outcome, (2) mediator–outcome, or (3) exposure–mediator, and (4) no mediator–outcome confounder affected by the exposure. In addition, for the use of logistic regression models, we need the assumption of rare outcomes, which was met in our study (with childhood cancer as the outcome). In the main analyses, we included a sex-birth defect interaction and, to address assumption (2), we adjusted for the following potential mediator–outcome confounders: birth year, country, and maternal age. We also performed sensitivity analyses where we included IVF and maternal smoking as confounders. Since sex was the exposure of interest in these analyses (with birth defects as a mediator), both assumptions (1) and (3) on unmeasured confounding are likely fulfilled. Assumption (4) is also plausible based on current knowledge. To evaluate whether mediation was present or not, we used the CIs and p-values for the natural indirect effect (the mediated effect) and calculated the proportion of the sex effect mediated through birth defects on a risk difference scale using the formula:

$$OR^{\text{Natural direct effect}}(OR^{\text{Natural indirect effect}}-1)/(OR^{\text{Natural direct effect}}\,OR^{\text{Natural indirect effect}}-1).$$[134]

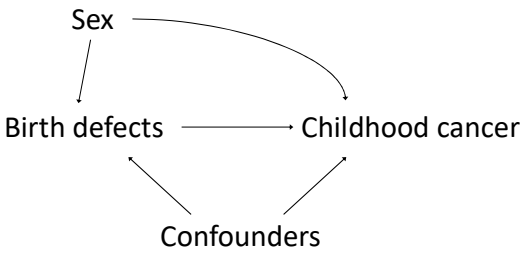

Figure 3.4 A simplified illustration of the assumed causal relationship between sex, birth defects and childhood cancer in the mediation analyses. Reprint of figure S1, Supplementary Content, paper II.[135]

3.5.3 Sensitivity analysis

In **paper I**, we performed analyses by country to evaluate the consistency of the findings. This was done for selected analyses with a sufficient number of cancer cases. In **paper II**, we calculated E-values for the OR and lower confidence limit to evaluate the robustness of the results.[136] The E-value can be defined as *"the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain away a specific treatment-outcome association, conditional on the measured covariates"*.[136] Also, to take into consideration differences between registries and calendar periods and to evaluate the possible impact of diagnostic and survival trends, we performed sensitivity analyses where we i) left out one country at the time, and ii) limited the study population to the ~60% born in 1990 and later. In **paper III**, we performed sensitivity analyses, using Norwegian data only, where we compared cancer risk among full siblings (same biological mother and father) with the cancer risk among maternal siblings.

3.6 Ethical evaluations and approvals

The studies were based on mandatory population-based registries and databases, without requirements of approval from the study subjects. The data was

pseudonymised, and stored and analysed on a secure server (SAFE) at UiB, a service for processing sensitive data in health research.[137]

The project was approved by the Data Protection Agency in Denmark (2015-57-0002), and the ethics committees in Norway (2015/317/REK vest) and Stockholm, Sweden (2015/1642-31/2). Permission to use health register data in Finland was granted by the Finnish Institute of Health and Welfare after consultation with the data protection authority (THL/68/5.05/2014 and THL/909/5.05/2015).

4. Summary of main results

4.1 Paper I: Cancer risk in children, adolescents, and adults with major birth defects

In total, more than 62,000 cancer cases aged 0 to 46 years and approximately 18,000 individuals with major birth defects were included in the study. We found that being born with a birth defect was associated with an overall increased risk of cancer compared to individuals without major birth defects (OR=1.7; 99% CI: 1.6-1.8). The risk was greater for individuals with chromosomal defects (OR=5.5; 99% CI: 4.7-6.5) compared to non-chromosomal birth defects (OR=1.5; 99% CI: 1.4-1.6). The relative increase in cancer risk was higher at younger ages but persisted into adulthood (Figure 4.1). Specifically, the increased cancer risk persisted among adults with congenital heart defects (OR=1.3; 99% CI: 1.0-1.6), genital organ defects (OR=1.4; 99% CI: 1.1-1.8), nervous system defects (OR=1.8; 99% CI: 1.2-2.7), skeletal dysplasia (OR=3.5; 99% CI: 1.5-8.2), and chromosomal anomalies (OR=1.5; 1.0-2.2). Generally, the OR

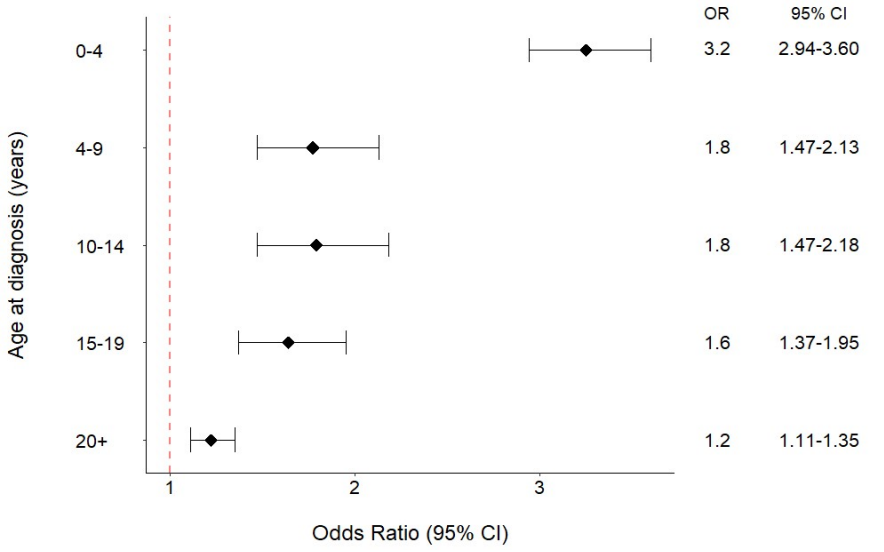

Figure 4.1 Risk of any cancer in individuals with any major birth defect by age at diagnosis. ORs are adjusted for matching variables (birth year and country) and sex.

decreased by age at diagnosis, except for genital organ defects. We also found that many structural birth defects were associated with cancer in the same anatomical location or organ system. This was observed for eye defects and cancer of the eye (OR=18; 99% CI: 7.5-4.4), nervous system defects and CNS tumours (OR=16; 99% CI: 13-21), urinary defects and cancer of urinary organs (OR=8.0; 99% CI: 4.5-14), digestive system defects and cancer of digestive organs (OR=3.1; 99% CI: 1.2-7.7), and genital defects and male genital cancer (OR=1.8; 99% CI: 1.3-2.5). In addition, we observed a dose-response relationship between the number of birth defects and the risk of cancer, with an almost 5-fold increased risk among those with four or more major non-chromosomal birth defects compared to those without major birth defects.

4.2 Paper II: Childhood cancer risk and major birth defects – sex differences

In total, 21,898 cancer cases aged 0 to 19 years and 218,980 controls without cancer, matched on country and birth year were included in the study. Among the cases, 5.1% had a major birth defect compared to 2.2% among the controls. We observed increased cancer risk among children with birth defects, with an OR of 1.9 for non-chromosomal defects and 10 for chromosomal defects. The strongest associations between specific birth defects and main cancer types were observed for genetic syndromes/microdeletion and renal tumours (OR=55; 95% CI: 26-117), Down syndrome and leukaemia (OR=41; 95% CI: 33-49), and nervous system defects and CNS tumours (OR=16; 95% CI: 12-22). The overall association between birth defects and childhood cancer was stronger among girls (OR=2.8; 95% CI: 2.6-3.1) than boys (OR=2.1; 95% CI: 1.9-2.2, $P_{interaction}<0.001$). Stronger associations among girls than boys were generally observed across the birth defect-cancer groups, and specifically, sex differences were seen for non-chromosomal birth defects and lymphoma, non-chromosomal birth defects and germ cell tumours, and chromosomal defects and leukaemia (Table 4.1). Male sex was an independent but modest risk factor for childhood cancer (OR=1.2; 95% CI: 1.1-1.2), but less than 5% of this association was mediated through birth defects. However, among the youngest children the proportions mediated were larger (10% in children < 5 years and 28% in children < 1 year).

Table 4.1 Risk of cancer among children with any or specific major birth defects by sex.

Major birth defect[a]	Cancer[b]	OR (95% CI)	OR (95% CI)
Any birth defect	Any cancer	2.1 (1.9-2.2)	2.8 (2.6-3.1)
Non-chromosomal	Lymphoma	1.2 (0.9-1.6)	2.0 (1.4-2.7)
Non-chromosomal	Germ cell tumours	2.0 (1.4-2.7)	4.8 (3.3-6.9)
Chromosomal	Leukaemia	26 (20-33)	39 (30-50)

[a]Classified by the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT) Guide 1.4.[56]
[b]Classified by the International Classification of Childhood Cancer, third edition (ICCC-3).[21]

4.3 Paper III: Cancer risk in siblings of individuals with major birth defects

In total, we included 40,538 cancer cases (0 to 46 years) and 466,917 controls matched on country and birth year, born between 1967 and 2014. We observed no overall difference in cancer risk among individuals whose siblings had birth defects compared to individuals with unaffected siblings in the total study population (OR=1.02; 95% CI: 0.97-1.08). We did, however, note a slight increase in the risk of lymphoid and haematopoietic malignancies (OR=1.16; 95% CI: 1.05-1.28) among individuals whose siblings had a birth defect. In the childhood cancer study population (aged 0–19 years), the overall risk of cancer was increased by 9% among children and adolescents whose siblings had birth defects (OR=1.09; 95% CI: 1.00-1.19) (Table 4.2). Specifically, children and adolescents with affected siblings had an increased risk of renal carcinomas, neuroblastoma, and lymphomas. Stratified by age at diagnosis, we observed an increased risk of kidney cancer (OR=1.90; 95% CI: 1.10-3.27) and CNS tumours (OR=1.29; 95% CI: 1.05-1.57) among adults (20+ years); of neuroblastoma,

renal tumours, leukaemia, and gonadal tumours among adolescents (15-19 years); and of lymphomas and neuroblastoma among children (0-14 years). In addition, in the total study population, the relative risk of cancer increased with the number of siblings with birth defects (P_{trend}=0.008).

Table 4.2 Risk of childhood cancer (ICCC-3 classification) in children and adolescents who had siblings with any major birth defect[a].

	OR (95% CI)		
Childhood cancer (ICCC-3)	Children (0–14 years)	Adolescents (15–19 years)	Children and adolescents
Any cancer	1.06 (0.96-1.17)	1.19 (1.01-1.39)	1.09 (1.00-1.19)
I Leukaemia	1.04 (0.88-1.24)	1.61 (1.08-2.42)	1.10 (0.94-1.30)
II Lymphomas	1.44 (1.09-1.89)	1.23 (0.90-1.69)	1.35 (1.09-1.66)
IV Neuroblastoma	1.42 (1.03-1.96)	6.50[b] (1.84-22.9)	1.51 (1.11-2.05)
VI Renal tumours	0.93 (0.61-1.41)	4.17[b] (1.23-14.1)	1.02 (0.69-1.51)
VIb Renal carcinomas	-	-	5.03[a] (1.73-14.6)
Xc Gonadal tumours	0.69[b] (0.26-1.87)	1.56 (1.03-2.35)	1.32 (0.90-1.94)

[a]Classified by the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT) Guide 1.4.[56]
[b]Less than 5 exposed cases. Abbreviations: CI, confidence interval; ICCC-3, International Classification of Childhood Cancer, third edition[21]; OR, odds ratio.

5. Discussion

Our studies aimed to investigate associations between major birth defects and cancer among children, adolescents, and adults, and to evaluate if the associations among children differed by sex. Our work demonstrated that the increased cancer risk in individuals with birth defects persisted into adulthood (investigated up to the age of 46 years). Our results also indicated that the birth defect–childhood cancer associations were stronger among girls than boys. In addition, our data suggested that among individuals whose siblings had birth defects, the risk of childhood cancer (ages 0–19 years) was elevated, while the overall cancer risk (ages 0–46 years) was not increased. All three studies revealed dose-response relationships with increasing cancer risk by increasing number of birth defects / siblings with birth defects. Lastly, our findings added to the existing literature by validating findings from others on associations between rare combinations of specific birth defects and specific cancer types.

5.1 Interpretation and contribution of the findings

The findings in **paper I** suggested that the increased cancer risk in individuals with birth defects persists into adulthood, in particular for skeletal dysplasia, nervous system defects, genital organ defects, and congenital heart defects. Few studies have previously investigated the overall association between birth defects and cancer in adults and with limited size and shorter follow-up.[14,15] Some previous studies have reported increased cancer risk in adults associated with specific birth defects, such as congenital heart defects (~2-fold risk).[16,17] A later study by Karazisi *et al*. (2022) reported similar risk estimates to ours (hazard ratio [HR] = 1.24 [18-39 years] and HR = 1.11 [40+ years], compared to our study OR = 1.28 [20 + years]).[138] The underlying causes for the association are mostly unknown, but genetic factors have been proposed (e.g., dysregulation of developmental genes).[139,140] Higher exposure to low-dose ionizing radiation among individuals with congenital heart defects has also been suggested as a risk factor, but so far, the results are conflicting and inconclusive.[139]

The results in **paper II** demonstrated stronger birth defect–childhood cancer associations among girls than boys, particularly for non-chromosomal defects and lymphomas and germ cell tumours, and chromosomal defects and leukaemia. Many of our findings on associations between birth defects and childhood cancer agreed with the earlier literature.[12,13] However, few studies have examined differences in these associations by sex. The increased risk of rhabdomyosarcoma among children with birth defects has been reported in boys but not in girls, but this finding was not supported by our results (~2-fold risk for both sexes).[141] Also, an increased risk of germ cell tumours in children with birth defects has been reported among boys but not girls.[142,143] In our study we also observed an increased risk of germ cell in boys with birth defects, but an even higher risk among girls. The causes of the observed sex-differences are not well understood but likely involve interactions between sex-specific factors (e.g. hormonal) and gene networks.[144]

Marcotte *et al*. (2020) reported birth defects to be a strong mediator in the established relationship between sex and childhood cancer, with an overall 38% proportion mediated for any cancer (0–18 years).[104] They reported varying proportions mediated by cancer type (e.g., 26% for leukaemia, 35% for neuroblastoma, 6% for non-Hodgkin lymphoma) and age at diagnosis (82% mediated in children < 1 year of age). In our study, we found that in the association between sex and any childhood cancer, the proportion mediated through birth defect status was 5% in children under the age of 20, and 28% in children under one year of age. Our estimated proportions for leukaemia, neuroblastoma, and non-Hodgkin lymphoma were 6%, 7%, and 1%, respectively. Overall, we did not find evidence supporting the findings by Marcotte *et al*. (2020) that birth defect status is a strong mediator in the association between sex and childhood cancer. This could indicate that other biological pathways are involved.

In both **paper I** and **paper II**, we found that many of the structural birth defects were associated with increased risk of cancer in the same organ system or anatomical site. This included the following combinations, several of which have been reported by others: nervous system defects and CNS tumours,[13] defects of the eye and cancer of the

eye,[12] birth defects of the digestive system and liver cancer,[12] genitourinary birth defects and kidney cancer.[12]

Our data in **paper III** suggested that among individuals whose siblings had birth defects the risk of childhood cancer (ages 0–19 years) was elevated, whereas the overall cancer risk (ages 0–46 years) was not increased. We observed varying increase in risks of cancer by age at diagnosis and found evidence for associations between specific birth defects among siblings and specific childhood cancer types. We also observed a dose-response relationship between the number of siblings with birth defects and cancer risk. Previous research had not found any associations between birth defects in siblings and cancer and this agrees with our results for the total study population.[15,105,107] The increased overall cancer risk in children had only previously been suggested in a small study.[106] Of the previously reported risks of specific cancers among individuals whose siblings had birth defects, we were able to confirm the risk of CNS tumours but not the risk of ALL.[109-111] Also, a few specific birth defects in siblings have been associated with increased cancer risk, such as nervous system defects, which was confirmed by our study, and ear, face, and neck defects, which was not confirmed by our study.[105] Overall, we found that the cancer risks associated with having a sibling with birth defects were lower than the cancer risks associated with having own birth defects, and we observed weaker and fewer birth defect-cancer associations between siblings' defects compared to own defects.[114,135] This could maybe imply that many of the observed associations in our first two studies are linked to prenatal developmental errors in addition to possible common genetic factors for birth defects and cancer.

We also observed a dose-response relationship between the number of birth defects and overall cancer risk in all three papers, in agreement with other studies.[12,15,91,145] Lupo *et al*. (2020) reported a HR=5.9 of any childhood cancer in children with four or more birth defects, Norwood *et al*. (2017) reported an OR=3.1 of any childhood cancer in children with three or more birth defects, and Bjørge *et al*. (2008) reported a standardized incidence ratio of 5.5 in Norway and 3.6 in Sweden of any cancer among individuals with two or more birth defects. We found an OR= 4.9 of any cancer (ages

0–46) in individuals with 4 or more non-chromosomal birth defects, an OR=4.0 of childhood cancer in children with two or more birth defects, and OR=1.4 in individuals with two or more siblings with birth defects. In addition, Lupo *et al*. (2020) reported greater risks of haematological cancers, CNS tumours, and non-CNS solid tumours among children with two or more major birth defects. In our studies, we also observed dose-response relationships between birth defects and specific cancers: In **paper I**, a dose-response relationship was observed between chromosomal birth defects and ALL, and non-chromosomal birth defects and soft tissue cancer, kidney cancer, CNS tumours, and other myeloid leukaemia. In **paper II**, a dose-response relationship was revealed between non-chromosomal birth defects and the majority of childhood cancers, and between chromosomal birth defects and leukaemia. In **paper III**, we observed a dose-response relationship between number of siblings with birth defects and leukaemia, both in children and adults. Greater risk by number of siblings with birth defects has not been reported before. Together, these findings support the hypothesis of a causal relationship.[146]

The main strengths of our studies were the study sizes, the reliable and almost complete information from population-based registries, and the long follow-up. This gave us a unique opportunity to assess cancer risk at different ages, to assess rare combinations of birth defects and cancer, and to link the information between siblings. The limitations of the studies include differences in birth defect ascertainment between countries and over time, low statistical power for specific combinations of birth defects and cancer, and the possible lack of information on unknown confounders.

5.2 Methodological considerations

The main objective of an epidemiological study is to obtain valid and precise estimates of distributions and determinants of health-related outcomes. Further, one might want to generalize the study findings from the source population to a broader target population.

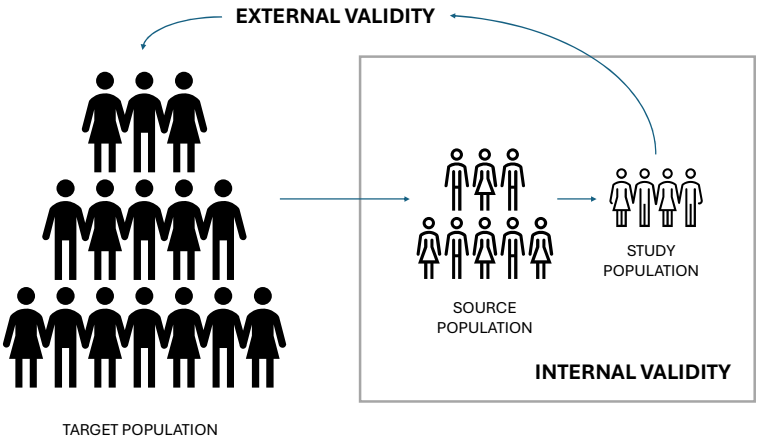

Figure 5.1 Illustration of study population, source population, and target population.

5.2.1 Internal validity

The internal validity of an epidemiological study relates to how well the observed study results represent the (unobservable) truth in the source population. In our study, the source population was individuals born between 1967 and 2014 in the four Nordic countries Denmark, Finland, Norway, and Sweden. Threats to internal validity are systematic errors, which can broadly be classified into three categories: confounding, selection bias, and information bias.[147]

Confounding

Confounding in epidemiological studies can be defined as *"confusion of effects"*.[147] That implies that the observed effect of an exposure can be explained, or partly

explained, by some other factor(s). The presence of confounding (i.e., common causes) can result in both overestimation and underestimation of the true effect. When estimating causal effects using regression models, it is necessary to adjust for confounders. This is typically done by including confounders as covariates in the regression models. The inclusion of covariates in statistical models of causal effects should be based on assumed causal relationships and not statistical reasons. One popular method for confounder selection is the use of *directed acyclic graphs* (DAGs).[148,149] A commonly used software for drawing and analysing DAGs is the web application or R package DAGitty.[150]

Confounder selection in our studies was based on DAGs (Figures 3.2, 3.3, and 3.4). We performed analyses with and without adjustment for the suggested potential confounders with available information and ran the final analyses with minimal adjustment (e.g., we adjusted for the matching factors, and sex in **paper I** and **II**) as additional adjustment did not impact the estimates substantially. In **paper I** and **II**, we also evaluated maternal age, maternal smoking, and IVF as potential confounders (IVF and smoking in sensitivity analyses due to missing data). Maternal smoking has been registered since 1991 in Denmark, 1987 in Finland, 1998 in Norway, and 1982 in Sweden. Thus, data for maternal smoking were only available for 35% of the total study population in **paper I**. The estimated cancer risk for exposed individuals (individuals with birth defects or whose siblings had birth defects) were almost identical with and without adjustment for maternal age and maternal smoking, indicating no strong confounding by maternal smoking or maternal age. We had information on IVF in Finland (from 1990), Norway (from 1984), and Sweden (from 1995). In total, 1% (1,424/140,639) of the individuals in this subpopulation in **paper I** were conceived through IVF. In analyses investigating the associations between birth defects and any cancer, IVF did not appear to confound the associations. Similar results were observed for children in **paper II**. Also, in **paper III**, adjusting for maternal age and maternal smoking did not affect the results.

However, there is likely unmeasured confounding in our studies. To address this, we calculated E-values to assess the potential impact of unmeasured confounding in **paper**

II. We concluded that for an unmeasured confounder to explain the overall association between non-chromosomal birth defects and cancer (OR=1.9), conditioned on the measured confounders, it had to be associated with a tripling of the risk of both cancer and birth defects. It is unlikely that such strong unknown confounders should exist.

Selection bias

Selection bias is a false association that is introduced as a result of the selection process for the inclusion of study participants. When selection bias occurs, the study population will not be representative of the source population. Possible selection bias must be handled by study design, as it is usually not possible to adjust for this in the analyses.[151] In case-control studies, selection bias can occur if the selection of controls is inappropriate.[152] In our studies, we used population-based registries with almost no loss to follow-up. Thus, it is unlikely that selection bias regarding the selection of controls is of major concern. However, due to the cumulative sampling scheme of controls, survivor bias is possible (discussed in Chapter 5.2.3 Study design).

Information bias

Information bias refers to systematic errors caused by incorrect information on study participants, often referred to as misclassification.[153] Misclassification can cause spurious associations between exposure and outcome. If the mechanism for misclassification is similar for cases and controls, we have non-differential misclassification, and the estimated odds ratios will tend to attenuate to 1.[154] If the misclassification mechanism is *not* similar among cases and controls, we have differential misclassification. This can cause the estimated effect to be biased in either direction.[154]

Misclassification of exposure

In our studies, we likely have some misclassification of the exposure. The ascertainment of birth defects has changed over time and varies by type of defect. There was likely heterogeneity in the ascertainment, with lower ascertainment for birth defects not easily visible at birth, especially in the first period of this study before ultrasound examination was established in prenatal care. Still, in all registries, information on birth defects is obtained from more than one source (e.g., from hospitals

and outpatient clinics treating the patients). Quality control and data verification are also given high priority in the registries.[155-157] Common coding practices across countries are facilitated by membership in EUROCAT who host annual meetings focusing on coding of birth defects. Also, we did not include minor birth defects, as their definition, diagnosis, and reporting vary considerably, both over time and between countries.[57]

We argue that the under-ascertainment of birth defects is unlikely to be associated with later cancer, and under this assumption, misclassification would cause our results to be biased towards the null. If this is not the case, i.e., if cancer cases are more likely to be diagnosed with a birth defect compared to controls, the results may be biased away from the null. The latter would only be possible among individuals diagnosed with cancer during their first year of life, as we did not include birth defects diagnosed after the first year of life.

In **paper I**, we performed a sensitivity analysis where we assessed the heterogeneity of ascertainment. We performed separate analyses by country where we only included data from the years when all countries had available data. We were then able to compare populations with the same age groups during the same period. The results from the sensitivity analyses supported the reported associations from the main analyses, with the country-specific odds ratio for any cancer (excluding chromosomal anomalies) varying between 1.8 and 2.7 and the risk estimates for the main cancer sites being similar to the main results. In **paper II**, we performed sensitivity analyses addressing differing ascertainment by running analyses where we only included children born in 1990 and onwards. This did not change our results substantially.

In all three papers, we classified birth defects according to the subgroups defined by EUROCAT. Although the purpose of this classification is to group birth defects that share aetiologic or clinical characteristics, it also takes into account that there has to be enough cases in each group.[56] It is therefore possible that some of the groups are too heterogenous to discover any effects. Also, for most birth defect groups, we were not able to investigate specific subgroups in our studies due to the rarity of both diseases.

Misclassification of outcome

The Nordic cancer registries have close to complete coverage of cancer in the total populations, with minor variations in completeness between countries, cancer type, age at diagnosis, and periods.[119-124,158] Misclassification of cancer is likely unrelated to the exposure.

Misclassification of other covariates

Covariates included or evaluated in our studies were country, birth year, sex, maternal age, maternal smoking, and IVF. Misclassification of the first four variables is negligible. In Norway, the sensitivity of the IVF variable in the medical birth registry is 85%.[159] The proportion of missing information on maternal smoking in the Norwegian medical birth registry was 14% during 1999–2014.[160]

Missing information on confounders can cause bias if individuals with missing information have a systematically higher or lower risk of cancer. When we evaluated maternal smoking as a possible confounder, data was not available for 65% of the study population in paper I. During the period when maternal smoking was recorded (since 1991 in Denmark, 1987 in Finland, 1998 in Norway, and 1982 in Sweden), the information was missing for 8.7% of controls and 8.4% of cases. We handled missing data by the complete case approach. If the missingness mechanism was not completely at random (i.e., if there were systematic differences between missing values and observed values), these analyses may be biased.[161] It is possible that information on maternal smoking was not missing completely at random. The missing data could be missing at random (systematic differences due to observed variables) or missing not at random (missingness depending on the values of the missing data). Several methods for handling these missing mechanisms exist, such as multiple imputation when data is missing at random. However, since the proportion of individuals with missing information was not too large in our study sample, and since our results indicate that maternal smoking is not strongly associated with birth defects or cancer, we believe that our main analyses using the complete case approach can be trusted.

Multiple comparisons

In all three papers, a large number of comparisons were carried out. A natural consequence of multiple comparisons is an increased risk of false-positive (type I) errors. However, as the nature of our analyses was exploratory, we did not want to adjust for multiple comparisons. Based on previous studies our *a priori* hypotheses were real associations between birth defects and childhood cancers. Therefore, we were less concerned about type I errors, even though they are possible. Although adjustment for multiple testing would reduce the probability of type 1 errors, it would increase the probability of false-negative (type II) errors. We believe that the latter is of greater concern in relation to our study question. The implications of type I errors in our study are not severe, and new findings would need to be confirmed by others, which is a desired implication. Systematic reviews and meta-analyses are required to confirm findings from explorative studies. In **paper I**, we used 99% CIs to decrease the probability of false positive results. Still, spurious associations from multiple comparisons could have resulted.

5.2.2 External validity

External validity relates to the extent the study findings can be generalized to other contexts. The results from our studies are likely generalizable to our target populations, the Nordic countries, and to other northern European countries with similar risk profiles. Exposures (both genetic and environmental) likely differ across the world; thus, the aetiologies may vary.

5.2.3 Study design

All three studies in the project were population-based nested case-control studies. The preferred study design would have been a cohort study including all individuals in the four countries, to avoid potential issues of selection bias, to simplify the statistical analysis methods, and to limit the possibilities for mistakes by the registries during case and control selection. Nonetheless, due to data protection legislation and the principle of data minimisation, we did not gain access to the complete registry data in the four Nordic countries. However, using ten controls per case approximates the efficiency obtained in a cohort design.

To improve the statistical precision of our estimates, the controls were frequency matched on birth year and country. Controls were selected among those still at risk by the end of follow-up, a so-called cumulative sampling scheme. The cumulative sampling scheme will give an estimate of the odds ratio. However, using the *rare disease assumption*, we were able to interpret the ORs as relative risks.[153] The matching of controls in a case-control study introduces a selection bias, but this can be removed in the analyses by either using conditional regression models or by adjusting for the matching variables in unconditional regression models.[154] However, there is a possibility of selection bias caused by survivor bias.[147] Controls were selected among those alive at the end of the study period and if individuals with birth defects are more likely to die early, the source population for the controls may differ from the source population for cases. Still, for most individuals with birth defects, the life expectancy exceeds 46 years. We also compared the annual birth defect prevalence in our study period among the selected controls from Norway to the birth defect prevalence in the Norwegian medical birth registry (the total population of Norway) in the same period and observed similar proportions.[162] We therefore conclude that the potential selection bias would be negligible.

Importantly, the pseudonymised data from all countries were merged into one combined data set. Therefore, we did not have to use meta-analysis methods/approaches. This had direct implications for the studies' possibilities to investigate rare co-occurring events which we could not have investigated with meta-analyses methods (i.e., with too few events in each country).

6. Conclusion

This work has contributed to new knowledge on the relationship between birth defects and cancer risk. Firstly, in **paper I**, we found an association between being born with a birth defect and cancer in children, adolescents, and adults. Secondly, in **paper II**, we concluded that the birth defects-cancer associations generally were stronger in girls compared to boys. Finally, in **paper III**, we observed an increased risk of cancer in siblings of individuals with birth defects among children, but not among adults. In all three papers, a dose-response relationship between the number of birth defects and cancer risk was seen. In summary, this work provides evidence consistent with the hypothesis of common aetiologies of some birth defects and cancers, in particular childhood cancers.

However, the clinical implications of our results so far are limited. The cumulative risk of cancer before the age of 45 in the Nordic countries was 2.2% in males and 3.6% in females in 2021, implying that the absolute risk of cancer in individuals with birth defects is low in this age group.[43] For that reason, cancer surveillance in individuals with birth defects has usually not been recommended. However, for specific birth defects with particularly high cancer risk, screening may be warranted. Guidelines from the British Society for Haematology, for instance, recommend a blood test within three days of life assessed by haematologists for all newborns with Down syndrome.[163] Some of our studies' findings can also be useful for clinicians who have patients with certain birth defects that require long-term follow-up. As noted by Spector and Kochilas (2020), physicians knowing that individuals with congenital heart defects have an increased risk of ovarian cancer (a hard-to-detect cancer) and non-melanoma skin cancer (possibly increased by the use of chlorothiazide) could be useful.[164]

7. Future perspectives

This thesis investigated cancer risk in individuals with major birth defects and their siblings and the results should generate new hypotheses for further aetiological research on the birth defects and cancer associations.

It has previously been suggested that parents of children with birth defects may have an increased risk of cancer.[15,165,166] The fact that we found an increased risk of childhood cancer in individuals with siblings with birth defects should further motivate this research. Therefore, to pursue this, we aim to perform a Nordic case-control study where we will be able to investigate cancer risk in parents of children with birth defects in greater detail compared to previous research by using a larger data material combining four countries.

Furthermore, research focusing on subgroups of the broader birth defect groups, such as congenital heart defects which is the largest birth defect group, should also be pursued. Combining all congenital heart defects into one large group could potentially mask possible associations between specific congenital heart defect subgroups and cancer, as their aetiologies may vary.

The consistent findings of associations between structural birth defects and later cancer in the same organ system or anatomical location should be investigated more extensively. This includes nervous system defects and CNS tumours, eye defects and cancer of the eye, digestive system defects and liver cancer, urinary defects and kidney cancer, and male genital defects and testicular cancer. Also of interest is the increased risk of kidney cancer and CNS tumours, observed among children and adults with birth defects and among adults whose siblings had birth defects.

Research on the associations between birth defects and childhood cancer should also be performed in other world regions, including LMICs. Comparison of results between different regions could give important clues regarding the aetiologies of the diseases. However, limited data availability in LMICs could make this challenging.

Many of the observed results in our studies would not have been discovered if we had not been able to combine the data from the four Nordic countries into one data file, due to the rarity of some co-occurring birth defects and cancers. Currently, strict data protection rules and regulations in different countries make it almost impossible to perform studies like ours. Therefore, efforts should be made to construct infrastructures and make regulations that better facilitate important Nordic as well as other international collaborative/joint research.

In conclusion, our novel findings should motivate further research into possible biological mechanisms and causes of both birth defects and childhood cancer, including epigenetic mechanisms.

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I

Cancer risk in individuals with major birth defects: large Nordic population based case-control study among children, adolescents, and adults

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ABSTRACT

OBJECTIVE

To examine associations between birth defects and cancer from birth into adulthood.

DESIGN

Population based nested case-control study.

SETTING

Nationwide health registries in Denmark, Finland, Norway, and Sweden.

PARTICIPANTS

62 295 cancer cases (0-46 years) and 724 542 frequency matched controls (matched on country and birth year), born between 1967 and 2014.

MAIN OUTCOME MEASURES

Relative risk of cancer in relation to major birth defects, estimated as odds ratios with 99% confidence intervals from logistic regression models.

RESULTS

Altogether, 3.5% (2160/62 295) of cases and 2.2% (15 826/724 542) of controls were born with major birth defects. The odds ratio of cancer for people with major birth defects compared with those without was 1.74 (99% confidence interval 1.63 to 1.84). For individuals with non-chromosomal birth defects, the odds ratio of cancer was 1.54 (1.44 to 1.64); for those with chromosomal anomalies, the odds ratio was 5.53 (4.67 to 6.54). Many structural birth defects were associated with later cancer in the same organ system or anatomical location, such as defects of the eye, nervous system, and urinary organs. The odds ratio of cancer increased with number of defects and decreased with age, for both non-chromosomal and chromosomal anomalies. The odds ratio of cancer in people with any non-chromosomal birth defect was lower in adults (≥20 years: 1.21, 1.09 to 1.33) than in adolescents (15-19 years: 1.58, 1.31 to 1.90) and children (0-14 years: 2.03, 1.85 to 2.23). The relative overall cancer risk among adults with chromosomal anomalies was markedly reduced from 11.3 (9.35 to 13.8) in children to 1.50 (1.01 to 2.24). Among adults, skeletal dysplasia (odds ratio 3.54, 1.54 to 8.15), nervous system defects (1.76, 1.16 to 2.65), chromosomal anomalies (1.50, 1.01 to 2.24), genital organs defects (1.43, 1.14 to 1.78), and congenital heart defects (1.28, 1.02 to 1.59) were associated with overall cancer risk.

CONCLUSIONS

The increased risk of cancer in individuals with birth defects persisted into adulthood, both for non-chromosomal and chromosomal anomalies. Further studies on the molecular mechanisms involved are warranted.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Being born with a birth defect is one of the strongest risk factors for childhood cancer

Several specific birth defect-cancer associations have been identified, and increasing risk with increasing number of birth defects has been reported

The risk of cancer is higher at younger ages, but few studies have investigated cancer risk beyond childhood and adolescence

WHAT THIS STUDY ADDS

Many structural birth defects were associated with later cancer in the same organ system or anatomical location

The increased cancer risk in individuals with birth defects persisted into adulthood

In particular, the increased risk in adults remained for those born with congenital heart defects, genital organs defects, chromosomal anomalies, nervous system defects, and skeletal dysplasia

Introduction

Globally, in 2017, birth defects and childhood cancer were the third and ninth top causes of childhood disease burden, respectively (excluding injuries and perinatal diseases).[1] Approximately 3% of liveborn children in the Nordic countries are born with major birth defects.[2] Birth defects, particularly chromosomal anomalies but also non-chromosomal defects, are one of the strongest and most consistent risk factors for childhood cancers.[3-6] This suggests that birth defects and childhood cancer may have a common aetiology—genetic, environmental, or a combination. Few established risk factors exist for both birth defects and childhood cancer,[6 7] and identifying specific birth defects and childhood cancer associations can facilitate further research on common factors that affect disease development.

The reported excess risk of cancer in children with birth defects varies by type of anomaly. Children with Down's syndrome are, for instance, at increased risk of developing leukaemia, whereas the elevated risk of cancer in children with non-chromosomal defects seems to be driven mostly by embryonal tumours.[3 4] Several specific associations have been observed in previous studies, and the gradient in risk

seems to increase with number of birth defects.[3 5 8] Risk of cancer is highest in young children, but few studies have investigated risk beyond childhood and adolescence.[8-14] Thus, the contribution of birth defects to risk of cancer in adulthood is to a large degree unknown.[15]

The rarity of both birth defects and childhood cancers makes studying these associations challenging, and very large studies are needed to identify enough individuals with birth defects to allow stable estimates of cancer risk. In this large population based nested case-control study of children, adolescents, and adults (age 0-46 years), we linked national health registries in four Nordic countries to examine the association between major birth defects and cancer, both overall and for specific types, and stratified by age at diagnosis of cancer. We aimed to identify associations between birth defects and cancer, assess whether risk of cancer changed with the number of birth defects, and determine whether these associations persisted into adulthood.

Methods

Data sources

All Nordic countries have national population based health registries that are based on compulsory notification from healthcare providers, and access to healthcare is universal and independent of income. Information on birth defects came from the medical birth registries, containing information on all births in Denmark, Finland, Norway, and Sweden since 1973, 1987, 1967, and 1973, respectively.[16] The Danish National Patient Registry (since 1977), the Register of Congenital Malformations at the Finnish Institute for Health and Welfare (since 1963), and the Swedish National Patient Register at the Swedish National Board of Health and Welfare (since 1964) provided additional information on birth defects.[17-19] As we were interested in major birth defects, we used only inpatient diagnoses during the first year of life from the patient registries. We obtained information on cancer from the cancer registries in Denmark, Finland, Norway, and Sweden, covering the entire populations since 1943, 1953, 1953, and 1958, respectively.[20] Information on deaths and emigration came from the national population registries. Figure 1 shows the data sources for the research database.

Study population

Every resident in the Nordic countries is assigned a country specific unique identification number used in all administrative and medical registries, which makes accurate record linkage possible. Cases were defined as liveborn individuals in the birth registries, with a subsequent cancer diagnosis recorded in the cancer registries. We selected controls from among people who were alive, living in the country, and with no cancer diagnosis by the end of follow-up (2013 in Denmark, Finland, and Norway; 2014 in Sweden). We frequency matched them on country and year of birth (case-control ratio 1:10). After exclusion of ineligible cases (but keeping the controls), the study population included 62 295 cases and 724 542 controls.

Classification of cancer

In Norway and Finland, and for leukaemia and lymphoma in Denmark, cases of cancer were classified according to the ICD-O-3 (international classification of diseases for oncology, third edition).[21] In Denmark, except for leukaemia and lymphoma, we used the ICD-10 (international classification of diseases, 10th revision) codes and ICD-O-3 morphology codes.[22] In Sweden, we used ICD-7 codes, combined with morphology diagnosis coded by ICD-O-2/3 or the WHO/HS/CANC/24.1 classification.[23] We excluded non-malignant neoplasms, except for tumours in the urinary tract or central nervous system and other intracranial tumours (other endocrine glands), and cases without verified morphology, except for central nervous system and other intracranial tumours. We also excluded basal cell carcinomas. We classified cases in ICD-10 groups,[24] except for leukaemia and lymphoma, which we classified in ICD-O-3 morphology groups [25] (supplementary table A).

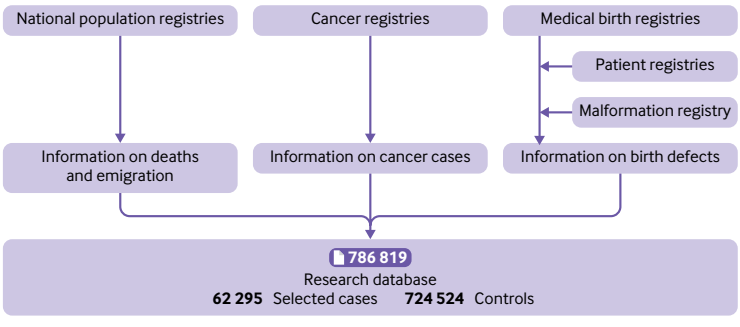

Fig 1 | Data sources in four Nordic countries. Controls were frequency matched on birth year in each country (1:10 case-control ratio with 100% successful matching). Some benign cases (for example, cervical precursor lesions) were later excluded from research database, resulting in final case-control ratio of 1:12

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Classification of major birth defects

The exposure of interest was major birth defects, classified in subgroups, registered in the birth registries, congenital malformation registry, or patient registries. We classified birth defects, and excluded minor birth defects, by using the definitions applied by the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT)[26] (using ICD-10 codes, but not including the British Paediatric Association extensions to ICD-10 as these codes were not available in all countries). In Denmark, the birth defects were coded according to ICD-8 throughout 1993 and ICD-10 thereafter.[17] The Finnish Register of Congenital Malformations coded birth defects according to ICD-9 Atlanta modification from 1986 onwards with the retrospective inclusion of ICD-10 codes from 1996. In Norway, the birth defects were coded according to ICD-8 during 1967-98, with the addition of some internally generated codes, and ICD-10 from 1999. In Sweden, the birth defects were coded according to the Swedish versions of ICD-8 during 1973-86, ICD-9 during 1987-96, and ICD-10 from 1997 onwards. We defined single birth defects, multiple defects within the same anatomical subgroup, and multiple defects when these were part of a sequence as isolated birth defects. We defined multiple birth defects from different anatomical subgroups, and not part of a sequence, as multiple birth defects according to the algorithm described by Garne et al.[27]

Statistical analysis

We used unconditional logistic regression models to obtain odds ratios of overall and specific types of cancer with 99% confidence intervals comparing individuals with major birth defects with those without major birth defects.[28] Because cancer is relatively rare among both exposed (individuals with major birth defects) and unexposed people, we interpreted the odds ratios as approximations of relative risks.[29 30] We adjusted odds ratios for the matching factors (country and birth year) and sex. Other possible confounders evaluated were in vitro fertilisation, maternal age, and smoking. We did not adjust for intermediate factors (birth weight and preterm birth) in order to estimate the total effect of birth defects on risk of cancer. Confounder selection is illustrated in a directed acyclic graph (supplementary figure A). We stratified by age at cancer diagnosis to evaluate risk of cancer at different ages. We assessed the association between number of major birth defects (1, 2, 3, or ≥4) as a categorical exposure and cancer and tested for linear trend by using orthogonal polynomial contrasts.[31] We analysed chromosomal anomalies and non-chromosomal birth defects separately. For selected analyses with enough cases, we stratified by country to evaluate whether the findings were consistent. When evaluating smoking as possible confounder, in the time period when this information was available, we used a complete case approach for handling missing data.[32] We chose 99% confidence intervals to reduce the probability of false positive results. We used Stata version 16 for all analyses.

Patient and public involvement

No patients or members of the public were involved in the study design, interpretation of results, or development of dissemination strategy. This study was entirely based on data already recorded in mandatory population based registers and databases.

Results

Table 1 shows characteristics of the population. Age at diagnosis of cancer ranged from 0 to 46 years, with a median of 23 (interquartile range 10-31) years. Thirty two per cent (19 881/62 295) of the cases were below 15 years of age, and 58% (36 068/62 295) were above 20. As the registries were established in different years, the age distribution differed between countries, with the oldest population in Norway. The median maternal age at delivery was 27 (23-31) years. Altogether, 2160 (3.5%) of cases and 15 826 (2.2%) of controls were registered with a major birth defect. The most common were congenital heart defects, limb defects, and genital anomalies (table 2). The three largest malignancy groups were lymphoid and haematopoietic malignancies, genitourinary cancers, and central nervous system tumours (fig 2).

Risk of overall cancer in people with birth defects

We observed an increase in overall cancer risk in people with any major birth defect compared with those without major birth defects (odds ratio 1.74, 99% confidence interval 1.63 to 1.84) (table 2). The odds ratio was highest for people with chromosomal anomalies (5.53, 4.67 to 6.54), with the highest overall relative cancer risk for those with Down's syndrome (6.08, 5.06 to 7.30). Risk of cancer was also elevated in people with non-chromosomal birth defects (odds ratio 1.54, 1.44 to 1.64), with the highest relative risks of any cancer in individuals with genetic syndromes/microdeletions (5.44, 3.57 to 8.28), nervous system defects (4.76, 3.89 to 5.83), and skeletal dysplasia (3.34, 1.97 to 5.67). Furthermore, we observed an increased risk of cancer for people with birth defects of the eye, digestive system, urinary organs, heart, genital organs, and limbs and other anomalies/syndromes.

Risk of specific cancer types in people with birth defects

Among people with non-chromosomal birth defects, we observed the highest relative risks of cancers of urinary organs (mainly kidney cancer) (odds ratio 2.7, 2.1 to 3.5), peripheral nerves and autonomic nervous system (2.4, 1.5 to 3.9), and central nervous system (2.3, 2.0 to 2.6) compared with people without major birth defects (fig 2). In addition, we observed increased risks of cancers of digestive organs (mainly liver), soft tissue, genital organs, nose/sinuses, thyroid and other endocrine glands, and lymphoid and haematopoietic tissue (non-Hodgkin's lymphoma in particular) and other or unspecified cancer. For people with chromosomal anomalies, we observed an increased risk of cancers of lymphoid and haematopoietic tissue, with the highest risk observed for acute

Table 1 | Characteristics of study population in Denmark (1977-2013), Finland (1987-2013), Norway (1967-2013), and Sweden (1973-2014). Values are numbers (percentages)

Characteristics	Cases (n=62 295)	Controls (n=724 542)
Major birth defects	2160 (3.5)	15 826 (2.2)
Sex*:		
Male	30 352 (48.7)	371 313 (51.2)
Female	31 943 (51.3)	353 229 (48.8)
Birth weight, g:		
<2500	2565 (4.1)	29 464 (4.1)
2500-3999	48 211 (77.4)	570 204 (78.7)
≥4000	11 353 (18.2)	123 009 (17.0)
Missing	166 (0.3)	1865 (0.3)
Gestational age, weeks:		
<37	3329 (5.3)	37 173 (5.1)
37-40	38 833 (62.3)	460 388 (63.5)
≥41	18 220 (29.2)	207 066 (28.6)
Missing	1913 (3.1)	19 915 (2.7)
Maternal smoking†:		
No	14 745 (23.7)	197 724 (27.3)
Yes	3869 (6.2)	57 622 (8.0)
Missing	43 681 (70.1)	469 196 (64.8)
Missing‡	1702/20 316 (8.4)	24 291/279 291 (8.7)
Maternal age, years:		
<25	20 460 (32.8)	236 312 (32.6)
25-29	22 137 (35.5)	260 778 (36.0)
30-34	13 603 (21.8)	159 422 (22.0)
≥35	6095 (9.8)	68 030 (9.4)
In vitro fertilisation§:		
No	12 356 (19.8)	126 859 (17.5)
Yes	159 (0.3)	1265 (0.2)
Missing	49 780 (79.9)	596 418 (82.3)
Year of birth:		
<1970	5596 (9.0)	48 412 (6.7)
1970-79	23 858 (38.3)	253 884 (35.0)
1980-89	17 413 (28.0)	250 660 (34.6)
1990-99	10 071 (16.2)	115 998 (16.0)
2000-09	4612 (7.4)	47 621 (6.6)
≥2010	745 (1.2)	7967 (1.1)
Age at primary cancer diagnosis, years¶:		
0-4	10 362 (16.6)	-
5-9	5057 (8.1)	-
10-14	4462 (7.2)	-
15-19	6346 (10.2)	-
20-29	16 977 (27.3)	-
30-39	15 692 (25.2)	-
≥40	3399 (5.5)	-
Year of primary cancer diagnosis¶:		
<1980	1320 (2.1)	-
1980-89	3970 (6.4)	-
1990-99	10 424 (16.7)	-
2000-09	24 924 (40.0)	-
2010-14	21 657 (34.8)	-

*Differences between cases and controls were due to sex ratio at birth and different cancer risk for males and females in study population (aged 0-46 years).
†Available from 1991 in Denmark, 1987 in Finland, 1998 in Norway, and 1982 in Sweden.
‡Percentage missing in time period when this information was recorded.
§Reported in 1990-2013 in Finland, 1984-2013 in Norway, and 1995-2014 in Sweden; not included for Denmark. Missingness in registration period cannot be calculated.
¶Reported only for cases.

myeloid leukaemia (odds ratio 88, 67 to 117) (fig 3). In addition, we saw increased risks for eye, testicular, and kidney cancer.

Risk of overall cancer in people with birth defects stratified by age at diagnosis

The overall risk of cancer associated with birth defects was elevated in all age groups (0-4, 5-9, 10-14, 15-19, ≥20 years) (fig 4). However, the odds ratios decreased with age at diagnosis for both non-chromosomal and chromosomal anomalies. The overall odds ratio of cancer in people with non-chromosomal birth defects was lower in adults (≥20 years: 1.21, 1.09 to 1.33) than in adolescents (15-19 years: 1.58, 1.31 to 1.90) and children (0-14 years: 2.03, 1.85 to 2.23) (supplementary table B). For skeletal dysplasia and congenital heart defects, the reduction in odds ratio in adults compared with

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Table 2 | Risk of overall cancer in people with any, or specific, major birth defects

Birth defect*	No (%)		Odds ratio (99% CI)
	Cases† (n=62 295)	Controls† (n=724 542)	
All anomalies	2160/62 295 (3.47)	15 826/724 542 (2.18)	1.74 (1.63 to 1.84)
All anomalies excluding chromosomal anomalies	1818/61 953 (2.93)	15 067/723 783 (2.08)	1.54 (1.44 to 1.64)
Specific sites			
Nervous system	225/60 360 (0.37)	593/709 309 (0.08)	4.76 (3.89 to 5.83)
Neural tube defects	90/60 225 (0.15)	216/708 932 (0.03)	5.00 (3.61 to 6.92)
Eye	60/60 195 (0.10)	373/709 089 (0.05)	2.07 (1.44 to 2.96)
Ear, face, and neck	8/60 143 (0.01)	92/708 808 (0.01)	1.13 (0.44 to 2.93)
Congenital heart defects	381/60 516 (0.63)	3512/712 228 (0.49)	1.42 (1.24 to 1.64)
Respiratory system	24/60 159 (0.04)	239/708 955 (0.03)	1.23 (0.71 to 2.15)
Oro-facial clefts	116/60 251 (0.19)	1242/709 958 (0.17)	1.12 (0.87 to 1.44)
Cleft palate only	32/60 167 (0.05)	397/709 113 (0.06)	0.97 (0.60 to 1.56)
Cleft lip with/without cleft palate	84/60 219 (0.14)	846/709 562 (0.12)	1.18 (0.88 to 1.59)
Digestive system	111/60 246 (0.18)	764/709 480 (0.11)	1.85 (1.43 to 2.41)
Abdominal wall defects	16/60 151 (0.03)	119/708 835 (0.02)	1.51 (0.76 to 3.01)
Urinary system	104/60 239 (0.17)	782/709 498 (0.11)	1.76 (1.34 to 2.30)
Genital organs	242/60 377 (0.40)	2538/711 254 (0.36)	1.30 (1.09 to 1.55)
Limb	292/60 427 (0.48)	2803/711 519 (0.39)	1.27 (1.09 to 1.49)
Skeletal dysplasia	30/60 165 (0.05)	114/708 830 (0.02)	3.34 (1.97 to 5.67)
Genetic syndromes and microdeletions	54/60 189 (0.09)	125/708 841 (0.02)	5.44 (3.57 to 8.28)
Chromosomal	342/60 477 (0.57)	759/709 475 (0.11)	5.53 (4.67 to 6.54)
Down's syndrome	301/60 436 (0.50)	604/709 320 (0.09)	6.08 (5.06 to 7.30)
Other anomalies/syndromes	424/60 559 (0.70)	2790/711 506 (0.39)	1.95 (1.70 to 2.23)

Odds ratios adjusted for matching variables (birth year and country) and sex. In all analyses for specific sites, other than for chromosomal anomalies, individuals with chromosomal anomalies were excluded. In all analyses, unexposed group was composed of individuals without major birth defects. Percentages of cases and controls are reported per analysis; study population consists of exposed (cases and controls with specific birth defect being analysed) and unexposed people (cases and controls without major birth defects).
*Categorised according to EUROCAT.
†Individuals with more than one diagnosis can be included in more than one sub-category; thus, the totals do not sum up to 2160.

children was less pronounced than for most other defects (skeletal dysplasia: adults 3.54 (1.54 to 8.15) versus children 3.59 (1.74 to 7.42); congenital heart defects: adults 1.28 (1.02 to 1.59) versus children 1.53 (1.26 to 1.86)). The relative overall cancer risk among adults with chromosomal anomalies was markedly reduced (odds ratio 1.50 (1.01 to 2.24) in adults versus 11.3 (9.35 to 13.8) in children). In contrast, genital birth defects were associated with a higher relative risk of cancer among adults (odds ratio 1.43, 1.14 to 1.78) than adolescents (1.04, 0.59 to 1.83) and children (1.25, 0.92 to 1.70). The highest relative risk of cancer among adults was for people with skeletal dysplasia (3.5-fold) followed by those with nervous system defects (odds ratio 1.76, 1.16 to 2.65). For birth defects of the eye, digestive system, respiratory system, limbs, abdominal wall, and urinary organs and oro-facial clefts, we found no association with adult cancer.

Risk of overall and specific cancer types in people with multiple birth defects

The risk of overall cancer in people with four or more non-chromosomal birth defects in different anatomical subgroups was nearly five times (odds ratio 4.9, 2.4 to 10.1) the risk in those without major birth defects (fig 5). Among people with non-chromosomal birth defects, the odds ratio of overall cancer increased with the number of birth defects in different subgroups (P for trend<0.001), as did the odds ratios of soft tissue cancer, kidney cancer, and central nervous system tumours (P for trend<0.001). Among people with chromosomal anomalies, we observed an increase in risk of overall cancer and acute lymphatic leukaemia as the number of birth defects in different subgroups increased (P for trend<0.001).

Associations between specific birth defects and specific types of cancers

We further explored the associations between specific major birth defects and specific cancers both in the entire study population and among adults (table 3). In the total population, the strongest associations were between defects involving genetic syndromes and microdeletions and cancers of urinary organs (odds ratio 35, 18 to 69), soft tissue (17, 5.6 to 49), and other endocrine glands (9.6, 3.0 to 31); between Down's syndrome and lymphoid/ haematopoietic malignancies (19, 16 to 23); between anomalies of the eye and eye cancer (18, 7.5 to 44); between nervous system defects and central nervous system tumours (16, 13 to 21); and between urinary organs defects and cancer of urinary organs (8.0, 4.5 to 14). In the adult population, the strongest associations were between nervous system defects and cancers of urinary organs (odds ratio 14, 4.7 to 40) and other endocrine glands (5.8, 1.8 to 19); between Down's syndrome and cancer of male genital organs (testicular cancer) (4.8, 2.7 to 8.6); between congenital heart defects and non-melanoma skin cancer (4.6, 1.6 to 13); between urinary organs defects and cancer of digestive organs (4.0, 1.2 to 13); between genital defects and cancer of digestive organs (2.3, 1.2 to 4.4) and male genital organs (testicular cancer) (1.9, 1.3 to 2.6); and between oro-facial clefts (mainly cleft lip) and breast cancer (2.3, 1.0 to 5.2).

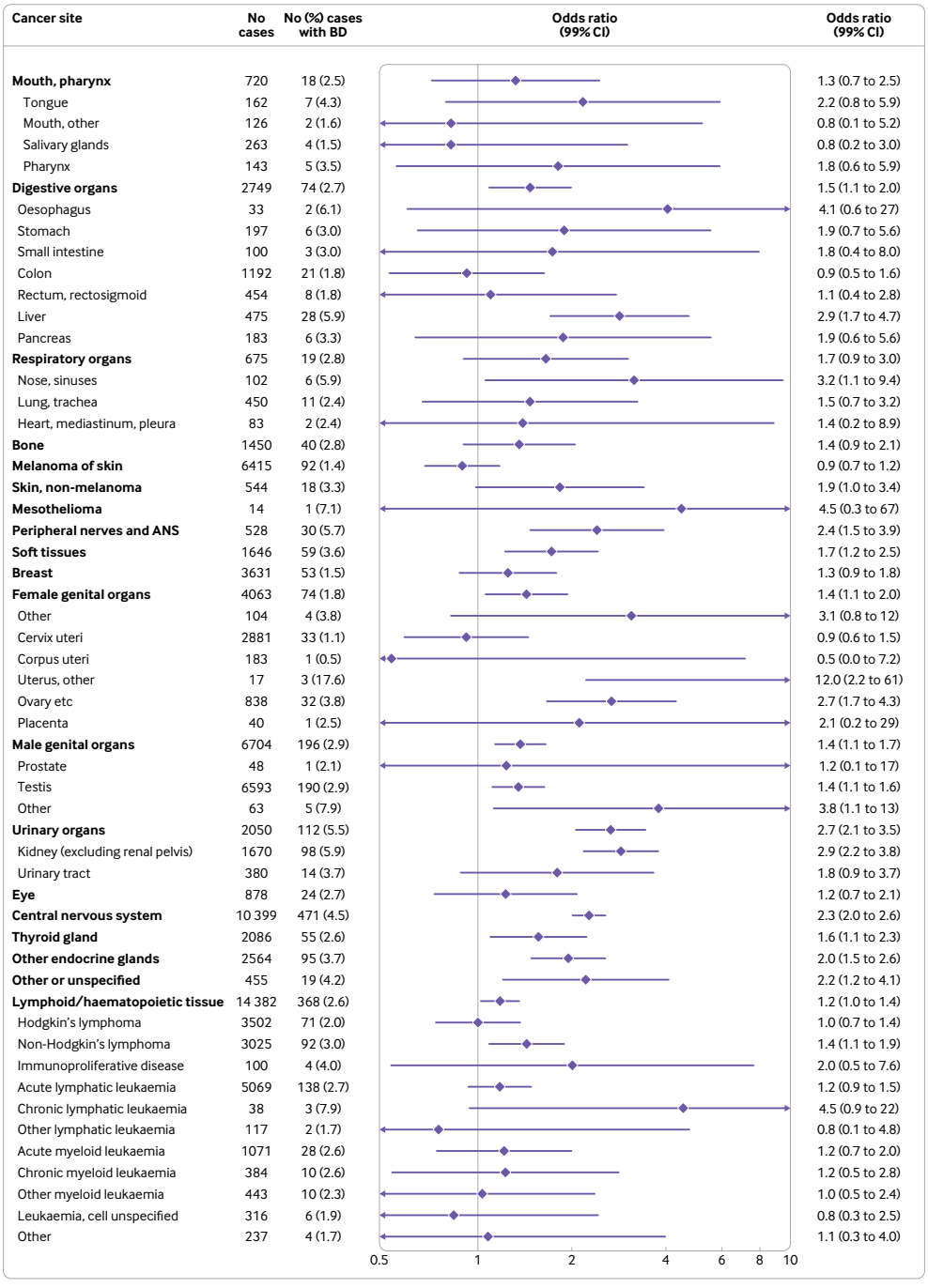

Fig 2 | Risk of specific cancers in people with any major non-chromosomal birth defects among 61 953 cases and 723 783 controls. Odds ratios (ORs) adjusted for matching variables (birth year and country) and sex. Cancer sites classified in ICD-10 groups; sites with no co-occurring birth defects and cancers are not included. ORs for cancer of urinary systems, central nervous system, and other endocrine glands are presented for benign and malignant cases combined. Separate effect estimates for malignant cases are 3.2 (2.4 to 4.1), 1.5 (1.2 to 1.9), and 2.8 (1.9 to 4.1) , respectively; estimates for benign cases are 0.7 (0.2 to 3.2), 3.3 (2.8 to 3.9), and 1.4 (0.9 to 2.1). ANS=autonomic nervous system; BD=birth defect

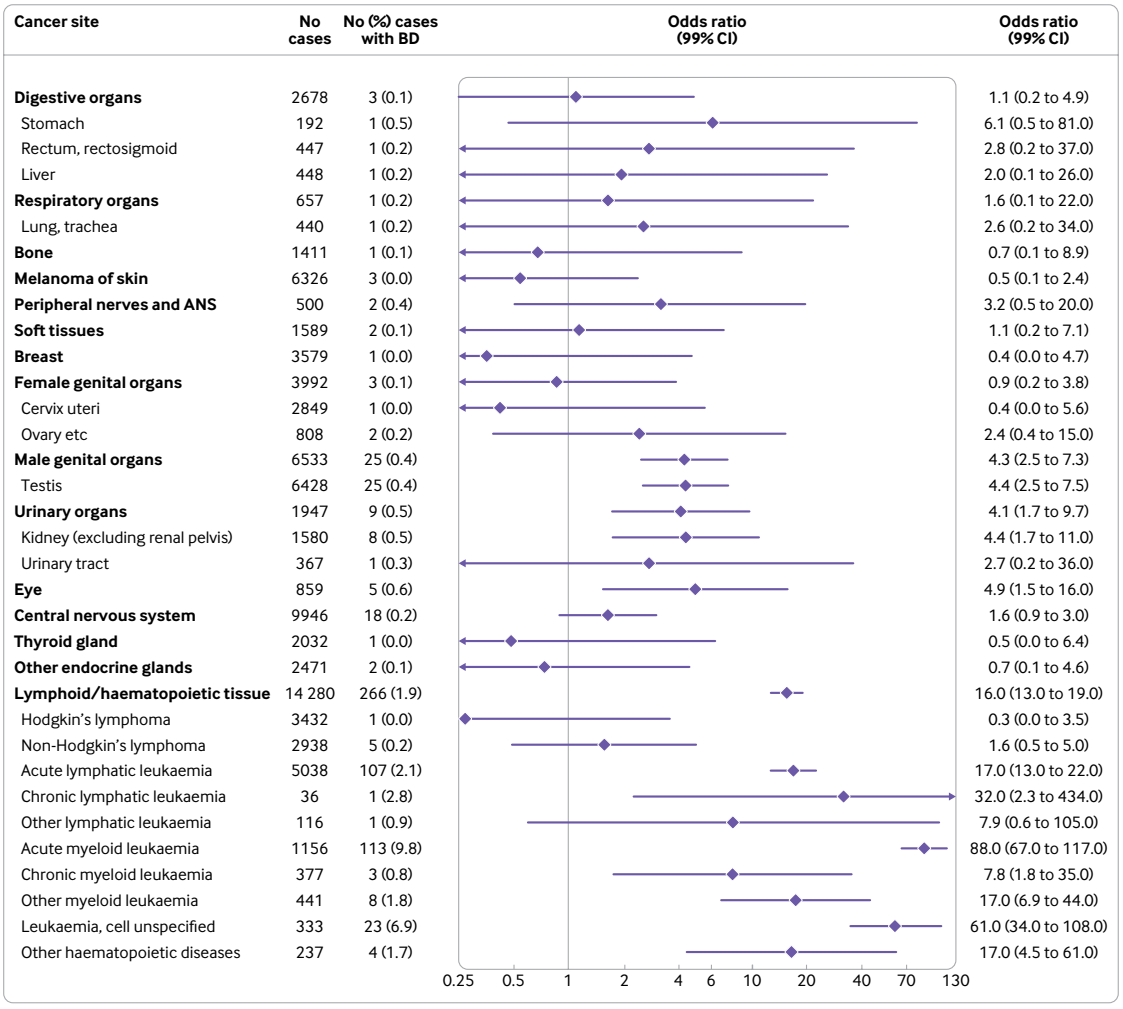

Fig 3 | Risk of specific cancers in people with chromosomal birth defects (n=1101; 905 Down's syndrome) among 60 477 cases and 709 475 controls. Odds ratios (ORs) adjusted for matching variables (birth year and country) and sex. Cancer sites classified in ICD-10 groups; sites with no co-occurring chromosomal anomalies and cancers are not included. ANS=autonomic nervous system; BD=birth defect

Discussion

In this large population based nested case-control study in four Nordic countries, people with chromosomal and non-chromosomal birth defects were at increased risk of overall cancer into adulthood (investigated for individuals up to the age of 46). People with non-chromosomal birth defects had an increased risk of cancer in several different organ systems, whereas the dominant malignancy for those with chromosomal anomalies was leukaemia. Many structural birth defects were associated with later cancer in the same organ system or anatomical location, and the relative risk of cancer increased with number of birth defects. Although the associations generally were stronger in children than adults, they persisted into adulthood. For instance, compared with people without major birth defects, those with two of the most common birth defect groups, congenital heart defects and genital defects, had an increased risk of cancer as adults (≥20 years).

Strengths and limitations of study

Among the strengths of our study were the large number of cancer cases (including all cases among births registered in the medical birth registries in four Nordic countries) and the ability to assess risk of cancer in adulthood and adolescence, as well as childhood in the same population. The large population meant that we could also study the associations between several specific birth defects and specific cancers.

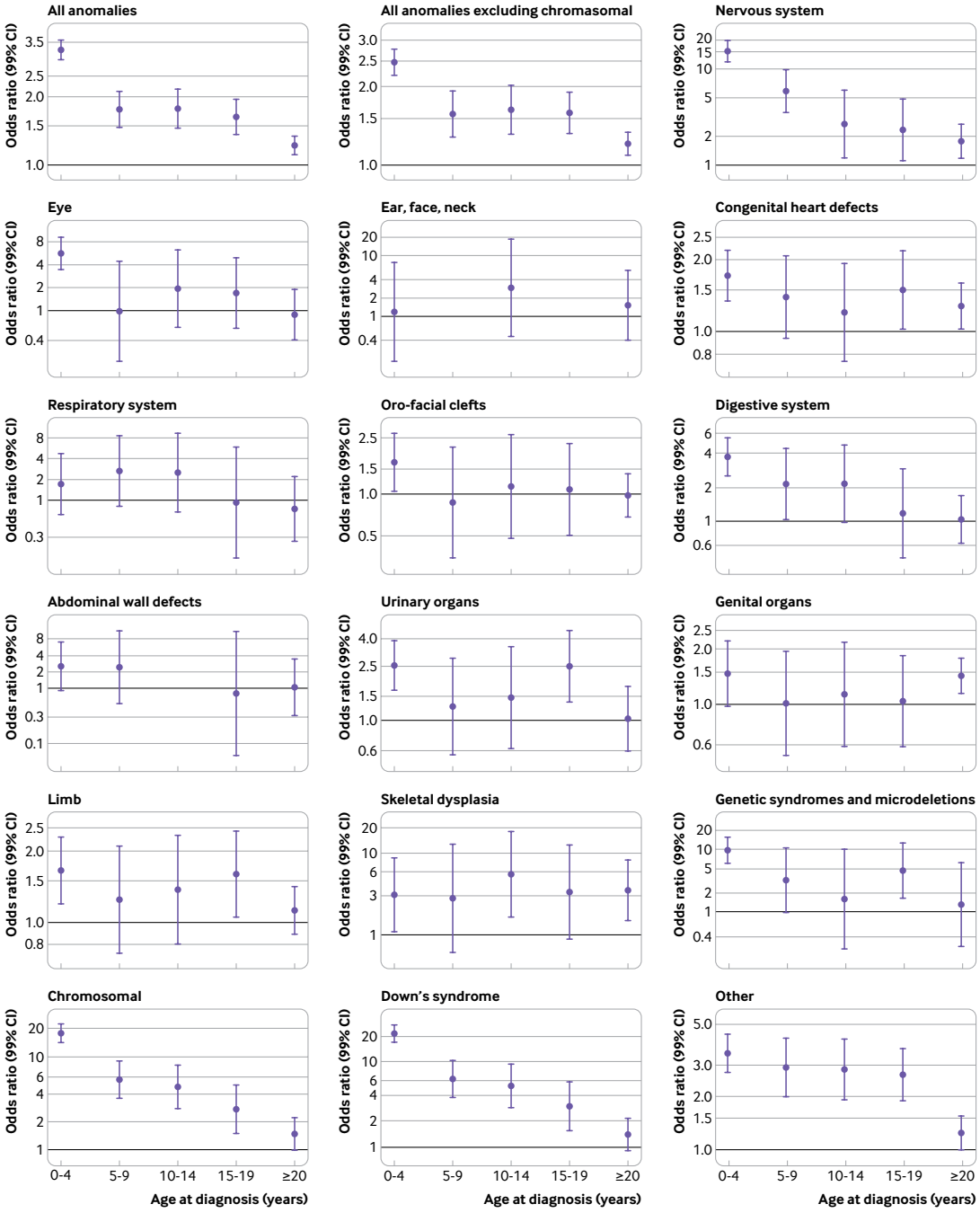

Fig 4 | Risk of any cancer in people with any, or specific, major birth defects, stratified by age at diagnosis. Note that scales differ across figures. Odds ratios (ORs) are adjusted for matching variables (birth year and country) and sex. In all analyses for specific sites, other than for chromosomal anomalies, people with chromosomal anomalies were excluded. In all analyses, the unexposed group was composed of people without major birth defects. Some age groups do not have an estimated OR owing to no co-occurring birth defect and cancer cases

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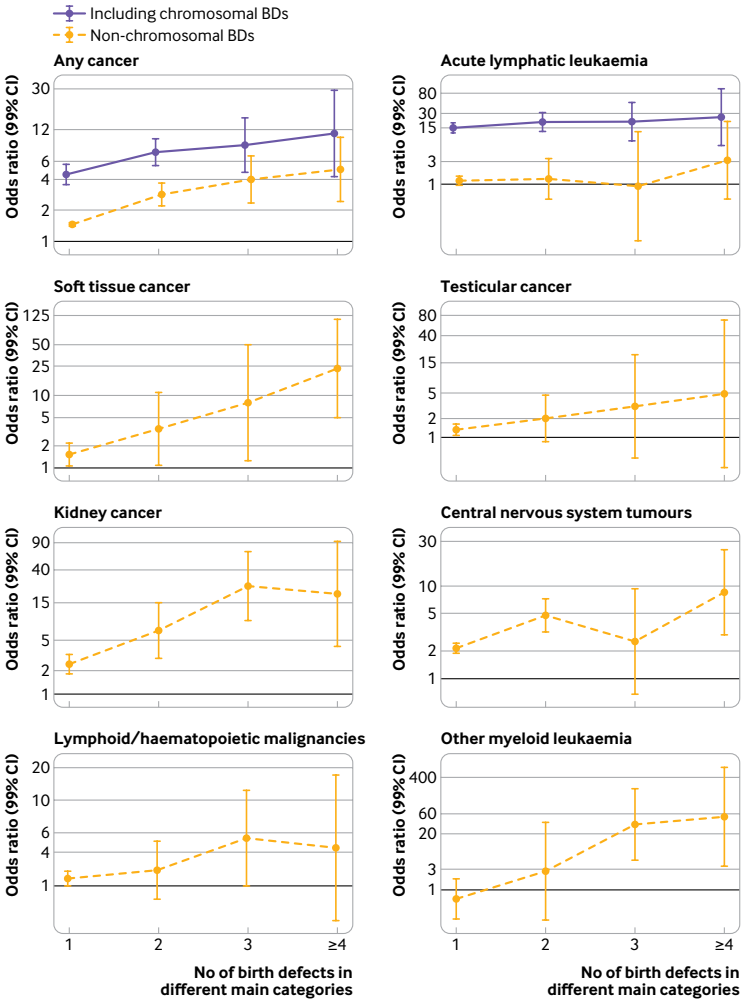

Fig 5 | Risk of selected cancers in people with major birth defects according to number of major birth defects in different anatomical subgroups. Results are presented separately for people with any birth defect (including chromosomal birth defects) and those with non-chromosomal defects only. Odds ratios (ORs) are adjusted for matching variables (birth year and country) and sex. Results are presented for all cancers in individuals with 1, 2, 3, and ≥4 birth defects (BDs)

The linkages of comprehensive and compulsory population based databases gave reliable and almost complete information on cancer diagnoses.[20] From the patient registries, we used only diagnoses of birth defects from inpatient registrations because of low validity of outpatient diagnoses.[19] In addition, we limited diagnoses to those occurring in the first year of life for consistency of exposure criteria in all four countries. For Finland, the data are from the Register of Congenital Malformation, which uses diagnoses given in hospital inpatient and outpatient care. However, all cases with major birth defect are validated from the hospitals before being entered in the register. We did a sensitivity analysis in which we stratified on country during 1987-2013 when all countries had available data and found similar risk estimates for any cancer among children with non-chromosomal anomalies (odds ratios from 1.8 to 2.7). Also, the risk estimates for larger cancer groups were in the same direction, supporting the reported associations.

In our study, ascertainment of birth defects may have differed both over time and between countries. Ascertainment depends on type and severity, so most studies, including ours, exclude minor birth defects. Variation also exists in the degree of ascertainment of major birth defects, especially if defects are registered

Table 3 | Associations between specific major birth defects and specific cancer groups (with ≥5 co-occurring cases) among total study population and among adults (≥20 years). Altogether, 104 associations, significant at 1% significance level, are reported after 264 analyses

	Total study population			Adults (≥20 years)		
Birth defect* and cancer site†	No of cases	No (%) cases with birth defects	Odds ratio (99% CI)	No of cases	No (%) cases with birth defects	Odds ratio (99% CI)
Nervous system						
Main groups:						
Central nervous system‡	10067	139 (1.4)	16 (13 to 21)	3612	6 (0.2)	2.4 (0.83 to 6.9)
Other endocrine glands	2484	15 (0.6)	7.7 (3.9 to 15)	1281	5 (0.4)	5.8 (1.8 to 19)
Eye	859	5 (0.6)	6.7 (2.1 to 22)	-	-	-
Urinary organs	1948	10 (0.5)	6.2 (2.7 to 14)	690	6 (0.9)	14 (4.7 to 40)
Thyroid gland	2038	7 (0.3)	4.6 (1.7 to 12)	-	-	-
Soft tissues	1593	6 (0.4)	4.4 (1.5 to 13)	-	-	-
Subgroups:						
Urinary tract	371	5 (1.3)	18 (5.6 to 59)	279	5 (1.8)	26 (8.1 to 86)
Kidney (excluding renal pelvis)	1577	5 (0.3)	3.8 (1.2 to 12)	-	-	-
Neural tube defects						
Main groups:						
Central nervous system	9979	51 (0.5)	16 (11.0 to 24)	-	-	-
Urinary organs	1944	6 (0.3)	10 (3.6 to 30)	689	5 (0.7)	26 (8.1 to 86)
Other endocrine glands	2476	7 (0.3)	9.5 (3.5 to 26)	-	-	-
Subgroups:						
Urinary tract	371	5 (1.3)	46 (14 to 151)	279	5 (1.8)	62 (19 to 204)
Eye						
Main groups:						
Eye	863	9 (1.0)	18 (7.5 to 44)	-	-	-
Urinary organs	1951	13 (0.7)	12 (6.0 to 26)	-	-	-
Subgroups:						
Kidney (excluding renal pelvis)	1585	13 (0.8)	14 (6.9 to 30)	-	-	-
Congenital heart defects						
Main groups:						
Skin, non-melanoma	533	7 (1.3)	3.5 (1.3 to 9.3)	412	6 (1.5)	4.6 (1.6 to 13)
Lymphoid/ haematopoietic tissue	14223	209 (1.5)	2.5 (2.1 to 3.0)	4700	19 (0.4)	1.1 (0.58 to 1.9)
Urinary organs	1963	25 (1.3)	2.3 (1.4 to 3.9)	-	-	-
Female genital organs	4015	26 (0.6)	1.9 (1.1 to 3.1)	3705	23 (0.6)	1.9 (1.1 to 3.3)
Male genital organs	6545	37 (0.6)	1.6 (1.1 to 2.5)	5740	31 (0.5)	1.7 (1.0 to 2.6)
Central nervous system§	10010	82 (0.8)	1.5 (1.2 to 2.1)	3625	19 (0.5)	1.6 (0.87 to 2.9)
Subgroups:						
Acute myeloid leukaemia	1092	49 (4.5)	7.8 (5.3 to 11)	-	-	-
Leukaemia, cell unspecified	322	12 (3.7)	6.6 (3.1 to 14)	-	-	-
Liver	459	12 (2.6)	4.5 (2.1 to 9.5)	-	-	-
Ovary etc.	817	11 (1.3)	3.1 (1.4 to 6.7)	558	8 (1.4)	4.0 (1.6 to 10)
Kidney (excluding renal pelvis)	1596	24 (1.5)	2.6 (1.5 to 4.4)	-	-	-
Acute lymphatic leukaemia	5021	90 (1.8)	2.5 (1.9 to 3.4)	-	-	-
Testis	6439	36 (0.6)	1.6 (1.0 to 2.5)	5667	30 (0.5)	1.6 (1.0 to 2.6)
Oro-facial clefts						
Main groups:						
Breast	3589	11 (0.3)	2.3 (1.0 to 5.1)	3578	11 (0.3)	2.3 (1.0 to 5.2)
Subgroups:				-	-	-
Ovary etc	811	5 (0.6)	4.3 (1.3 to 14)	-	-	-
Cleft palate only						
Subgroups:						
Ovary etc	811	5 (0.6)	11 (3.4 to 36)	-	-	-
Cleft lip with without cleft palate						
Main groups:						
Other endocrine glands	2477	8 (0.3)	2.8 (1.1 to 7.1)	-	-	-
Breast	3587	9 (0.3)	2.8 (1.1 to 6.7)	3576	9 (0.3)	2.8 (1.1 to 6.7)
Digestive system						
Main groups:						
Urinary organs	1947	9 (0.5)	4.0 (1.7 to 9.4)	-	-	-
Other endocrine glands	2479	10 (0.4)	3.7 (1.6 to 8.5)	-	-	-
Digestive organs	2683	8 (0.3)	3.1 (1.2 to 7.7)	-	-	-
Lymphoid/ haematopoietic tissue	14064	50 (0.4)	2.9 (2.0 to 4.2)	4688	7 (0.1)	1.5 (0.58 to 4.1)
Subgroups:						
Liver	1050	7 (0.7)	5.5 (2.0 to 15)	-	-	-
Acute myeloid leukaemia	1580	8 (0.5)	4.2 (1.7 to 11)	-	-	-
Kidney (excluding renal pelvis)	2945	12 (0.4)	3.5 (1.7 to 7.5)	-	-	-
Non-Hodgkin's lymphoma				-	-	-
Acute lymphatic leukaemia	4951	20 (0.4)	3.0 (1.7 to 5.4)	-	-	-

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Table 3 | Continued

Birth defect* and cancer site†	Total study population			Adults (≥20 years)		
	No of cases	No (%) cases with birth defects	Odds ratio (99% CI)	No of cases	No (%) cases with birth defects	Odds ratio (99% CI)
Urinary						
Main groups:						
Urinary organs	1958	20 (1.0)	8.0 (4.5 to 14)	-	-	-
Other endocrine glands	2480	11 (0.4)	4.2 (1.9 to 9.2)	-	-	-
Digestive organs	2684	9 (0.3)	3.9 (1.6 to 9.3)	2028	5 (0.2)	4.0 (1.2 to 13)
Subgroups:						
Kidney (excluding renal pelvis)	1589	17 (1.1)	8.0 (4.2 to 15)	-	-	-
Genital						
Main groups:						
Urinary organs	1957	19 (1.0)	2.9 (1.6 to 5.2)	-	-	-
Digestive organs	2692	17 (0.6)	2.0 (1.0 to 3.7)	2038	15 (0.7)	2.3 (1.2 to 4.4)
Male genital organs	6576	68 (1.0)	1.8 (1.3 to 2.5)	5770	61 (1.1)	1.9 (1.3 to 2.6)
Subgroups:						
Rectum, rectosigmoid	451	5 (1.1)	3.5 (1.1 to 11)	438	5 (1.1)	3.7 (1.1 to 12)
Liver	452	5 (1.1)	3.3 (1.0 to 11)	-	-	-
Kidney (excluding renal pelvis)	1588	16 (1.0)	3.2 (1.7 to 6.2)	-	-	-
Testis	6469	66 (1.0)	1.8 (1.3 to 2.5)	5698	61 (1.1)	1.9 (1.3 to 2.6)
Limb						
Main groups:						
Thyroid gland	2048	17 (0.8)	2.4 (1.3 to 4.5)	1624	9 (0.6)	1.6 (0.69 to 3.9)
Urinary organs	1956	18 (0.9)	2.3 (1.2 to 4.2)	-	-	-
Other endocrine glands	2489	20 (0.8)	2.1 (1.2 to 3.8)	1284	8 (0.6)	1.7 (0.7 to 4.4)
Subgroups:						
Kidney (excluding renal pelvis)	1588	16 (1.0)	2.5 (1.3 to 4.8)	-	-	-
Skeletal dysplasia						
Main groups:						
Lymphoid/ haematopoietic tissue	14 026	12 (0.1)	4.3 (1.9 to 9.4)	-	-	-
Central nervous system	9934	6 (0.1)	3.4 (1.2 to 10)	-	-	-
Subgroups:						
Non-Hodgkin's lymphoma	2940	7 (0.2)	13 (4.9 to 37)	-	-	-
Genetic syndromes and microdeletions						
Main groups:						
Urinary organs	1955	17 (0.9)	35 (18 to 69)	-	-	-
Soft tissues	1593	6 (0.4)	17 (5.6 to 49)	-	-	-
Other endocrine glands	2474	5 (0.2)	9.6 (3.0 to 31)	-	-	-
Central nervous system	9935	7 (0.1)	3.1 (1.1 to 8.3)	-	-	-
Lymphoid/ haematopoietic tissue	14 025	11 (0.1)	2.9 (1.3 to 6.5)	-	-	-
Subgroups:						
Kidney (excluding renal pelvis)	1589	17 (1.1)	39 (20 to 77)	-	-	-
Down's syndrome						
Main groups:						
Lymphoid/ haematopoietic tissue	14 269	255 (1.8)	19 (16 to 23)	4689	8 (0.2)	2.2 (0.86 to 5.4)
Male genital organs	6532	24 (0.4)	4.8 (2.7 to 8.3)	5730	21 (0.4)	4.8 (2.7 to 8.6)
Subgroups:						
Acute myeloid leukaemia	1155	112 (9.7)	111 (84 to 148)	-	-	-
Leukaemia, cell unspecified	333	23 (6.9)	80 (45 to 141)	-	-	-
Acute lymphatic leukaemia	5034	103 (2.0)	22 (16 to 29)	-	-	-
Other myeloid leukaemia	440	7 (1.6)	18 (6.8 to 49.0)	-	-	-
Testis	6427	24 (0.4)	4.8 (2.8 to 8.4)	5658	21 (0.4)	4.9 (2.7 to 8.7)
Other anomalies/ syndromes						
Main groups:						
Central nervous system¶	10 084	156 (1.5)	4.3 (3.4 to 5.3)	3629	23 (0.6)	1.9 (1.1 to 3.2)
Peripheral nerves and autonomic nervous system	505	7 (1.4)	3.6 (1.3 to 9.6)	-	-	-
Urinary organs	1961	23 (1.2)	3.2 (1.8 to 5.4)	690	6 (0.9)	2.4 (0.84 to 7.0)
Soft tissues	1605	18 (1.1)	3.0 (1.6 to 5.6)	-	-	-
Bone	1421	11 (0.8)	2.2 (1.0 to 4.8)	-	-	-
Lymphoid/ haematopoietic tissue	14 100	86 (0.6)	1.6 (1.2 to 2.1)	4705	24 (0.5)	1.3 (0.79 to 2.3)
Male genital organs	6547	39 (0.6)	1.5 (1.0 to 2.4)	5741	32 (0.6)	1.5 (0.92 to 2.3)
Subgroups:						
Kidney (excluding renal pelvis)	1595	23 (1.4)	4.0 (2.3 to 6.9)	416	6 (1.4)	4.4 (1.5 to 13)
Acute myeloid leukaemia	1053	10 (0.9)	2.5 (1.1 to 5.7)	-	-	-
Acute lymphatic leukaemia	4961	30 (0.6)	1.6 (1.0 to 2.6)	-	-	-
Testis	6442	39 (0.6)	1.6 (1.0 to 2.4)	5669	32 (0.6)	1.5 (0.93 to 2.3)

Chromosomal anomalies are excluded from all birth defect groups other than Down's syndrome. In all analyses, unexposed group was composed of individuals without major birth defects. Odds ratios adjusted for matching variables (birth year and country) and sex.
*Categorised according to EUROCAT.
†Categorised according to Cancer in Norway (2017)/NORDCAN.
‡Separate odds ratios and 99% CIs for malignant and benign cases: 7.8 (4.9 to 13) and 24 (18 to 33), respectively, in total study population; 3.9 (1.2 to 12), only benign cases, among adults.
§Separate odds ratios and 99% CIs for malignant and benign cases: 1.3 (0.8 to 2.0) and 2.0 (1.4 to 3.1), respectively, in total study population; 1.7 (0.8 to 3.9) and 1.5 (0.6 to 3.5), respectively, among adults.
¶Separate odds ratios and 99% CIs for malignant and benign cases: 2.3 (1.5 to 3.4) and 8.0 (6.2 to 10.3), respectively, in total study population; 0.8 (0.3 to 2.6) and 3.0 (1.6 to 5.5), respectively, among adults.

only at or immediately after birth. Visibility of the defect at birth is associated with higher ascertainment than for less visible birth defects.[33 34] However, under-ascertainment of birth defects is unlikely to be associated with later diagnosis of cancer and should generally bias associations towards the null. On the other hand, if cases among individuals aged under 1 year are more likely to be diagnosed as having a birth defect than controls, the results may be biased away from the null. Although adjustments for in vitro fertilisation, maternal age, and maternal smoking habits did not change the results substantially (supplementary tables C, D, and E), we may lack information for other unknown confounders. For instance, we could not include information on parental income or education owing to strict data regulations in some study countries. Also, if the missingness of data on maternal smoking was not completely at random, this analysis may be biased. For some of the analyses of combinations of specific birth defects and cancers, statistical power was limited. Spurious associations resulting from multiple comparisons may also be a concern. Therefore, we attempted to evaluate patterns of associations with regard to aetiology and relevant biological mechanisms.

Comparison with other studies

Previous studies have reported declining risk of cancer with age, but most were limited by size, shorter follow-up time, or both, and few were able to assess specific birth defects.[8-13 35 36] Only three studies included adults, and these evaluated only nervous and circulatory system defects and congenital heart defects.[14 35 36] In our study, we found that although the increase in overall cancer risk declined with age, it persisted into adulthood for both non-chromosomal and chromosomal anomalies. Furthermore, we were able to look at anatomical subgroups of birth defects and observed that the increased risk at younger ages was more pronounced for some subgroups, such as nervous system defects, genetic syndromes and microdeletions, and chromosomal anomalies. Most cancers associated with birth defects appear during childhood owing to the exposure being congenital and the typical latency of cancer. This is supported by odds ratios for cancer being higher during childhood (0-14 years) than adulthood (20 years or older). The exception was for people with defects in genital organs relative those without such defects, for which the odds ratio for cancer (one third of which were testicular) was 1.43 (99% confidence interval 1.14 to 1.78) for adults compared with 1.25 (0.92 to 1.70) for children. The long latency could be explained by the current model for this tumour's development, comprising genetic susceptibility for both genital organ defects and testicular cancer, combined with environmental factors exerting their effect during fetal life.[37] Incidence of testicular cancer rises with the testosterone surge in puberty and peaks at 30-35 years. In addition to testicular cancer, our study provided evidence for other associations between birth defects and cancer diagnosed in adulthood. For example, the odds ratio for congenital heart defects and overall cancer was 1.28 (1.02 to 1.59), similar to or lower than those previously suggested for adults.[14 35 36] Another example was nervous system defects, with a 15-fold increased risk of cancer before the age of 5, whereas the odds ratio for adults was reduced to 1.76 (1.16 to 2.65). This trend has been suggested previously but was limited to the first 12 years of life and/or with few co-occurring cases.[13 14]

An increasing number of (non-chromosomal) birth defects in different organ systems have been associated with increased risk of cancer overall.[3 5 8 9 14] Our results support this, and we also saw the same trend for chromosomal birth defects. We observed an increase in relative risk of overall cancer with increasing number of birth defects and, in addition, for some specific cancers such as acute lymphatic leukaemia (for chromosomal birth defects), soft tissue cancer, kidney cancer, central nervous system tumours, and other myeloid leukaemia (for non-chromosomal birth defects).

As expected, the increased overall cancer risk was lower than in previous studies limited to childhood cancer, but the results for children were in line with previous findings when stratified by age at diagnosis.[3 4] The associations between chromosomal birth defects (driven mainly by Down's syndrome) and cancer are well known, such as the high risks for leukaemia. Specifically, our estimated odds ratios of 111 and 22 for acute myeloid leukaemia and acute lymphatic leukaemia, respectively, are in concordance with the corresponding hazard ratio estimates of 125 and 28 recently published by Lupo et al.[3] In addition, adults with Down's syndrome were at increased risk of testicular cancer (odds ratio 4.9, 2.7 to 8.7), which has also been suggested previously but with less precision.[38]

Implications of findings and future research

Our study showed that birth defects are associated with risk of cancer in adulthood as well as in adolescence and childhood, a finding of clinical importance for healthcare workers responsible for follow-up of people with birth defects. Surveillance for cancer in children with birth defects has been discussed, but thus far the absolute cancer risk has been regarded as too low. In the Nordic countries, for instance, the cumulative risk of any cancer in the 0-44 year age group was 2.3% for males and 3.8% for females in 2016.[39] Thus, the most important implication of our results is to provide further rationale for additional studies on the molecular mechanisms involved in the developmental disruptions underlying both birth defects and cancer.

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Data sharing: The datasets analysed during the current study are not freely available owing to national regulations, but similar data can be obtained from the register authorities.

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The results of this study will be disseminated to relevant user organisations (Norwegian Cancer Society), patient groups, and healthcare workers.

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Web appendix: Supplementary materials

Supplementary Content

Table A. Classification of cancer. In Finland and Norway, we used ICD-O-3 codes for the whole period, in Denmark we used ICD-10 codes for the whole period, except for leukaemia and lymphoma which we classified according to ICD-O-3 morphology codes. In Sweden we used ICD-7 codes for the whole period.

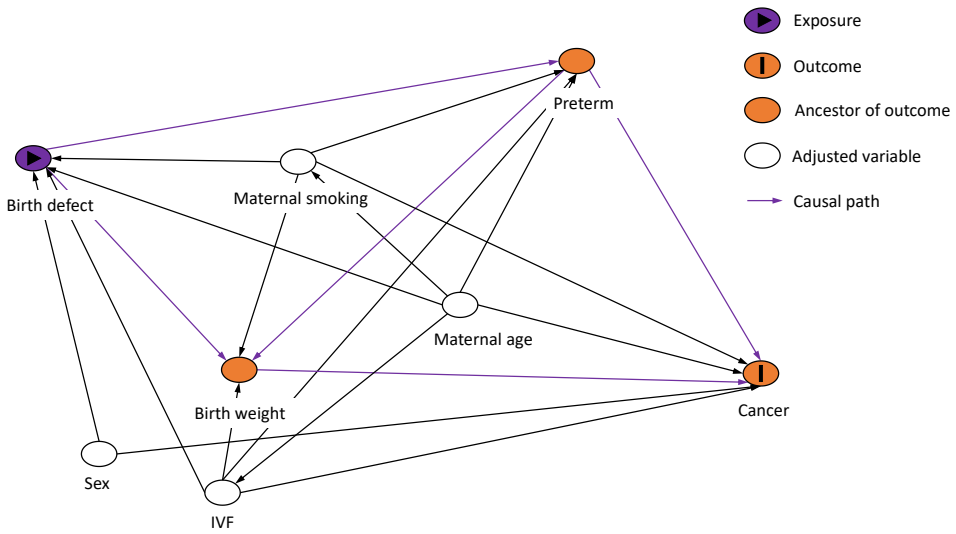
ICD-10 group	ICD-O-3 rev. 1		Swedish ICD-7
	Topography	**Morphology Site**	
From Cancer in Norway 2017*	Converting from ICD-O-3 to ICD-10 group, based on International classification of diseases for oncology (ICD-O) – 3rd edition, 1st revision.		Swedish ICD-7 with minor adjustments.
1 'Lip (C00)'	C00	Lip	140.0, 140.1, 140.9
2 'Tongue (C01–02)'	C01 C02	Base of Tongue Other and unspecified parts of tongue	141.0, 141.7, 141.9
3 'Mouth, other (C03–06)'	C03 C04 C05 C06	Gum Floor of mouth Palate Other and unspecified parts of mouth	143, 144,141.8
4 'Salivary glands (C07–08)'	C07 C08	Parotid gland Other and unspecified major salivary glands	142
5 'Pharynx (C09–14)'	C09 C10 C11 C12 C13 C14	Tonsil Oropharynx Nasopharynx Pyriform sinus Hypopharynx Other and ill-defined sites in lip, oral cavity and pharynx	145.0, 145.7, 145.8, 145.9, 146, 147, 148
6 'Oesophagus (C15)'	C15	Oesophagus	150
7 'Stomach (C16)'	C16	Stomach	151
8 'Small intestine (C17)'	C17	Small intestine	152
9 'Colon (C18)'	C18	Colon	153
10 'Rectum, rectosigmoid (C19–20)'	C19 C20	Rectosigmoid junction Rectum	154.0
11 'Anus (C21)'	C21	Anus and anal canal	153.9, 154.1, 154.8
12 'Liver (C22)'	C22	Liver and intrahepatic bile ducts	155.0, 156
13 'Gallbladder, bile ducts (C23–24)'	C23 C24	Gallbladder Other and unspecified parts of biliary tract	152.0, 155.1, 155.2, 155.3, 155.8, 155.9
14 'Pancreas (C25)'	C25	Pancreas	157, 195.5
15 'Other digestive organs (C26)'	C26	Other and ill-defined digestive organs	
16 'Nose, sinuses (C30–31)'	C30 C31	Nasal cavity and middle ear Accessory sinuses	160
17 'Larynx, epiglottis (C32)'	C32	Larynx	161
18 'Lung, trachea (C33–34)'	C33 C34	Trachea Bronchus and lung	162.0, 162.1
19 'Heart, mediastinum and pleura (C38)'	C38	Heart, mediastinum, and pleura	162.2, 164, 197.5, (except if pad equals 776)

ICD-10 group	ICD-O-3 rev. 1			Swedish ICD-7
	Topography	Morphology	Site	
20 'Bone (C40–41)'	C40 C41		Bones, joints and articular cartilage Bones, joints and articular cartilage of other and unspecified sites	196
21 'Melanoma of the skin (C43)'	C44	872-879		190
22 'Skin, non-melanoma (C44)'	C44		Skin (excludes skin of vulva C51, skin of penis C60.9, skin of scrotum C63.2)	191
23 'Mesothelioma (C45)'	C _ _._	905		162.2, 197.5, 158 or 179.7, AND pad 776
24 'Peripheral nerves and autonomic nervous system (C47)'	C47		Peripheral nerves and autonomic nervous system (include autonomic nervous system, ganglia, nerve, parasympathetic nervous system, peripheral nerve, spinal nerve, sympathetic nervous system)	193.3, 193.8, 193.9
25 'Soft tissues (C48–49)'	C48 C49		Retroperitoneum and peritoneum Connective, subcutaneous and other soft tissues	158 (except if pad equals 776), 197.0-197.4, 197.7-197.9
26 'Breast (C50)'	C50		Breast (excludes skin of breast C44.5)	170
27 'Other female genital (C51–52, C57.7-9)'	C51 C52 C57.7 C57.8 C57.9		Vulva Vagina Other specified parts of female genital organs Overlapping lesion of female genital organs Female genital tract, NOS	176
28 'Cervix uteri (C53)'	C53		Cervix uteri	171
29 'Corpus uteri (C54)'	C54		Corpus uteri	172
30 'Uterus, other (C55)'	C55		Uterus, NOS	174
31 'Ovary etc. (C56, C57.0-4)'	C56 C57.0 C57.1 C57.2 C57.3 C57.4		Ovary Fallopian tube Broad ligament Round ligament Parametrium Uterine adnexa	175
32 'Placenta (C58)'	C58		Placenta	173
33 'Prostate (C61)'	C61		Prostate gland	177
34 'Testis (C62)'	C62		Testis	178
35 'Other male genital (C60, C63)'	C60 C63		Penis Other and unspecified male genital organs	179 (except 179.7 if pad equals 776)
36 'Kidney (excl. renal pelvis) (C64)'	C64		Kidney	180.0, 180.9
37 'Urinary tract (C65–68)'	C65 C66 C67		Renal pelvis Ureter Bladder	180.1, 181

ICD-10 group	ICD-O-3 rev. 1			Swedish ICD-7
	Topography	Morphology	Site	
	C68		Other and unspecified urinary organs	
38 'Eye (C69)'	C69		Eye and adnexa	192
39 'Central nervous system (C70–72, D32–33, D42–43)	C70 C71 C72		Meninges Brain Spinal cord, cranial nerves and other parts of central nervous system (excludes peripheral nerves, sympathetic and parasympathetic nerves and ganglia C47)	193.0, 193.1,193.8,193.9
40 Thyroid gland (C73)	C73		Thyroid gland	194
41 'Other endocrine glands (C37, C74-75, D35.2–35.4, D44.3–44.5)	C37 C74 C75		Thymus Adrenal gland Other endocrine glands and related structures	195, 164
42 Other or unspecified (C39, C76, C80)	C39 C76 C80		Other and ill-defined sites within respiratory system and intrathoracic organs Other and ill-defined sites Unknown primary site	199, 163
43 Hodgkin lymphoma (C81)	C_ _._	959-999**	Lymphoid and hematopoietic diseases	201
44 Non-Hodgkin lymphoma (C82–86)				200.0, 200.1, 202.1, 202.2
45 Immunoproliferative disease (C88)				200.2, 200.3
46 Multiple myeloma (C90)				203
47 Acute lymphatic leukaemia (C91.0)				204.0
48 Chronic lymphatic leukaemia (C91.1)				204.1
49 Other and unspecified lymphatic leukaemia (C91.2-9)				202.4, 204.9
50 Acute myeloid leukaemia (C92.0+C93.0+C94.0+C94.2+C94.4-5)				205.0, 206.0
51 Chronic myeloid leukaemia (C92.1+C93.1+C94.1)				205.1
52 Other and unspecified myeloid leukaemia (C92.2-9+C93.2-9+C94.3+C94.7)				205.9
53 Leukaemia, cell unspecified (C95)				206.1, 206.9, 207.0, 207.2, 207.3, 209
54 Other hematopoietic diseases (C94.6, D45-47)				208, 207.9

*Grouped according to *Cancer Registry of Norway. Cancer in Norway 2017 - Cancer incidence, mortality, survival and prevalence in Norway. Oslo: Cancer Registry of Norway (2018)* except for leukaemia (C91–95, D45-47) which is grouped according to classification table from NORDCAN with minor adjustments.
**Classified by morphology according to conversion table from IARC. In addition, from ICD-O-3 rev.1: Morphology 9751/3 - Use this code for all types of Langerhans cell histiocytosis, including the former 9751/1 through 9754/3 terms.

Figure A. Directed acyclic graph (DAG) illustrating confounder selection.



Potential confounders evaluated were sex, *in vitro* fertilization (IVF), maternal age, and maternal smoking. Since IVF and maternal smoking were only available in a subset of the study sample, adjustments for these were made in sensitivity analyses. We chose to perform the main analysis with minimal adjustment, including the matching variables (country and birth year) and sex only, since additional adjustment for maternal age did not change the effect estimates substantially. We did not adjust for intermediate factors (birth weight and being preterm) in order to estimate the total effect of birth defects on cancer risk.

Table B. Risk of any cancer in individuals with any, or specific, birth defects, stratified by age at diagnosis.

Birth defect*		**0-14 years**			**15-19 years**			**20+ years**		
	Controls n (%) N=724 542	**Cases n (%) N=19 881**	**OR**	**99 % CI**	**Cases n (%) N=6 346**	**OR**	**99 % CI**	**Cases n (%) N=36 068**	**OR**	**99 % CI**
All anomalies	15,826 (2.18)	1,164 (5.85)	2.52	2.32 to 2.74	225 (3.55)	1.64	1.37 to 1.95	771 (2.14)	1.22	1.11 to 1.35
All anomalies excl. chromosomal anomalies	15,067 (2.08)	887 (4.52)	2.03	1.85 to 2.23	206 (3.26)	1.58	1.31 to 1.90	725 (2.01)	1.21	1.09 to 1.33
Nervous system	593 (0.08)	170 (0.9)	9.72	7.66 to 12.3	12 (0.2)	2.30	1.09 to 4.89	43 (0.12)	1.76	1.16 to 2.65
NTD	216 (0.03)	62 (0.33)	10.1	6.84 to 15.0	7 (0.11)	3.93	1.46 to 10.6	21 (0.06)	2.08	1.14 to 3.79
Eye	373 (0.05)	42 (0.22)	3.54	2.29 to 5.46	6 (0.1)	1.68	0.58 to 4.85	12 (0.03)	0.88	0.41 to 1.88
Ear. face and neck	92 (0.01)	4 (0.02)	1.26	0.33 to 4.78	0 (0)			4 (0.01)	1.52	0.40 to 5.74
CHD	3 512 (0.49)	189 (1)	1.53	1.26 to 1.86	47 (0.76)	1.49	1.02 to 2.18	145 (0.41)	1.28	1.02 to 1.59
Respiratory system	239 (0.03)	16 (0.09)	2.06	1.04 to 4.06	2 (0.03)	0.93	0.15 to 5.81	6 (0.02)	0.75	0.26 to 2.19
Oro-facial clefts	1 242 (0.17)	48 (0.26)	1.35	0.92 to 1.98	12 (0.2)	1.08	0.51 to 2.29	56 (0.16)	0.98	0.69 to 1.40
CPO	397 (0.06)	14 (0.07)	1.05	0.52 to 2.14	4 (0.07)	1.08	0.30 to 3.96	14 (0.04)	0.90	0.44 to 1.83
CL	846 (0.12)	34 (0.18)	1.51	0.95 to 2.38	8 (0.13)	1.08	0.43 to 2.69	42 (0.12)	1.01	0.67 to 1.53
Digestive system	764 (0.11)	73 (0.39)	2.93	2.11 to 4.06	8 (0.13)	1.17	0.47 to 2.92	30 (0.08)	1.03	0.63 to 1.67
Abdominal wall defects	119 (0.02)	10 (0.05)	2.04	0.85 to 4.87	1 (0.02)	0.81	0.06 to 10.8	5 (0.01)	1.04	0.32 to 3.45
Urinary system	782 (0.11)	62 (0.33)	2.00	1.41 to 2.83	19 (0.31)	2.51	1.38 to 4.57	23 (0.07)	1.03	0.59 to 1.78
Genital organs	2 538 (0.36)	74 (0.39)	1.25	0.92 to 1.70	21 (0.34)	1.04	0.59 to 1.83	147 (0.41)	1.43	1.14 to 1.78
Limb	2 803 (0.39)	115 (0.61)	1.48	1.15 to 1.90	39 (0.63)	1.60	1.05 to 2.43	138 (0.39)	1.12	0.89 to 1.40
Skeletal dysplasia	114 (0.02)	15 (0.08)	3.59	1.74 to 7.42	4 (0.07)	3.38	0.91 to 12.6	11 (0.03)	3.54	1.54 to 8.15
Genetic syndromes and microdeletions	125 (0.02)	44 (0.23)	6.47	4.05 to 10.3	7 (0.11)	4.64	1.70 to 12.7	3 (0.01)	1.34	0.29 to 6.15
Chromosomal	759 (0.11)	277 (1.46)	11.3	9.35 to 13.8	19 (0.31)	2.75	1.51 to 5.00	46 (0.13)	1.50	1.01 to 2.24
Down syndrome	604 (0.09)	247 (1.3)	13.3	10.8 to 16.4	16 (0.26)	3.01	1.57 to 5.79	38 (0.11)	1.42	0.92 to 2.21
Other anomalies/ syndromes	2 790 (0.39)	211 (1.11)	3.11	2.57 to 3.76	60 (0.97)	2.64	1.88 to 3.71	153 (0.43)	1.24	1.00 to 1.54

ORs are adjusted for matching variables (birth year and country) and sex. In all analyses for specific sites, other than for chromosomal anomalies, individuals with chromosomal anomalies were excluded. In all analyses, the unexposed group was individuals without major birth defects. Abbreviations: OR odds ratio; CI confidence interval; NTD Neural Tube Defects; CHD Congenital Heart Defects; CPO Cleft palate only; CL Cleft lip with/ without cleft palate. *Birth defects classified according to EUROCAT.

Table C. Risk of overall cancer in individuals with any, or specific, major birth defects, adjusted for country, birth year, sex and maternal age, among 62 295 cases and 724 542 controls.

Birth defect*	**OR**	**99% CI**
All anomalies	1.73	1.63 to 1.84
All anomalies excl. chromosomal anomalies	1.54	1.44 to 1.64
Specific sites		
Nervous system	4.76	3.89 to 5.83
NTD	4.99	3.61 to 6.91
Eye	2.07	1.44 to 2.96
Ear, face and neck	1.13	0.44 to 2.93
CHD	1.42	1.24 to 1.63
Respiratory system	1.24	0.71 to 2.15
Oro-facial clefts	1.12	0.87 to 1.44
CPO	0.97	0.60 to 1.56
CL	1.18	0.88 to 1.59
Digestive system	1.85	1.43 to 2.41
Abdominal wall defects	1.52	0.76 to 3.02
Urinary system	1.76	1.34 to 2.30
Genital organs	1.30	1.09 to 1.55
Limb	1.27	1.09 to 1.49
Skeletal dysplasia	3.34	1.97 to 5.67
Genetic syndromes and microdeletions	5.42	3.56 to 8.25
Chromosomal	5.46	4.61 to 6.46
Down syndrome	5.99	4.99 to 7.20
Other anomalies/ syndromes	1.95	1.70 to 2.23

In all analyses for specific sites, other than for chromosomal anomalies, individuals with chromosomal anomalies were excluded. In all analyses, the unexposed group was composed of individuals without major birth defects. Abbreviations: OR, odds ratio; CI, confidence interval; NTD, Neural Tube Defects; CHD, Congenital Heart Defects; CPO, Cleft palate only; CL, Cleft lip with/ without cleft palate. *Categorized according to EUROCAT.

Table D. Risk of overall cancer in individuals with any, or specific, major birth defects, adjusted for country, birth year, sex, maternal age and smoking in the time period when smoking information was collected (1991-2013 in Denmark, 1987-2013 in Finland, 1998-2013 in Norway, and 1982-2014 in Sweden), among 18 614 cases and 255 346 controls.

Birth defect*	Adjusted[†] for maternal age		Adjusted[†] for maternal age and smoking[‡]	
	OR	**99% CI**	**OR**	**99% CI**
All anomalies	2.29	2.12 to 2.49	2.36	2.17 to 2.56
All anomalies excl. chromosomal anomalies	1.95	1.79 to 2.13	2.00	1.82 to 2.19
Specific sites				
Nervous system	6.06	4.60 to 8.00	5.97	4.46 to 7.99
NTD	5.59	3.34 to 9.35	4.84	2.73 to 8.56
Eye	2.78	1.78 to 4.34	2.99	1.90 to 4.70
Ear, face and neck	1.67	0.63 to 4.39	1.52	0.54 to 4.27
CHD	1.52	1.28 to 1.81	1.56	1.30 to 1.87
Respiratory system	1.68	0.85 to 3.32	1.54	0.74 to 3.18
Oro-facial clefts	1.13	0.76 to 1.70	1.22	0.81 to 1.85
CPO	1.00	0.51 to 1.95	1.00	0.50 to 1.99
CL	1.22	0.73 to 2.04	1.38	0.83 to 2.31
Digestive system	2.48	1.79 to 3.44	2.39	1.68 to 3.40
Abdominal wall defects	1.12	0.37 to 3.35	0.84	0.22 to 3.18
Urinary system	1.77	1.27 to 2.45	1.70	1.21 to 2.40
Genital organs	1.33	1.01 to 1.77	1.40	1.04 to 1.87
Limb	1.60	1.27 to 2.01	1.70	1.35 to 2.15
Skeletal dysplasia	3.92	2.17 to 7.07	3.91	2.11 to 7.23
Genetic syndromes and microdeletions	5.23	3.36 to 8.13	4.83	3.05 to 7.66
Chromosomal	7.86	6.37 to 9.71	8.21	6.59 to 10.2
Down syndrome	9.37	7.39 to 11.9	9.82	7.66 to 12.6
Other anomalies/ syndromes	3.46	2.90 to 4.12	3.52	2.93 to 4.22

In all analyses for specific sites, other than for chromosomal anomalies, individuals with chromosomal anomalies were excluded. In all analyses, the unexposed group was composed of individuals without major birth defects. Abbreviations: OR, odds ratio; CI, confidence interval; NTD, Neural Tube Defects; CHD, Congenital Heart Defects; CPO, Cleft palate only; CL, Cleft lip with/ without cleft palate. *Categorized according to EUROCAT. [†]Also adjusted for country, birth year and sex. [‡]Smoking information was missing for 8.4% of cases and 8.7% of controls.

Table E. OR (99% CI) of overall cancer in individuals with any major birth defects, adjusted for country, birth year, sex, maternal age and IVF in the time period when IVF information was reported (1990-2013 in Finland, 1984-2013 in Norway, and 1995-2014 in Sweden). In total, 1 424 out of 140 639 children were conceived through IVF.

Birth defect	**Adjusted for country, birth year, and sex**	**Adjusted for country, birth year, sex, and IVF**	**Adjusted for country, birth year, sex, IVF and maternal age**
All anomalies excl. chromosomal anomalies	2.22 (1.98 to 2.50)	2.22 (1.98 to 2.50)	2.21 (1.96 to 2.48)
Chromosomal anomalies	10.3 (7.87 to 13.6)	10.3 (7.86 to 13.6)	9.50 (7.22 to 12.5)

Abbreviations: OR, odds ratio; CI, confidence interval; IVF in vitro fertilization.

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Sex differences in childhood cancer risk among children with major birth defects: a Nordic population-based nested case-control study

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Abstract

Background: Childhood cancer is more common among children with birth defects, suggesting a common aetiology. Whether this association differs by sex is unclear.
Methods: We performed a population-based nested case-control study using nationwide health registries in four Nordic countries. We included 21 898 cancer cases (0–19 years) and 218 980 matched population controls, born 1967–2014. Associations between childhood cancer and major birth defects were calculated as odds ratios (ORs) with 95% confidence intervals (CIs) using logistic regression models. Effect modification was evaluated using a counterfactual framework to estimate confidence intervals and *P*-values for the natural indirect effects.
Results: Birth defects were present for 5.1% (1117/21 898) of childhood cancer cases and 2.2% (4873/218 980) of controls; OR of cancer was higher for chromosomal (OR = 10, 95%

CI = 8.6–12) than for non-chromosomal defects (OR = 1.9, 95% CI = 1.8–2.1), strongest between genetic syndromes/microdeletion and renal tumours, Down syndrome and leukaemia, and nervous system defects and central nervous system tumours. The association between birth defects and cancer was stronger among females (OR = 2.8, 95% CI = 2.6–3.1) than males (OR = 2.1, 95% CI = 1.9–2.2, $P_{interaction}$ <0.001). Male sex was an independent risk factor for childhood cancer, but very little of the overall association between sex and childhood cancer was mediated through birth defects (4.8%, P_{NIE} <0.001), although more at younger ages (10% below years and 28% below 1 year).

Conclusions: The birth defect–cancer associations were generally stronger among females than males. Birth defects did not act as a strong mediator for the modest differences in childhood cancer risk by sex, suggesting that other biological pathways are involved.

Key words: Childhood cancer, birth defects, congenital anomalies, sex differences, cancer risk

Key Messages

- Having a birth defect is one of the strongest confirmed risk factors for childhood cancer.
- In this large population-based nested case-control study of more than 21 000 incident childhood cancer cases, we observed sex differences in the birth defect–cancer associations.
- Our study indicates that the birth defect–cancer associations, in general, are stronger among females than males, particularly for non-chromosomal defects and lymphomas and germ cell tumours, and chromosomal defects and leukaemia.
- We did not find evidence supporting the hypothesized role of birth defects as a strong mediator in the sex–childhood cancer association.
- The sex differences in the birth defect–cancer association suggest that further studies on the underlying mechanisms are needed.

Introduction

Globally, approximately 400 000 new childhood cancer cases (ages 0–19 years) are diagnosed each year, and the estimated age-standardized incidence rate is 16.2 per 100 000 person-years.[1] The global burden of childhood cancer is unequally distributed, with 82% of disability-adjusted life-years (DALYs) due to childhood cancer occurring in resource-limited populations (which include more than 90% of children at risk of cancer).[1] Still, few strong risk factors for childhood cancer have been identified.[2]

Existing evidence of an association between birth defects and childhood cancer [3–5] suggests a common aetiology. Increases in childhood cancer risk are observed for both chromosomal (~11-fold) and non-chromosomal (~2–3-fold) birth defects.[3,4] Associations between several specific birth defects and childhood cancers have been identified (e.g. Down syndrome and leukaemia, central nervous system (CNS) defects and CNS tumours), and a positive risk gradient by the number of birth defects has been observed.[3–5] There is also evidence that the increased cancer risk among individuals with birth defects persists into adulthood.[3]

Approximately 2% to 3% of liveborn children in the Nordic countries have major birth defects.[6] The prevalence of birth defects and incidence of childhood cancer are higher among males than females (~1.2-fold).[7,8] Like childhood cancer, most birth defects have an unknown aetiology.[9] Although the association between birth defects and childhood cancer is well established, research on possible sex differences in this association is sparse.[10–12] However, a recent study suggests that birth defects may act as a strong mediator, explaining up to 40% of the association between sex and childhood cancer.[13]

Large populations are needed to study associations between birth defects and childhood cancer, particularly by sex, since the frequencies of both conditions are low. By linking national registries in four Nordic countries, we examined the risk of cancer before the age of 20 years among individuals with birth defects by sex and evaluated the role of birth defects as a mediator in the sex–childhood cancer relationship.

Methods

Data sources and study population

The Nordic countries have high-quality national population-based health registries with close to complete nationwide coverage, and unique personal identification numbers for all individuals residing in the countries facilitate accurate linkage between registries.[3,14] We performed a nested case-control study and defined cases as individuals recorded in the medical birth registries with diagnoses in the cancer registries before the age of 20 years (born from 1977 in Denmark, 1987 in Finland, 1967 in Norway and 1973 in Sweden). Controls were frequency-matched on country and year of birth among persons who were alive, residing in the country and with no cancer diagnoses by the end of follow-up (2013 in Denmark, Finland, and Norway; 2014 in Sweden).

We obtained information on cancer diagnoses from cancer registries. The cancer registries have close to complete coverage of the entire populations from 1943 in Denmark, 1953 in Finland and Norway and 1958 in Sweden, with minor variations in completeness between countries, time periods and age at diagnosis.[15–20] Information on birth defects was collected from the medical birth registries, congenital malformations registry (Finland) and patient registries (Denmark and Sweden).[21–23] From the patient registries, we included birth defects identified during hospitalizations in the first year of life. Information on death and emigration was obtained from the national population registries. The data sources have been described in detail previously[3] (see Supplementary Table S1, available as Supplementary data at *IJE* online, for more details).

Birth defect classification

Major birth defects were defined and classified according to the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT).[24] Isolated birth defects were defined as single birth defects, multiple defects within the same anatomical subgroup, or multiple defects when part of a sequence. Multiple birth defects were defined as birth defects from different anatomical subgroups that are not part of a sequence.[3]

Childhood cancer classification

Cancer cases were classified according to the *International Classification of Childhood Cancer,* Third Edition (ICCC-3) (IARC 2017).[25] We excluded non-malignant neoplasms, except for central nervous system (CNS) tumours (ICCC-3 site group III, CNS and Miscellaneous Intracranial and Intraspinal Neoplasms) and intracranial and intraspinal germ cell tumours [ICCC-3 site group X(a)], cases without verified morphology and cases not classified by the ICCC-3.

Statistical analysis

We used unconditional logistic regression to compute odds ratios (ORs) of cancer with 95% confidence intervals (CIs), comparing individuals with and without major birth defects. ORs were adjusted for sex and matching factors. Other available confounders considered were in vitro fertilization (IVF), maternal age and smoking. Information on IVF (not available for Denmark) and smoking was not available for the entire study period. Potential confounding was evaluated by comparing estimates with and without these factors included in the models, using a complete case approach for handling missing data. To evaluate the robustness of the results, we calculated E-values for the OR and the lower confidence limit.[26] Analyses stratified by sex and analyses including a sex–birth defect interaction term were performed to evaluate possible sex differences in birth defect–cancer associations. Chromosomal and non-chromosomal birth defects were analysed separately.

To evaluate birth defects as a potential mediator of the sex–childhood cancer association, we used a counterfactual framework allowing for exposure–mediator interaction. We estimated the controlled direct effect (CDE), the natural direct effect (NDE), the natural indirect effect (NIE) and the marginal total effect (TE, i.e. the product of NDE and NIE).[27] We included a sex–birth defect interaction and adjusted for the following potential mediator–outcome confounders: birth year, country and maternal age. Also, we performed sensitivity analyses where we included IVF and maternal smoking as confounders. To assess whether effect modification was present, we used CIs and *P*-values for the NIE and calculated the proportion of the sex effect mediated through birth defects.[27] Supplementary Figure S1 (available as Supplementary data at *IJE* online) shows a simplified illustration of the assumed causal relationship between sex, birth defects and childhood cancer.

Given differences in registries and time periods, we performed additional sensitivity analyses leaving out one country at a time. Also, to evaluate the possible impact of diagnostic and survival trends on our results, we performed sensitivity analyses limited to the ~60% of the cases and controls born in 1990 and after.

All analyses were performed using Stata version 16, and causal mediation effects were estimated using the Stata PARAMED macro.

Table 1 Characteristics of the study population in Denmark (1977–2013), Finland (1987–2013), Norway (1967–2013) and Sweden (1973–2014)

Characteristics	Cases		Controls	
	n	%	*n*	%
Study population	21 898	9.1	218 980	90.9
Major birth defects	1117	5.1	4873	2.2
Sex[a]				
Males	11 937	54.5	111 260	50.8
Females	9961	45.5	107 720	49.2
Birthweight (g)				
< 2500	942	4.3	9104	4.2
2500–3999	16 301	74.4	169 802	77.5
4000 or more	4573	20.9	39 403	18.0
Missing	82	0.4	671	0.3
Gestational age (weeks)				
< 37	1336	6.1	11 730	5.4
37–41	18 172	83.0	183 176	83.6
42 or more	1832	8.4	18 541	8.5
Missing	558	2.5	5533	2.5
In vitro fertilization[b]				
No	7778	55.7	78 003	55.9
Yes	127	0.9	1047	0.7
Not collected	6056	43.4	60 560	43.4
Maternal smoking[c]				
No	10 612	48.5	105 339	48.1
Yes	2391	10.9	24 872	11.4
Missing[d]	958	6.9	9399	6.7
Not collected	8895	40.6	88 769	40.5
Maternal age (years)				
< 25	5164	23.6	58 481	26.7
25–29	7744	35.4	79 584	36.3
30–34	6029	27.5	56 009	25.6
35 or more	2961	13.5	24 906	11.4
Paternal age (years)[e]				
< 25	1257	5.7	13 015	5.9
25–29	2666	12.2	26 599	12.1
30–34	2562	11.7	25 886	11.8
35 or more	2161	9.9	20 835	9.5
Missing	13 252	60.5	132 645	60.6
Year of birth				
1967–1970	525	2.4	5250	2.4
1970–1979	2541	11.6	25 410	11.6
1980–1989	5405	24.7	54 050	24.7
1990–1999	8285	37.8	82 850	37.8
2000–2009	4418	20.2	44 180	20.2
2010–2014	724	3.3	7240	3.3
Age at primary cancer diagnosis (years)[f]				
0–4	8259	37.7		
5–9	4109	18.8		
10–14	3774	17.2		
15–19	5756	26.3		
Year of primary cancer diagnosis[f]				
Before 1980	798	3.6		
1980–1989	1961	9.0		
1990–1999	6146	28.1		
2000–2009	8572	39.1		
2010 or later	4421	20.2		

[a]Differences between cases and controls were due to birth:sex ratio and different cancer risk for males and females in the study population.
[b]Reported from 1990 in Finland, 1984 in Norway and 1995 in Sweden; not included for Denmark.
[c]Available from 1991 in Denmark, 1987 in Finland, 1998 in Norway and 1982 in Sweden.
[d]Percentage missing in the time period when this information was recorded.
[e]Not reported in Sweden and Finland.
[f]Reported only for cases.

Results

In all, 21 898 children were diagnosed with cancer during the study period. The largest malignancy group was leukaemia ($n = 5552$, 25%), followed by CNS tumours ($n = 5177$, 24%) and lymphomas ($n = 2907$, 13%). Among cancer cases, 5.1% ($n = 1117$) were born with major birth defects, compared with 2.2% ($n = 4873$) among controls. The three largest birth defect categories were congenital heart defects ($n = 1754$, 0.73%), limb defects ($n = 1017$, 0.42%) and genital defects ($n = 600$, 0.25%). Median age at primary cancer diagnosis was 8 years (interquartile range: 3 to 15 years), and 38% (8259/21 898) were diagnosed with cancer before the age of 5 years (Table 1). The overall male-to-female ratio of cancer was 1.14, and the male-to-female ratio of any birth defect was 1.30 (Supplementary Tables S2 and S3, respectively, available as Supplementary data at *IJE* online).

Risk of any and specific cancers

The OR of cancer for children with major birth defects was higher for chromosomal (OR 10, 95% CI 8.6–12) than for non-chromosomal defects (1.9, 1.8–2.1; Figure 1). ORs were adjusted for country, birth year and sex. Additional adjustment for IVF, maternal age and smoking, during the time period when these were recorded, did not change the results and were not included in the final models (Supplementary Tables S4–S6, available as Supplementary data at *IJE* online). The highest risk was observed among children with Down syndrome (12, 9.9–14), followed by genetic syndromes/microdeletions (7.0, 4.1–12) and nervous system defects (6.1, 4.7–7.9; Figure 2). Also, children with skeletal dysplasia and defects of the eye, digestive system, urinary system, limbs, heart and other defects had an increased overall cancer risk. The

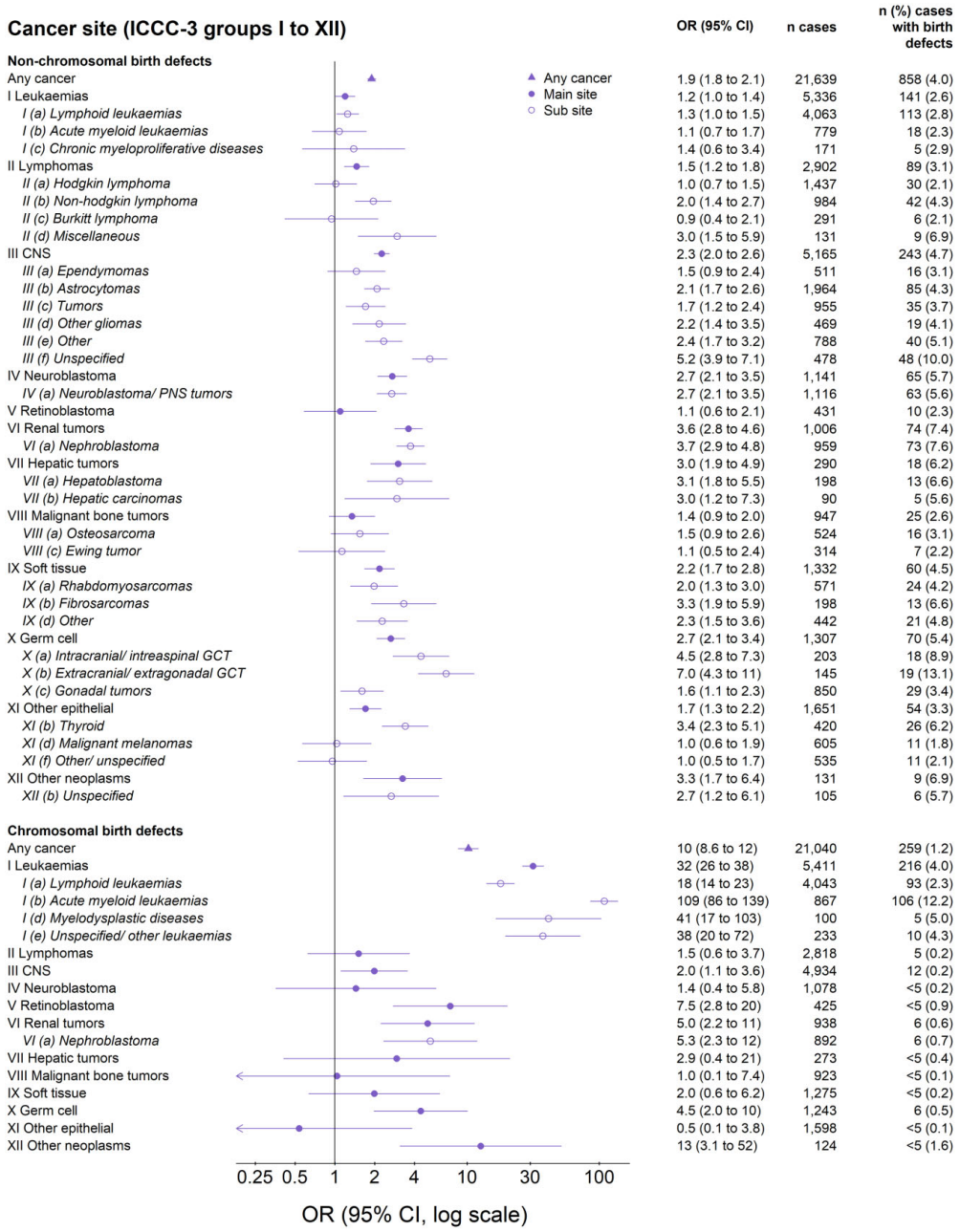

Figure 1 Risk of specific cancers in individuals with any major birth defect. Odds ratios (ORs) adjusted for matching variables (birth year and country) and sex. Adding additional confounders during the period when these were recorded did not change the results and was not included in the final models. Cancers classified into International Classification of Childhood Cancer, Third Edition (ICCC-3) groups I-XII (not included are sites with less than five co-occurring birth defects and cancers). OR, odds ratio; CI, confidence interval; CNS, central nervous system; PNS, peripheral nervous system; GCT, germ cell tumour

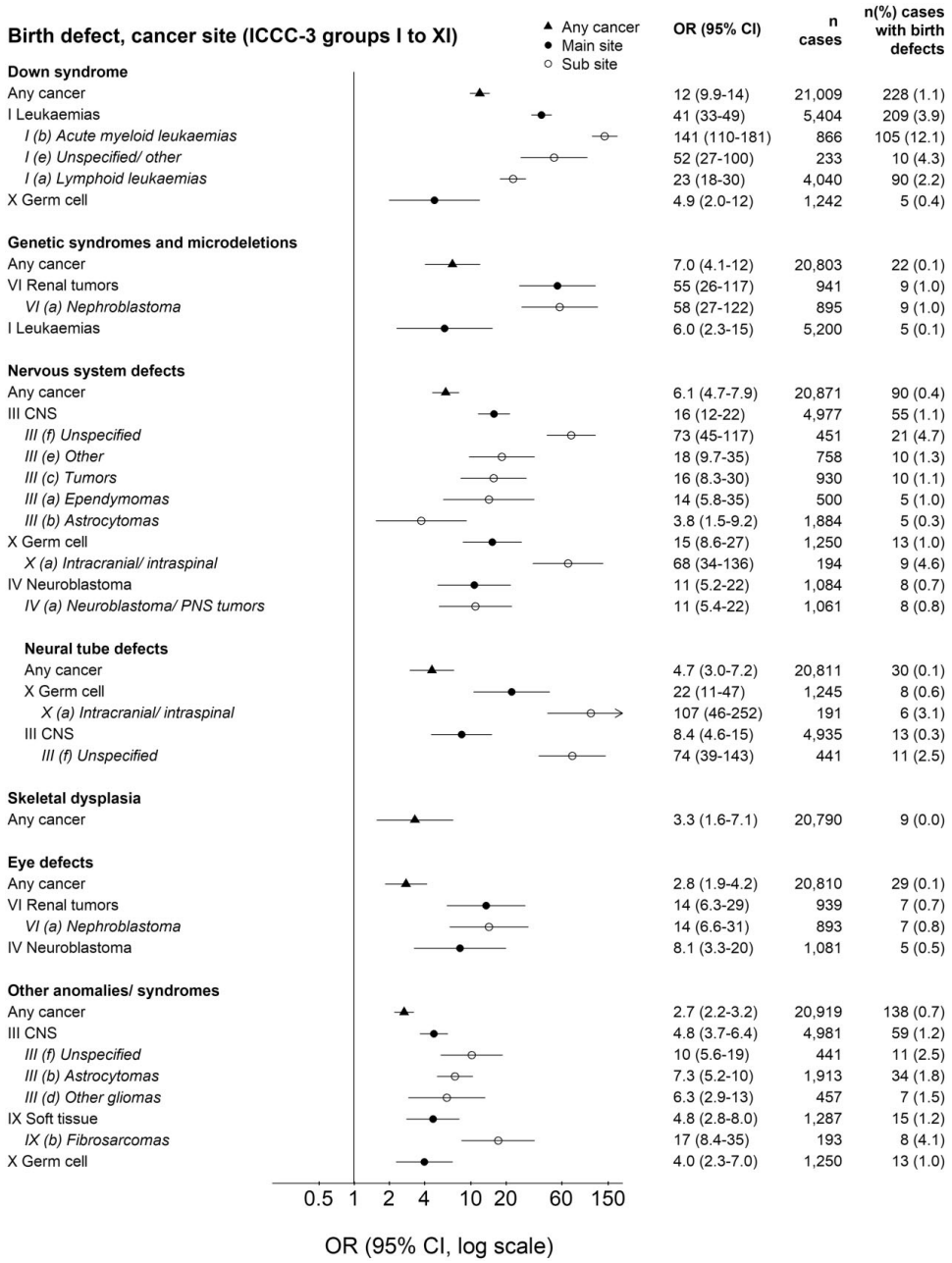

Figure 2 Associations between specific major birth defects and any or specific cancers. Odds ratios (ORs) adjusted for matching variables (birth year and country) and sex. Cancers classified into International Classification of Childhood Cancer, Third Edition (ICCC-3) groups I-XII (not included are sites with less than five co-occurring birth defects and cancers). Other anomalies/syndromes include, among others, congenital skin disorders ($n = 158$), craniosynostosis ($n = 55$), neurofibromatosis ($n = 52$), tuberous sclerosis ($n = 37$), vascular disruption anomalies ($n = 36$) and teratogenic syndromes with malformations ($n = 30$). Analyses of specific non-chromosomal birth defects included only isolated defects, see Supplementary Table S12 (available as Supplementary data at *IJE* online) for additional combinations of birth defects and childhood cancer. OR, odds ratio; CI, confidence interval; CNS, central nervous system; PNS, peripheral nervous system

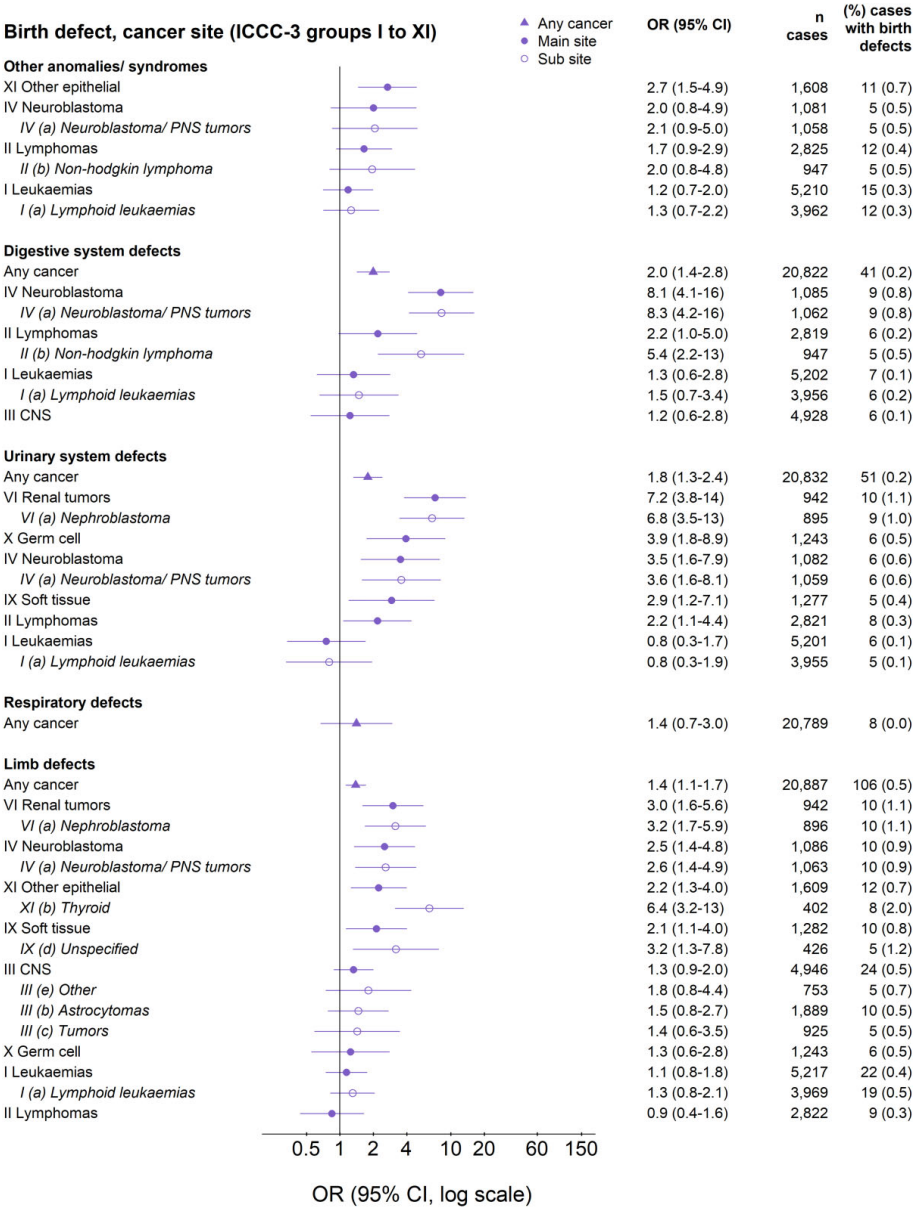

Figure 2 (Continued)

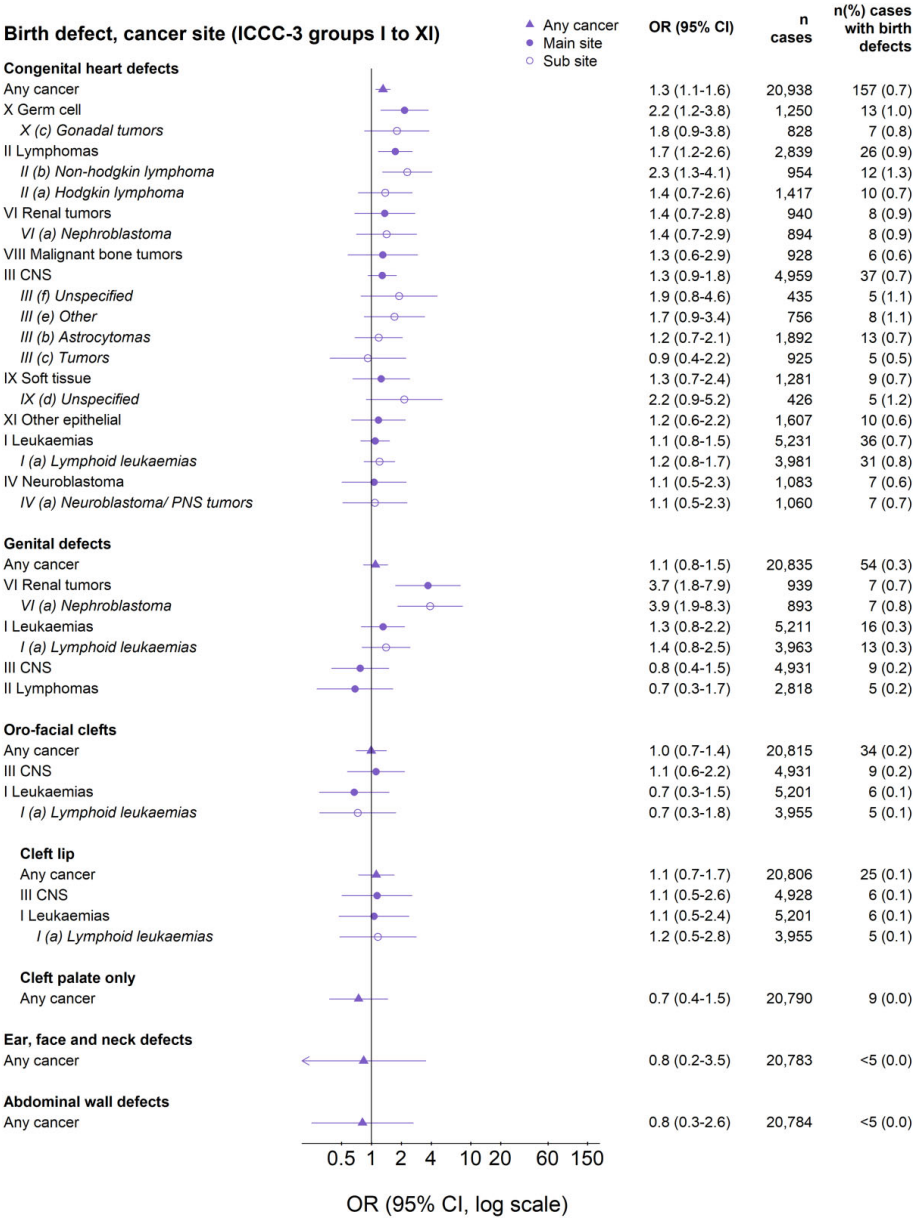

Figure 2 (Continued)

strongest associations between specific birth defects and specific cancers were observed for genetic syndromes/microdeletion and renal tumours (*55*; 26–117), Down syndrome and leukaemia (41, 33–49), and nervous system defects and central nervous system tumours (16, 12–22). Cancer risks increased by number of birth defects and were greatest for the youngest children (Supplementary Figures S2 and S3, available as Supplementary data at *IJE* online). Specifically among children with Down syndrome, the risk of acute lymphoid leukaemia (ALL) increased by age at

Table 2 Risk of any cancer among children with birth defects, stratified by sex

	Males			Females			$P_{interaction}$
Birth defects	Cases *n* (%)	Controls *n* (%)	OR (95% CI)	Cases *n* (%)	Controls *n* (%)	OR (95% CI)	
All anomalies	608 (5.1%)	2848 (2.6%)	2.1 (1.9–2.2)	509 (5.1%)	2025 (1.9%)	2.8 (2.6–3.1)	<0.001
All anomalies excluding chromosomal anomalies	486 (4.1%)	2716 (2.4%)	1.7 (1.6–1.9)	372 (3.8%)	1893 (1.8%)	2.2 (2.0–2.5)	0.001
Specific sites							
Nervous system	48 (0.4%)	70 (0.1%)	6.6 (4.5–9.5)	42 (0.4%)	83 (0.1%)	5.7 (3.9–8.2)	0.59
Neural tube defects	15 (0.1%)	28 (0%)	5.1 (2.7–9.6)	15 (0.2%)	39 (0%)	4.3 (2.4–7.8)	0.70
Eye	12 (0.1%)	57 (0.1%)	2.0 (1.1–3.7)	17 (0.2%)	51 (0%)	3.8 (2.2–6.6)	0.15
Ear, face and neck	<5 (0%)	14 (0%)	NA	<5 (0%)	11 (0%)	2.1 (0.5–9.6)	NA
Congenital heart defects	79 (0.7%)	599 (0.5%)	1.3 (1.0–1.6)	78 (0.8%)	650 (0.6%)	1.3 (1.1–1.7)	0.71
Respiratory system	<5 (0%)	25 (0%)	1.2 (0.3–3.8)	5 (0.1%)	34 (0%)	1.6 (0.6–4.2)	0.65
Orofacial clefts	24 (0.2%)	203 (0.2%)	1.1 (0.7–1.7)	10 (0.1%)	144 (0.1%)	0.8 (0.4–1.5)	0.34
Cleft palate only	<5 (0%)	53 (0%)	0.5 (0.2–1.7)	6 (0.1%)	75 (0.1%)	0.9 (0.4–2.1)	0.49
Cleft lip with/without cleft palate	21 (0.2%)	153 (0.1%)	1.3 (0.8–2.1)	<5 (0%)	69 (0.1%)	0.6 (0.2–1.8)	0.21
Digestive system	22 (0.2%)	106 (0.1%)	2.0 (1.3–3.2)	19 (0.2%)	106 (0.1%)	2.0 (1.2–3.3)	0.97
Abdominal wall defects	<5 (0%)	20 (0%)	1.0 (0.2–4.1)	<5 (0%)	18 (0%)	0.6 (0.1–4.7)	0.73
Urinary system	29 (0.3%)	195 (0.2%)	1.4 (1.0–2.1)	22 (0.2%)	95 (0.1%)	2.6 (1.6–4.2)	0.05
Genital organs	46 (0.4%)	434 (0.4%)	1.0 (0.8–1.4)	8 (0.1%)	40 (0%)	2.4 (1.1–5.0)	0.05
Limb	61 (0.5%)	482 (0.4%)	1.2 (0.9–1.6)	45 (0.5%)	290 (0.3%)	1.7 (1.3–2.4)	0.07
Skeletal dysplasia	<5 (0%)	17 (0%)	2.2 (0.8–6.7)	5 (0.1%)	11 (0%)	5.3 (1.8–15)	0.29
Genetic syndromes and microdeletions	12 (0.1%)	18 (0%)	6.4 (3.1–13)	10 (0.1%)	15 (0%)	7.5 (3.4–17)	0.79
Chromosomal	122 (1.1%)	132 (0.1%)	9.0 (7.0–12)	137 (1.4%)	132 (0.1%)	12 (9.1–15)	0.13
Down syndrome	107 (0.9%)	98 (0.1%)	11 (8.1–14)	121 (1.3%)	101 (0.1%)	13 (10.3–17)	0.21
Other anomalies/ syndromes	73 (0.6%)	306 (0.3%)	2.3 (1.8–2.9)	65 (0.7%)	220 (0.2%)	3.3 (2.5–4.4)	0.06

OR, odds ratio; CI, confidence interval.

diagnosis: OR = 12, 22 and 27 for ages <2, 2–4 and ≥5 years, respectively. Also, the risk of acute myeloid leukaemia (AML) was extremely high before the age of five, with few cases with Down syndrome above the age of five: OR = 253, 451, 256 and 7.7 for ages <1, 1, 2–4, and ≥5 years, respectively (Supplementary Table S7, available as Supplementary data at *IJE* online).

Sex differences in the association between birth defects and cancer

The association between birth defects and risk of any cancer differed for males and females (Table 2). The OR of cancer among males with any birth defect was 2.1 (1.9–2.3) compared with 2.8 (2.6–3.1) among females ($P_{interaction}$ <0.001). Results were similar when chromosomal defects were excluded [males: 1.7 (1.6–1.9) and females: 2.2 (2.0–2.5), $P_{interaction}$ = 0.001]. When examining specific birth defects in relation to any cancer, the effect sizes were mostly larger in females than males, for instance for urinary system defects [males: 1.3 (0.9–2.0) and females: 2.8 (1.8–4.5), $P_{interaction}$ = 0.053] and genital organs defects [males: 1.0 (0.8–1.4) and females: 2.4 (1.8–5.0), $P_{interaction}$ = 0.052]. Also, when investigating associations between any birth defect and specific cancers, we observed sex differences (Table 3). The effect sizes were greater among females than males for the majority of cancer sites, and interactions were observed for non-chromosomal birth defects and lymphomas [males: 1.2 (0.9–1.6) and females: 2.0 (1.4–2.7), $P_{interaction}$ = 0.04], non-chromosomal birth defects and germ cell tumours [males: 2.0 (1.4–2.7) and females: 4.8 (3.3–6.9), $P_{interaction}$ <0.001] and chromosomal birth defects and leukaemia [males: 26 (20–33) and females: 39 (30–50), $P_{interaction}$ = 0.02]. The female birth–defect cancer associations were stronger than among males at all ages (Supplementary Table S8, available as Supplementary data at *IJE* online).

Birth defects as a mediator for the association between sex and childhood cancer

Analysing sex separately as a risk factor for childhood cancer resulted in a male-to-female OR for any cancer of 1.16 (1.13–1.19), adjusted for birth year and country

Table 3 Risk of specific cancers in individuals with any major birth defect, stratified by sex

Cancer site	Males			Females			$P_{interaction}$
	No. cases	No. (%) cases with BD	OR (95% CI)	No. cases	No. (%) cases with BD	OR (95% CI)	
Non-chromosomal birth defects							
I Leukaemias, myeloproliferative and myelodysplastic diseases	2942	87 (3.0%)	1.2 (1.0–1.5)	2394	54 (2.3%)	1.2 (0.9–1.6)	0.86
II Lymphomas and reticuloendothelial neoplasms	1765	52 (2.9%)	1.2 (0.9–1.6)	1137	37 (3.3%)	2.0 (1.4–2.7)	0.04
III CNS and miscellaneous intracranial and intraspinal neoplasms	2790	137 (4.9%)	2.1 (1.7–2.4)	2375	106 (4.5%)	2.6 (2.2–3.2)	0.08
IV Neuroblastoma and other peripheral nervous cell tumours	623	36 (5.8%)	2.4 (1.7–3.4)	518	29 (5.6%)	3.2 (2.2–4.7)	0.28
V Retinoblastoma	231	5 (2.2%)	0.9 (0.4–2.2)	200	5 (2.5%)	1.4 (0.6–3.5)	0.46
VI Renal tumours	484	36 (7.4%)	3.1 (2.2–4.4)	522	38 (7.3%)	4.2 (3.0–5.9)	0.23
VII Hepatic tumours	173	10 (5.8%)	2.5 (1.3–4.7)	117	8 (6.8%)	4.1 (2.0–8.4)	0.30
VIII Malignant bone tumours	518	16 (3.1%)	1.3 (0.8–2.2)	429	9 (2.1%)	1.4 (0.7–2.6)	0.98
IX Soft-tissue and other extraosseous sarcomas	747	40 (5.4%)	2.3 (1.6–3.1)	585	20 (3.4%)	2,0 (1.3–3.2)	0.67
IX (a) Rhabdomyosarcoma	330	15 (4.5%)	1.9 (1.1–3.2)	241	9 (3.7%)	2.1 (1.1–4.2)	0.76
X Germ cell tumours, trophoblastic tumours and neoplasms of gonads	908	40 (4.4%)	2.0 (1.4–2.7)	399	30 (7.5%)	4.8 (3.3–6.9)	<0.001
XI Other malignant epithelial neoplasms and malignant melanomas	580	23 (4.0%)	1.7 (1.1–2.5)	1071	31 (2.9%)	1.8 (1.2–2.5)	0.87
XII Other and unspecified malignant neoplasms	54	<5 (7.4%)	3.1 (1.1–8.7)	77	5 (6.5%)	3.4 (1.4–8.4)	0.81
Chromosomal birth defects							
I Leukaemias, myeloproliferative and myelodysplastic diseases	2951	96 (3.3%)	26 (20–33)	2460	120 (4.9%)	39 (30–50)	0.02
III CNS and miscellaneous intracranial and intraspinal neoplasms	2661	8 (0.3%)	2.5 (1.2–5.0)	2273	<5 (0.2%)	1.4 (0.5–3.9)	0.36
VI Renal tumours (a.1 nephroblastoma)	419	<5 (0.2%)	1.9 (0.3–14)	456	5 (1.1%)	8.7 (3.5–21)	0.16
X Germ cell tumours, trophoblastic tumours and neoplasms of gonads	874	6 (0.7%)	6.8 (3.0–16)	369	<5 (0%)	NA	NA

ORs are adjusted for matching variables (birth-year and country). Not included are cancers classified in ICCC-3 groups and subsites with less than five co-occurring birth defects and cancers (for both males and females).

BD, birth defect; CNS, central nervous system.

(Supplementary Table S2). Males had an increased risk of cancer for most cancer sites, lymphomas and germ cell tumours in particular, whereas females had an increased risk of other malignant epithelial neoplasms and malignant melanomas. Birth defects appeared to mediate very little of the overall association between sex and childhood cancer risk (proportion mediated: 4.8%, P_{NIE} <0.001; Table 4). Specifically, we observed evidence of mediation for the risk of neuroblastoma and other peripheral nervous system tumours (6.5%, P_{NIE} = 0.001), leukaemia (6.0%, P_{NIE} <0.001), CNS tumours (5.7%, P_{NIE} <0.001), soft-tissue sarcomas (4.2%, P_{NIE} = 0.001), and germ cell tumours (1.3%, P_{NIE} = 0.001). Among children diagnosed with cancer before the age of five, the proportion mediated by birth defects was larger (11%, P_{NIE} <0.001). Mediation was observed for CNS tumours (8.2%, P_{NIE} <0.001) and soft-tissue sarcomas (4.1%, P_{NIE} = 0.001). For children diagnosed with cancer before the age of one, 28% (P_{NIE} <0.001) of the male sex effect was mediated by birth defects. Separate analyses excluding chromosomal birth defects resulted in lower percentages mediated for overall cancer among children of all ages (Supplementary Table S9, available as Supplementary data at *IJE* online). Sensitivity analyses where we adjusted for potential mediator–outcome confounders (IVF and smoking) did not alter the results (Supplementary Table S10, available as Supplementary data at *IJE* online).

Sensitivity analyses

When leaving out one country at a time, we observed small differences from the results displayed in Figures 1 and 2

Table 4 Mediation analyses of the effect of birth defects on the association between sex (males versus females) and childhood cancer, overall and by cancer site[a]

Cancer site	Controlled direct effect[b] (CDE) OR (95% CI)	Natural indirect effect[c] (NIE) OR (95% CI)	Natural direct effect[d] (NDE) OR (95% CI)	Marginal total effect (MTE) OR (95% CI)	Percentage (%) mediated[e]
Total study population (0–19 years)					
Any cancer	1.17 (1.14–1.20)	1.007 (1.005–1.008)	1.16 (1.12–1.19)	1.16 (1.13–1.20)	4.80
I Leukaemias, myeloproliferative and myelodysplastic diseases	1.19 (1.12–1.25)	1.009 (1.006–1.012)	1.16 (1.10–1.22)	1.17 (1.11–1.24)	5.95
(a) Lymphoid leukaemias	1.19 (1.12–1.27)	1.005 (1.003–1.008)	1.18 (1.11–1.25)	1.18 (1.11–1.26)	3.42
Other leukaemias	1.33 (1.11–1.60)	1.008 (1.001–1.015)	1.32 (1.11–1.57)	1.33 (1.11–1.58)	3.16
II Lymphomas and reticuloendothelial neoplasms	1.53 (1.42–1.66)	1.002 (1.000–1.004)	1.52 (1.41–1.63)	1.52 (1.41–1.64)	NA
(b) Non-Hodgkin lymphomas	1.95 (1.71–2.24)	1.004 (1.000–1.009)	1.92 (1.68–2.19)	1.93 (1.69–2.20)	0.92
Other lymphomas	2.92 (2.37–3.61)	1.003 (0.998–1.009)	2.88 (2.34–3.54)	2.89 (2.35–3.55)	NA
III CNS and miscellaneous intracranial and intraspinal neoplasms	1.14 (1.08–1.21)	1.007 (1.004–1.010)	1.13 (1.08–1.21)	1.14 (1.08–1.20)	5.69
(a.1) Ependymomas	1.30 (1.06–1.59)	1.000 (0.995–1.006)	1.29 (1.06–1.58)	1.29 (1.06–1.58)	NA
(c.1) Medulloblastomas	1.70 (1.44–2.00)	1.000 (0.996–1.004)	1.64 (1.40–1.93)	1.64 (1.40–1.93)	NA
(c.2) Primitive neuroectodermal tumour	1.36 (1.06–1.74)	1.003 (0.995–1.011)	1.31 (1.03–1.68)	1.32 (1.03–1.68)	NA
IV Neuroblastoma and other peripheral nervous cell tumours	1.16 (1.03–1.31)	1.009 (1.004–1.014)	1.15 (1.02–1.29)	1.16 (1.03–1.30)	6.52
(a) Neuroblastoma	1.14 (1.01–1.29)	1.009 (1.004–1.014)	1.13 (1.01–1.27)	1.14 (1.01–1.29)	7.08
VII Hepatic tumours	1.44 (1.13–1.84)	1.009 (0.999–1.018)	1.40 (1.11–1.77)	1.41 (1.12–1.78)	2.94
(a.1) Hepatoblastoma	1.69 (1.25–2.29)	1.006 (0.996–1.017)	1.59 (1.19–2.13)	1.60 (1.19–2.14)	NA
VIII Malignant bone tumours	1.16 (1.02–1.32)	1.002 (0.999–1.006)	1.16 (1.02–1.32)	1.17 (1.03–1.33)	NA
(a) Osteosarcoma	1.25 (1.05–1.49)	1.002 (0.996–1.007)	1.23 (1.04–1.47)	1.24 (1.04–1.47)	NA
IX Soft-tissue and other extraosseous sarcomas	1.22 (1.09–1.36)	1.008 (1.003–1.013)	1.22 (1.10–1.37)	1.23 (1.11–1.38)	4.18
(a) Rhabdomyosarcoma	1.31 (1.11–1.56)	1.005 (0.999–1.011)	1.31 (1.11–1.55)	1.32 (1.12–1.56)	NA
Other soft tissue	1.16 (1.00–1.34)	1.010 (1.003–1.017)	1.16 (1.01–1.34)	1.18 (1.02–1.36)	6.68
X Germ cell tumours, trophoblastic tumours and neoplasms of gonads	2.30 (2.04–2.60)	1.007 (1.003–1.012)	2.21 (1.96–2.48)	2.22 (1.97–2.50)	1.33
(a) Intracranial germ cell tumours	2.09 (1.53–2.84)	1.015 (1.002–1.029)	1.95 (1.45–2.61)	1.98 (1.48–2.65)	3.08
(b) Extracranial germ cell tumours	0.68 (0.48–0.97)	1.025 (1.002–1.048)	0.64 (0.46–0.90)	0.66 (0.47–0.92)	NA
(c), (d), and (e) Gonadal germ cell tumours	2.86 (2.47–3.32)	1.004 (1.000–1.009)	2.83 (2.45–3.28)	2.85 (2.46–3.29)	0.67
XI Other malignant epithelial neoplasms and malignant melanomas	0.53 (0.48–0.59)	1.004 (1.000–1.009)	0.53 (0.48–0.59)	0.53 (0.48–0.59)	NA
XII Other and unspecified malignant neoplasms	0.68 (0.47–0.97)	1.016 (0.996–1.036)	0.67 (0.48–0.95)	0.68 (0.48–0.97)	NA

(Continued)

Table 4 Continued

Cancer site	Controlled direct effect[b] (CDE) OR (95% CI)	Natural indirect effect[c] (NIE) OR (95% CI)	Natural direct effect[d] (NDE) OR (95% CI)	Marginal total effect (MTE) OR (95% CI)	Percentage (%) mediated[e]
Children younger than 5 years at time of diagnosis					
Any cancer	1.13 (1.08–1.18)	1.011 (1.008–1.014)	1.10 (1.05–1.15)	1.11 (1.06–1.16)	10.69
II Lymphomas and reticuloendothelial neoplasms	2.28 (1.82–2.85)	1.006 (0.999–1.013)	2.27 (1.82–2.83)	2.28 (1.83–2.84)	NA
III CNS and miscellaneous intracranial and intraspinal neoplasms	1.16 (1.05–1.28)	1.013 (1.008–1.018)	1.16 (1.05–1.27)	1.17 (1.07–1.29)	8.21
VII Hepatic tumours	1.78 (1.31–2.41)	1.004 (0.995–1.013)	1.64 (1.22–2.19)	1.64 (1.23–2.20)	NA
IX Soft-tissue and other extraosseous sarcomas	1.29 (1.07–1.56)	1.009 (1.001–1.017)	1.27 (1.06–1.53)	1.28 (1.07–1.54)	4.14
X Germ cell tumours, trophoblastic tumours and neoplasms of gonads	1.58 (1.22–2.04)	1.007 (0.998–1.017)	1.38 (1.09–1.75)	1.39 (1.09–1.77)	NA
XII Other and unspecified malignant neoplasms	0.56 (0.35–0.91)	1.025 (0.995–1.057)	0.57 (0.36–0.89)	0.58 (0.37–0.91)	NA
Children younger than 1 year at time of diagnosis					
Any cancer	1.10 (0.99–1.21)	1.025 (1.018–1.033)	1.06 (0.97–1.17)	1.09 (0.99–1.20)	28.15
I Leukaemias, myeloproliferative and myelodysplastic diseases	0.67 (0.53–0.86)	1.043 (1.023–1.063)	0.70 (0.56–0.88)	0.73 (0.59–0.91)	NA
IV Neuroblastoma and other peripheral nervous cell tumours	1.40 (1.14–1.73)	1.020 (1.009–1.031)	1.36 (1.12–1.66)	1.39 (1.14–1.70)	6.85
XII Other and unspecified malignant neoplasms	0.45 (0.23-0.91)	1.044 (0.990-1.102)	0.47 (0.25-0.88)	0.49 (0.26-0.91)	NA

OR, odds ratio; CI, confidence interval; CNS, central nervous system.

[a]A causal interpretation of the mediation analyses assumes no unmeasured confounding with respect to (i) exposure–outcome, ii) mediator–outcome or (iii) exposure–mediator and (4) no mediator–outcome confounder affected by the exposure. The assumption of rare outcome (childhood cancer) was met for the use of logistic regression models. To address assumption (2), we adjusted for the following potential mediator–outcome confounders: birth-year, country and maternal age, and performed sensitivity analyses where we included IVF (in vitro fertilization) and maternal smoking as confounders (did not change the results, see Supplementary Table S10, available as Supplementary data at *IJE* online). Since sex was the exposure of interest in these analyses (with birth defects as a mediator), both assumptions (i) and (iii) regarding unmeasured confounding are plausible. Assumption (iv) is likely also fulfilled based on current knowledge. Results shown only for the cancer types for which there was a sex effect, for full table see Supplementary Table S11 (available as Supplementary data at *IJE* online).

[b]The CDE is the effect of sex (with females as reference) not mediated through birth defects (estimated for no birth defect).

[c]The NIE captures the portion of the sex effect explained by birth defect mediation alone.

[d]The NDE compares cancer risk in males with that in females if birth defect status for males was set to what would have been observed had they been females.

[e]Percentage mediated not calculated when the NDE and NIE were in opposite directions or when the CI for NIE contained the null.

and Tables 2–4. Leaving out Finland resulted in slightly lower ORs, as expected due to the younger population. Additional sensitivity analyses including only children born 1990 onwards yielded similar results, with slightly higher ORs due to the younger population (see Supplementary sensitivity analyses—Description of results, available as Supplementary data at *IJE* online).

Discussion

This large Nordic population-based study showed an increased risk of cancer among children with birth defects, with a greater risk among children with chromosomal compared with non-chromosomal birth defects. Among children with non-chromosomal birth defects, the strongest association was observed between neural tube defects and intracranial and intraspinal germ cell tumours. For chromosomal birth defects, the strongest association was seen between Down syndrome and AML. The birth defect–cancer associations were generally stronger among females than males with sex–birth defect interactions for any birth defect and overall cancer, non-chromosomal birth defects and germ cell tumours, non-chromosomal birth defects and lymphomas, and chromosomal birth defects and leukaemia. Sex was not a strong risk factor for childhood cancer, and mediation analysis suggested that only a relatively small percentage of the overall association between sex and childhood cancer was mediated through birth defects, although larger among the youngest children.

The major strengths of this study are the large number of cancer cases, classified according to ICCC-3, from population-based national registries with accurate and nearly complete information on cancer cases.[14] Also, due to the national identification numbers, all individuals in the Nordic countries can be followed from birth till death, and there is little emigration. Whereas a limitation of the study is the lack of information on other possible confounders (e.g. parental income and education), there are no established risk factors associated strongly enough with both birth defects and cancer to explain our results. For an unmeasured confounder to explain the observed OR of 1.9 for any non-chromosomal birth defect and childhood cancer association, conditioned on the measured covariates, it would have to be associated with a 3-fold increased risk of both birth defects and childhood cancer (E-value for estimate E = 3.2, and E = 3.0 for lower confidence limit). In addition, multiple sensitivity analyses yielded stable results, supporting the main conclusions of the paper. There was limited statistical precision for specific combinations of birth defects and cancers, especially for analyses stratified by sex, and spurious associations from multiple comparisons could have resulted. Birth defect ascertainment has changed over time and among countries,[3] but this would likely be random regarding a subsequent cancer diagnosis. Also, survival from birth defects has improved over time, and it is possible that this has been differential by sex. However, sensitivity analyses including only children born from 1990 indicate that these trends did not affect the results significantly. For the mediation analyses, non-differential misclassification of the mediator (birth defect), if present, would lead to underestimation of the NIE and overestimation of the NDE; hence the proportion mediated would be underestimated.

Our findings are consistent with previous studies that were smaller or had less complete data, whereas we included all cancer cases in the Nordic countries.[4,5] Further, many of the observed specific birth defect–cancer associations agree with previous results, such as the risk of AML among children with Down syndrome and the risk of CNS tumours among children with nervous system defects. Also, the increasing risk by the numbers of defects and by younger age agrees with the literature.[4,5]

The biology underlying the association between birth defects and the risk of cancer later in life is poorly understood, but both genetic and environmental (epigenetic) factors are thought to be involved. One notion is that genetic abnormalities impairing normal development may predispose to both birth defects and malignancy. Large genome-wide association studies have, for instance, identified common genetic risk loci for orofacial clefts and co-occurring cancers.[28] How epigenetics (DNA methylation) is involved in the aetiology of birth defects has been shown in individuals with orofacial clefts, displaying epigenome-wide hypomethylation compared with controls.[29] In gene set enrichment analysis of oral cleft-associated differentially methylated regions, there was an over-representation of genes involved in the development of the palate[29] which also are involved in tumour development, thus underscoring the association between birth defects and risk of cancer. Although we did not observe an association between orofacial clefts and cancer in our study, this has been reported before.[3–5]

Few studies have examined sex-specific differences in the association between birth defects and childhood cancer. Instead, they adjusted for sex. Yang *et al.* (1995)[12] reported a 3-fold increase in the risk of rhabdomyosarcoma for males with birth defects but no increased risk for females, in contrast to our findings based on a larger number of cases (males: OR = 1.9, 1.1–3.2; females: OR = 2.1, 1.1–4.2). Johnson *et al.* (2009)[11] reported an association between birth defects (including minor birth defects) and germ cell tumours for males (OR = 2.5, 95% CI 1.4–4.9) but not for females (1.1, 0.7–1.8). Based on a larger number of cases, we observed a similar risk estimate for germ

cell tumours among males (2.0, 1.4–2.7) but an even higher risk among females (4.8, 3.3–6.9).

Different mechanisms may explain the male excess in both birth defects and childhood cancer, including genetic/chromosomal, environmental/epigenetic, hormonal and other biological factors. Studies have suggested aetiological heterogeneity by sex for childhood cancers for gestational age, maternal education, race/ethnicity and paternal age.[30] Furthermore, sex differences in the immune system, hormonal milieu and dosage of the X chromosome may also play a role.[30–34] As for childhood cancer, several studies have shown a male excess in birth defects, both overall and for most isolated birth defects with exceptions such as isolated cleft palate, choanal atresia and most neural tube defects (NTDs).[8,35–38] Although the evidence for explaining the male-to-female sex ratio is scarce, several factors have been proposed. Interaction with sex has, for instance, been reported for the association between growth restriction and NTD, paternal age and cleft lip with or without cleft palate, and multigravidity and postaxial polydactyly as well as spina bifida without hydrocephalus.[36] A higher prenatal mortality in male fetuses with birth defects may also influence the observed sex ratio at birth.

In contrast to the male excess in both birth defects and childhood cancer in our study, the birth defect–cancer association was in general stronger in females. The reason for this is unclear but likely involves a multitude of interactions between sex-specific factors and gene networks both pre- and postnatally.[39]

Marcotte *et al.* (2020)[13] recently proposed that birth defects are a strong mediator for the association between sex and childhood cancer and noted large variations in the proportion mediated across cancer types and age at diagnosis. On the contrary, our data suggest that the proportions mediated by birth defects are smaller. For instance, whereas they estimated that 38% of the risk of any childhood cancer (0–18 years) was mediated by birth defects, we estimated 5% (0–19 years). Among children below 1 year of age they estimated 85% and we estimated 28%. Like Marcotte *et al.*,[13] we observed an NIE for extracranial germ cell tumours and an inverse association for the NDE, also for renal tumours and leukaemia among children diagnosed before the age of one, indicating that the observed sex effect would have been stronger in the absence of an effect of birth defects. The greater proportion of children with birth defects in the study of Marcotte *et al.*[13] (14.1% among cancer cases and 5.3% among births without cancer) than in our study (5.1% among cancer cases and 2.2% among controls) may partly explain the different findings. Only 70% of their cancer cases were successfully linked to birth certificates and included in the study population, whereas 95% of the children with birth defects were included, which could have introduced selection bias. The availability of information on potential confounders varied between the studies, but this is unlikely to explain the differences in results.

Conclusion

Overall, our study showed an increased cancer risk among individuals with birth defects, and sex differences for some birth defect–cancer associations, with stronger associations among females. Further, we found that only a small proportion of the association between sex and childhood cancer was explained by birth defects, although higher among the youngest, suggesting that most of the association between sex and childhood cancer risk operates through other pathways. Our findings contribute new knowledge about sex differences in the association between birth defects and childhood cancer and suggest further research into the underlying mechanisms.

Ethics approval

The study was approved by ethics committees in Norway (2015/317/REK vest) and Stockholm, Sweden (2015/1642–31/2), and by the Data Protection Agency in Denmark (2015–57-0002). Permission to use health register data in Finland was granted by the Finnish Institute of Health and Welfare (THL/68/5.05/2014 and THL/909/5.05/2015) after consultation with the country's data protection authority.

Data availability

The datasets analysed during the current study are not freely available due to national regulations, but similar data can be obtained from the register authorities.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

T.B., A.En. and K.K. designed and planned the study. T.B., I.G., M.G., H.T.S. obtained access to data and took part in the planning of the study. D.S.D., K.K., A.En. and T.B. had access to all data. D.S.D. performed the data analyses and wrote the first draft of the manuscript with support from T.B., A.En. and K.K. All authors were involved in interpreting the results, revising the manuscript and approving the final version.

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Conflict of interest

None declared.

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Supplemental content

Supplementary Table S1. Description of the registries.

Registry	Country	Description	Coding	Supporting references
The Medical Birth Registries	All countries	Contains information on all births in Denmark, Finland, Norway, and Sweden since 1973, 1987, 1967, and 1973, respectively.	Denmark: 1973-1993: ICD-8, 1994 onwards: ICD-10. Finland:1987-1995: ICD-9, 1996 onwards: ICD-10. Norway: 1967-1998: ICD-8 (with some internally generated codes), 1999 onwards: ICD-10. Sweden: 1973-1986: the Swedish versions of ICD-8, 1987-1996: ICD-9, 1997 onwards: ICD-10.	Langhoff-Roos J, Krebs L, Klungsoyr K, *et al*. The Nordic medical birth registers--a potential goldmine for clinical research. Acta obstetricia et gynecologica Scandinavica. 2014;93(2):132-7.
The National Patient Registries	Denmark and Sweden	Administrative nationwide registries on inpatient care since 1978 in Denmark and 1987 in Sweden.	Same as in the Birth Registries.	Schmidt M, Schmidt SA, Sandegaard JL, *et al*. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol 2015;7:449-90. Ludvigsson JF, Andersson E, Ekbom A, *et al*. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:450.
The Register of Congenital Malformations	Finland	Information on birthdefects on live and stillborn. since 1963.	1986 onwards: ICD-9 Atlanta modification, retrospective inclusion of ICD-10 codes from 1996.	Ritvanen A. Epämuodostumat 1993-2011 – Congenital anomalies 1993-2011. National Institute for Health and Welfare in Finland, 2014.
The Cancer Registries	All countries	Covers the entire populations in Denmark, Finland, Norway, and Sweden since 1943, 1953, 1953, and 1958, respectively.	All countries currently provides ICD-O-3 codes. Older cancer cases coded with older ICD versions, see Pukkala *et al*. (2018).	Pukkala E, Engholm G, Hojsgaard Schmidt LK *et al*. Nordic Cancer Registries – an overview of their procedures and data comparability. Acta oncologica (Stockholm, Sweden). 2018;57(4):440-55.
The National Population Registries.	All countries	Administrative registry of the whole population in Denmark, Finland, Norway, and Sweden since 1968, 1971, 1964, and 1968, respectively. Contains information on deaths and emigration.	NA	Laugesen K, Ludvigsson JF, Schmidt M, *et al*. Nordic Health Registry-Based Research: A Review of Health Care Systems and Key Registries. Clinical epidemiology 2021; 13: 533-54.

Supplementary Table S2. Male-to-female sex ratios for the main cancer groups in the total study population, and associations between male sex and any or specific cancers.

Cancer site[a]	N cases	M:F sex ratio	OR	95% CI
Any cancer	21,898	1.14	1.16	(1.13–1.19)
I Leukaemia, myeloproliferative and myelodysplastic diseases	5552	1.17	1.16	(1.10–1.23)
(a) Lymphoid leukaemia	4156	1.18	1.18	(1.11–1.25)
(a.1) Precursor cell leukaemia	4089	1.17	1.17	(1.10–1.24)
(a.2) Mature B-cell leukaemia	45	2.14	2.13	(1.13–4.01)
(a.3) Mature T-cell and NK cell leukaemia	8	6.78	6.57	(0.81–53.4)
(a.4) Lymphoid leukaemia, NOS	14	1.29	1.30	(0.45–3.74)
(b) Acute myeloid leukaemia	885	1.03	1.03	(0.90–1.17)
(c) Chronic myeloproliferative diseases	173	1.18	1.19	(0.88–1.60)
(d) Myelodysplastic syndrome and other myeloproliferative diseases	103	1.30	1.26	(0.85–1.87)
(e) Unspecified and other specified leukaemia	235	1.45	1.49	(1.15–1.93)
II Lymphomas and reticuloendothelial neoplasms	2907	1.49	1.51	(1.41–1.63)
(a) Hodgkin lymphomas	1438	1.06	1.08	(0.97–1.20)
(b) Non-Hodgkin lymphomas (except Burkitt lymphoma)	987	1.89	1.92	(1.68–2.19)
(b.1) Precursor cell lymphomas	186	2.43	2.39	(1.74–3.29)
(b.2) Mature B-cell lymphomas (except Burkitt lymphoma)	280	1.88	1.92	(1.50–2.45)
(b.3) Mature T-cell and NK-cell lymphomas	177	1.59	1.57	(1.16–2.13)
(b.4) Non-Hodgkin lymphomas, NOS	344	1.83	1.93	(1.54–2.41)
(c) Burkitt lymphoma	292	4.36	4.32	(3.21–5.82)
(d) Miscellaneous lymphoreticular neoplasms	131	1.79	1.72	(1.20–2.46)
(e) Unspecified lymphomas	59	1.75	1.73	(1.01–2.95)
III CNS and miscellaneous intracranial and intraspinal neoplasms	5177	1.14	1.14	(1.08–1.20)
(a) Ependymomas and choroid plexus tumour	514	1.36	1.35	(1.13–1.61)
(a.1) Ependymomas	397	1.29	1.29	(1.06–1.58)
(a.2) Choroid plexus tumour	117	1.61	1.58	(1.08–2.29)
(b) Astrocytoma	1967	1.04	1.04	(0.95–1.14)
(c) Intracranial and intraspinal embryonal tumours	958	1.56	1.55	(1.36–1.76)
(c.1) Medulloblastomas	637	1.64	1.64	(1.40–1.93)
(c.2) Primitive neuroectodermal tumour (PNET)	266	1.33	1.31	(1.03–1.68)
(c.3) Medulloepithelioma	12	0.97	0.94	(0.30–2.92)
(c.4) Atypical teratoid/rhabdoid tumour	43	2.23	2.14	(1.12–4.10)
(d) Other gliomas	469	0.93	0.95	(0.79–1.14)
(d.1) Oligodendrogliomas	125	1.08	1.08	(0.76–1.53)
(d.2) Mixed and unspecified gliomas	326	0.84	0.86	(0.69–1.06)
(d.3) Neuroepithelial glial tumours of uncertain origin	18	2.52	2.63	(0.94–7.38)
(e) Other specified intracranial and intraspinal neoplasms	789	1.07	1.07	(0.93–1.23)
(e.1) Pituitary adenomas and carcinomas	51	0.37	0.36	(0.19–0.66)
(e.2) Tumours of the sellar region (craniopharyngiomas)	232	0.97	0.96	(0.74–1.25)
(e.3) Pineal parenchymal tumours	57	0.76	0.76	(0.45–1.28)
(e.4) Neuronal and mixed neuronal-glial tumours	334	1.43	1.44	(1.15–1.79)
(e.5) Meningiomas	115	1.06	1.07	(0.74–1.54)
(f) Unspecified intracranial and intraspinal neoplasms	480	1.01	1.00	(0.83–1.19)
IV Neuroblastoma and other peripheral nervous cell tumours	1143	1.16	1.15	(1.03–1.30)
(a) Neuroblastoma and ganglioneuroblastoma	1118	1.15	1.14	(1.01–1.28)
(b) Other peripheral nervous cell tumours	25	2.06	2.07	(0.89–4.80)

Cancer site[a]	N cases	M:F sex ratio	OR	95% CI
V Retinoblastoma	435	1.13	1.12	(0.93–1.35)
VI Renal tumours	1012	0.89	0.88	(0.78–1.00)
(a) Nephroblastoma and other non-epithelial renal tumours	965	0.88	0.87	(0.77–0.99)
(a.1) Nephroblastoma	947	0.89	0.88	(0.78–1.00)
(a.2) Rhabdoid renal tumour	7	0.39	0.37	(0.07–1.91)
(a.3) Kidney sarcomas	11	0.81	0.79	(0.24–2.58)
(b) Renal carcinomas	38	1.48	1.51	(0.79–2.89)
(c) Unspecified malignant renal tumours	9	0.28	0.28	(0.06–1.33)
VII Hepatic tumours	291	1.42	1.40	(1.11–1.77)
(a) Hepatoblastoma and mesenchymal tumours of liver	199	1.53	1.50	(1.13–2.00)
(a.1) Hepatoblastoma	193	1.63	1.59	(1.19–2.13)
(a.3) Embryonal sarcoma of liver	5	0.24	0.23	(0.03–2.04)
(b) Hepatic carcinomas	90	1.16	1.17	(0.77–1.78)
VIII Malignant bone tumours	948	1.17	1.16	(1.02–1.32)
(a) Osteosarcomas	524	1.24	1.24	(1.04–1.47)
(b) Chondrosarcomas	48	0.97	0.97	(0.55–1.71)
(c) Ewing tumour and related sarcomas of bone	314	1.16	1.14	(0.92–1.43)
(c.1) Ewing tumour and Askin tumour of bone	310	1.16	1.15	(0.92–1.43)
(d) Other specified malignant bone tumours	40	0.79	0.79	(0.42–1.47)
(d.2) Malignant chordomas	25	0.89	0.88	(0.40–1.94)
(d.4) Miscellaneous malignant bone tumours	9	0.77	0.79	(0.21–2.94)
(e) Unspecified malignant bone tumours	22	1.16	1.16	(0.50–2.68)
IX Soft tissue and other extraosseous sarcomas	1335	1.23	1.23	(1.11–1.38)
(a) Rhabdomyosarcomas	571	1.32	1.32	(1.11–1.56)
(b) Fibrosarcoma, peripheral nerve sheath tumours, and other fibrous neoplasms	199	1.10	1.11	(0.84–1.46)
(b.1) Fibroblastic and myofibroblastic tumours	111	1.32	1.32	(0.91–1.93)
(b.2) Nerve sheath tumours	86	0.88	0.89	(0.58–1.35)
(d) Other specified soft tissue sarcomas	444	1.19	1.20	(1.00–1.45)
(d.1) Ewing tumour and Askin tumour of soft tissue	69	1.26	1.24	(0.77–2.00)
(d.2) Peripheral neuroectodermal tumour (pPNET) of soft tissue	34	1.38	1.45	(0.73–2.88)
(d.3) Extrarenal extrahepatic rhabdoid tumour	7	0.73	0.69	(0.15–3.08)
(d.4) Liposarcomas	21	0.39	0.38	(0.15–0.99)
(d.5) Fibrohistiocytic tumours	101	1.20	1.21	(0.82–1.79)
(d.6) Leiomyosarcomas	20	1.80	1.77	(0.71–4.43)
(d.7) Synovial sarcomas	124	1.30	1.30	(0.91–1.85)
(d.8) Blood vessel tumours	14	0.39	0.39	(0.12–1.24)
(d.9) Osseous and chondromatous neoplasms of soft tissue	13	1.13	1.14	(0.38–3.39)
(d.10) Alveolar soft parts sarcoma	7	0.16	0.16	(0.02–1.35)
(d.11) Miscellaneous soft tissue sarcomas	34	2.69	3.07	(1.43–6.59)
(e) Unspecified soft tissue sarcomas	119	1.21	1.20	(0.83–1.72)
X Germ cell tumours. trophoblastic tumours and neoplasms of gonads	1313	2.21	2.22	(1.98–2.50)
(a) Intracranial and intraspinal germ cell tumours	204	1.98	1.98	(1.48–2.65)
(a.1) Intracranial and intraspinal germinomas	116	2.33	2.35	(1.57–3.50)
(a.2) Intracranial and intraspinal teratomas	64	1.33	1.31	(0.80–2.16)
(a.3) Intracranial and intraspinal embryonal carcinomas	5	3.87	3.84	(0.43–34.3)
(a.4) Intracranial and intraspinal yolk sac tumour	6	0.97	0.95	(0.19–4.70)

Cancer site[a]	N cases	M:F sex ratio	OR	95% CI
(a.6) Intracranial and intraspinal tumours of mixed forms	12	4.84	4.87	(1.07–22.0)
(b) Malignant extracranial and extragonadal germ cell tumours	146	0.66	0.65	(0.47–0.91)
(b.2) Malignant teratomas of extracranial and extragonadal sites	95	0.49	0.48	(0.32–0.74)
(b.3) Embryonal carcinomas of extracranial and extragonadal sites	9	1.21	1.23	(0.33–4.58)
(b.4) Yolk sac tumour of extracranial and extragonadal sites	27	0.67	0.67	(0.31–1.44)
(c) Malignant gonadal germ cell tumours	854	3.79	3.82	(3.23–4.52)
(c.1) Malignant gonadal germinomas	117	1.21	1.20	(0.84–1.73)
(c.2) Malignant gonadal teratomas	254	2.44	2.44	(1.86–3.21)
(c.3) Gonadal embryonal carcinomas	165	52.21	51.90	(16.6–163)
(c.4) Gonadal yolk sac tumour	123	2.34	2.35	(1.59–3.47)
(c.5) Gonadal choriocarcinoma	30	8.71	8.64	(2.62–28.5)
(c.6) Malignant gonadal tumours of mixed forms	165	21.82	22.00	(10.3–46.9)
(d) Gonadal carcinomas	49	0.04	0.04	(0.01–0.17)
(e) Other and unspecified malignant gonadal tumours	60	1.36	1.34	(0.80–2.24)
XI Other malignant epithelial neoplasms and malignant melanomas	1652	0.53	0.53	(0.48–0.59)
(a) Adrenocortical carcinomas	29	0.68	0.68	(0.32–1.42)
(b) Thyroid carcinomas	420	0.30	0.30	(0.24–0.38)
(c) Nasopharyngeal carcinomas	34	2.02	1.99	(0.97–4.08)
(d) Malignant melanomas	605	0.53	0.53	(0.45–0.63)
(e) Skin carcinomas	28	0.97	0.97	(0.46–2.04)
(f) Other and unspecified carcinomas	536	0.67	0.69	(0.58–0.82)
(f.1) Carcinomas of salivary glands	106	0.35	0.35	(0.23–0.54)
(f.2) Carcinomas of colon and rectum	74	0.66	0.75	(0.47–1.19)
(f.3) Carcinomas of appendix	161	0.61	0.63	(0.46–0.86)
(f.4) Carcinomas of lung	48	1.61	1.62	(0.90–2.9)
(f.6) Carcinomas of breast	10	0.11	0.11	(0.01–0.85)
(f.8) Carcinomas of bladder	7	2.42	3.06	(0.59–15.9)
(f.10) Carcinomas of other specified sites	100	1.14	1.15	(0.77–1.70)
(f.11) Carcinomas of unspecified site	19	0.56	0.56	(0.22–1.43)
XII Other and unspecified malignant neoplasms	133	0.68	0.68	(0.48–0.96)
(a) Other specified malignant tumours	26	0.43	0.43	(0.19–0.99)
(a.3) Pulmonary blastoma and pleuropulmonary blastoma	9	0.77	0.74	(0.20–2.75)
(a.4) Other complex mixed and stromal neoplasms	7	0.39	0.41	(0.08–2.11)
(a.5) Mesothelioma	5	0.24	0.25	(0.03–2.23)
(b) Other unspecified malignant tumours	107	0.76	0.76	(0.52–1.11)

[a]Sites with < 5 cases or with no female cases are not included. ORs adjusted for matching variables (birth year and country). Cancers classified in ICCC-3 groups.
Abbreviations: OR, odds ratio; CI, confidence interval; NOS, not otherwise specified; CNS, central nervous system.

Supplementary Table S3. Sex distribution [N (per 10 000) for males and females, and M:F sex ratios] for the major anomaly groups in the total study population.

Major birth defects	N (per 10 000) boys	N (per 10 000) girls	M:F Sex ratio
All anomalies	281	215	1.30
All anomalies excluding chromosomal anomalies	260	193	1.35
Nervous system	14	14	1.00
Neural tube defects	4	5	0.81
Eye	8	7	1.05
Ear, face, and neck	2	2	1.14
Congenital heart defects	70	76	0.91
Respiratory system	3	5	0.70
Oro-facial clefts	21	16	1.35
Cleft palate only	6	9	0.67
Cleft lip with/without cleft palate	16	7	2.25
Digestive system	15	16	0.97
Abdominal wall defects	3	2	1.14
Urinary system	22	12	1.82
Genital organs	44	5	8.93
Limb	50	34	1.49
Skeletal dysplasia	3	3	1.22
Genetic syndromes and microdeletions	6	6	1.03
Chromosomal	21	23	0.90
Down syndrome	17	19	0.88
Other anomalies/syndromes	41	32	1.29

Supplementary Table S4. Sensitivity analyses: adjusting for maternal age.

Cancer site	OR	95% CI
Non-chromosomal birth defects		
Any cancer	1.9	(1.8-2.0)
I Leukaemia, myeloproliferative and myelodysplastic diseases	1.2	(1.0-1.4)
II Lymphomas and reticuloendothelial neoplasms	1.5	(1.2-1.8)
III CNS and miscellaneous intracranial and intraspinal neoplasms	2.3	(2.0-2.6)
IV Neuroblastoma and other peripheral nervous cell tumours	2.7	(2.1-3.5)
V Retinoblastoma	1.1	(0.6-2.1)
VI Renal tumours	3.6	(2.8-4.6)
VII Hepatic tumours	3.0	(1.8-4.8)
VIII Malignant bone tumours	1.3	(0.9-2.0)
IX Soft tissue and other extraosseous sarcomas	2.2	(1.7-2.8)
X Germ cell tumours, trophoblastic tumours, and neoplasms of gonads	2.6	(2.1-3.4)
XI Other malignant epithelial neoplasms and malignant melanomas	1.7	(1.3-2.2)
XII Other and unspecified malignant neoplasms	3.2	(1.6-6.3)
Chromosomal birth defects		
Any cancer	9.6	(8.1-11)
I Leukaemia, myeloproliferative and myelodysplastic diseases	29.3	(24-35)
II Lymphomas and reticuloendothelial neoplasms	1.4	(0.6-3.5)
III CNS and miscellaneous intracranial and intraspinal neoplasms	1.9	(1.1-3.4)
IV Neuroblastoma and other peripheral nervous cell tumours	1.4	(0.3-5.6)
V Retinoblastoma	7.1	(2.6-19)
VI Renal tumours	5.0	(2.2-11)
VII Hepatic tumours	2.6	(0.4-19)
VIII Malignant bone tumours	1.0	(0.1-7.1)
IX Soft tissue and other extraosseous sarcomas	1.9	(0.6-6.1)
X Germ cell tumours, trophoblastic tumours, and neoplasms of gonads	4.2	(1.9-9.5)
XI Other malignant epithelial neoplasms and malignant melanomas	0.5	(0.1-3.7)
XII Other and unspecified malignant neoplasms	11.0	(2.7-45)

Abbreviations: OR, odds ratio; CI, confidence interval.

Supplementary Table S5. Sensitivity analyses: adjusting for maternal age and smoking.

Cancer site	Adjusted* for maternal age OR	95% CI	Adjusted* for maternal age and smoking OR	95% CI
Non-chromosomal birth defects				
Any cancer	2.1	(1.9-2.2)	2.1	(1.9-2.3)
I Leukaemia, myeloproliferative and myelodysplastic diseases	1.2	(1.0-1.5)	1.3	(1.1-1.6)
II Lymphomas and reticuloendothelial neoplasms	1.8	(1.4-2.2)	1.8	(1.4-2.3)
III CNS and miscellaneous intracranial and intraspinal neoplasms	2.5	(2.2-2.9)	2.5	(2.2-2.9)
IV Neuroblastoma and other peripheral nervous cell tumours	2.9	(2.2-3.8)	2.9	(2.2-3.9)
V Retinoblastoma	1.0	(0.5-2.2)	1.1	(0.5-2.4)
VI Renal tumours	4.1	(3.2-5.3)	4.2	(3.2-5.5)
VII Hepatic tumours	3.7	(2.2-6.1)	3.7	(2.2-6.2)
VIII Malignant bone tumours	1.3	(0.8-2.2)	1.4	(0.9-2.4)
IX Soft tissue and other extraosseous sarcomas	2.6	(2.0-3.5)	2.6	(2.0-3.5)
X Germ cell tumours, trophoblastic tumours, and neoplasms of gonads	3.2	(2.4-4.2)	3.1	(2.3-4.1)
XI Other malignant epithelial neoplasms and malignant melanomas	1.4	(1.0-2.0)	1.4	(1.0-2.0)
XII Other and unspecified malignant neoplasms	3.2	(1.5-6.9)	3.5	(1.6-7.5)
Chromosomal birth defects.				
Any cancer	10.5	(8.7-13)	10.7	(8.7-13)
I Leukaemia, myeloproliferative and myelodysplastic diseases	29.7	(24.1-37)	29.6	(24-37)
II Lymphomas and reticuloendothelial neoplasms	1.9	(0.8-4.7)	2.1	(0.9-5.1)
III CNS and miscellaneous intracranial and intraspinal neoplasms	2.5	(1.4-4.4)	2.7	(1.5-4.8)
IV Neuroblastoma and other peripheral nervous cell tumours	1.8	(0.5-7.4)	1.9	(0.5-7.7)
V Retinoblastoma	7.2	(2.3-23)	7.7	(2.4-24)
VI Renal tumours	5.2	(2.1-13)	5.5	(2.2-13)
VII Hepatic tumours	3.5	(0.5-25)	3.9	(0.5-28)
VIII Malignant bone tumours	1.5	(0.2-11)	1.6	(0.2-11)
IX Soft tissue and other extraosseous sarcomas	2.6	(0.8-8.2)	2.8	(0.9-8.8)
X Germ cell tumours, trophoblastic tumours, and neoplasms of gonads	4.2	(1.6-11)	4.6	(1.7-12)
XI Other malignant epithelial neoplasms and malignant melanomas	0.7	(0.1-5.1)	0.8	(0.1-5.5)
XII Other and unspecified malignant neoplasms	14.9	(3.6-62)	16.3	(3.9-68)

*Also adjusted for matching variables (country and birth year) and sex. Abbreviations: OR, odds ratio; CI, confidence interval, CNS, central nervous system.

Supplementary Table S6. Sensitivity analyses: adjusting for maternal age, smoking and IVF.

	OR (95%CI) Adjusted for country, birth year, and sex	OR (95%CI) Adjusted for country, birth year, sex, and IVF	OR (95%CI) Adjusted for country, birth year, sex, IVF, and maternal age
Non-chromosomal birth defects	2.1 (1.9-2.4)	2.1 (1.9-2.3)	2.1 (1.9-2.3)
Chromosomal birth defects	11.8 (9.5-14.7)	11.8 (9.5-14.7)	10.7 (8.5-13.3)

Abbreviations: OR, odds ratio; CI, confidence interval; IVF, *in vitro* fertilization.

Supplementary Table S7. Association between Down syndrome and leukaemia by age at diagnosis.

Birth defect	*Cancer*	*Age at diagnosis*	*OR (95% CI)*	*n cases*	*n (%) cases with BD*
Down Syndrome	ALL	<2 year	12 (5.4-28)	455	6 (1.3)
Down Syndrome	ALL	2-4 years	22 (15-31)	1 714	38 (2.2)
Down Syndrome	ALL	5+ years	27 (20-37)	1871	46 (2.5)
Down Syndrome	AML	<1 year	253 (155-413)	110	24 (22)
Down Syndrome	AML	1 year	451 (305-667)	143	45 (31)
Down Syndrome	AML	2-4 years	256 (170-387)	163	33 (20)
Down Syndrome	AML	5+ years	7.7 (2.4-24)	450	3 (0.7)

Abbreviations: OR, odds ratio; CI, confidence interval; BD, birth defect; ALL, acute lymphoid leukaemia; AML, acute myeloid leukaemia.

Supplementary Table S8. Risk [OR (95% CI)] of any cancer in children with major birth defects stratified by sex and age at diagnosis.

	0-4 years		5-9 years		10-14 years		15-19 years	
	Males	Females	Males	Females	Males	Females	Males	Females
All anomalies	2.7 (2.4-3.1)	4.1 (3.6-4.6)	1.7 (1.4-2.1)	2.2 (1.7-2.8)	1.8 (1.5-2.3)	2.0 (1.5-2.5)	1.4 (1.2-1.7)	1.8 (1.4-2.3)
All anomalies excl. chromosomal	2.1 (1.9-2.4)	2.8 (2.4-3.3)	1.4 (1.1-1.8)	1.9 (1.5-2.5)	1.6 (1.3-2.0)	1.8 (1.3-2.4)	1.4 (1.1-1.7)	1.7 (1.4-2.2)

Abbreviations: OR, odds ratio; CI, confidence interval.

Supplementary Table S9. Mediation analyses of the effect of non–chromosomal birth defects on the association between sex (males versus females) and childhood cancer, overall and by cancer site.

	Controlled direct effect[a] OR (95% CI)	Natural indirect effect OR (95% CI)	Natural direct effect OR (95% CI)	Marginal total effect OR (95% CI)	Percentage (%) mediated[b]
Total study population 0–19 years					
Any cancer	1.17 (1.14–1.20)	1.005 (1.003–1.006)	1.16 (1.13–1.19)	1.17 (1.13–1.20)	3.29
I Leukaemia, myeloproliferative and myelodysplastic diseases	1.19 (1.12–1.25)	1.001 (0.999–1.003)	1.19 (1.12–1.25)	1.19 (1.12–1.25)	..
II Lymphomas and reticuloendothelial neoplasms	1.53 (1.42–1.65)	1.002 (0.999–1.004)	1.52 (1.41–1.63)	1.52 (1.41–1.64)	..
III CNS and miscellaneous intracranial and intraspinal neoplasms	1.14 (1.08–1.21)	1.007 (1.004–1.010)	1.13 (1.07–1.19)	1.14 (1.08–1.20)	5.70
IV Neuroblastoma and other peripheral nervous cell tumours	1.16 (1.03–1.31)	1.009 (1.004–1.015)	1.15 (1.02–1.29)	1.16 (1.03–1.30)	6.80
V Retinoblastoma	1.12 (0.93–1.36)	0.999 (0.994–1.005)	1.11 (0.92–1.35)	1.11 (0.92–1.34)	..
VI Renal tumours	0.90 (0.79–1.02)	1.014 (1.007–1.021)	0.88 (0.78–1.00)	0.89 (0.79–1.01)	..
VII Hepatic tumours	1.44 (1.13–1.84)	1.010 (0.999–1.020)	1.41 (1.11–1.78)	1.42 (1.12–1.80)	..
VIII Malignant bone tumours	1.16 (1.02–1.32)	1.002 (0.999–1.006)	1.16 (1.02–1.31)	1.16 (1.02–1.32)	..
IX Soft tissue and other extraosseous sarcomas	1.22 (1.09–1.36)	1.008 (1.003–1.013)	1.23 (1.10–1.37)	1.24 (1.11–1.38)	4.33
X Germ cell tumours, trophoblastic tumours, and neoplasms of gonads	2.30 (2.04–2.60)	1.006 (1.002–1.010)	2.19 (1.95–2.47)	2.21 (1.96–2.48)	1.13
XI Other malignant epithelial neoplasms and malignant melanomas	0.53 (0.48–0.59)	1.004 (1.000–1.009)	0.53 (0.48–0.59)	0.53 (0.48–0.59)	..
XII Other and unspecified malignant neoplasms	0.68 (0.47–0.97)	1.016 (0.996–1.036)	0.67 (0.48–0.95)	0.68 (0.48–0.97)	..
Children younger than 5 years at time of diagnosis					
Any cancer	1.13 (1.08–1.18)	1.007 (1.005–1.010)	1.11 (1.07–1.17)	1.12 (1.07–1.17)	6.71
Children younger than 1 year at time of diagnosis					
Any cancer	1.10 (0.99–1.21)	1.021 (1.015–1.029)	1.07 (0.97–1.18)	1.09 (0.99–1.20)	24.82

[a]Estimated for no birth defect. [b]Proportion mediated not calculated when the NDE and NIE were in opposite directions or when the CI for NIE contained the null effect. Abbreviations: OR, odds ratio; CI, confidence interval.

Supplementary Table S10. Sensitivity analyses for the mediation analyses.

	Controlled direct effect[a] OR (95% CI)	Natural indirect effect OR (95% CI)	Natural direct effect OR (95% CI)	Marginal total effect OR (95% CI)	Percentage (%) mediated
Restricted to countries and time period when IVF was reported[b].	1.11 (1.07-1.16)	1.009 (1.007-1.011)	1.11 (1.07-1.16)	1.12 (1.08-1.17)	8.27
Including IVF as a confounder.	1.11 (1.07-1.16)	1.009 (1.007-1.011)	1.11 (1.07-1.16)	1.12 (1.08-1.17)	8.27
Restricted to time period when maternal smoking was reported[c].	1.14 (1.10-1.18)	1.011 (1.009-1.013)	1.14 (1.10-1.18)	1.15 (1.11-1.20)	7.93
Including maternal smoking as a confounder.	1.14 (1.10-1.18)	1.011 (1.009-1.013)	1.14 (1.10-1.18)	1.15 (1.11-1.20)	7.93

[a]Estimated for no birth defect. [b]Median age at diagnosis in this subpopulation was 5 years (compared to 8 years in the total study population). [c]Median age at diagnosis in this sub population was 6 years. Abbreviations: OR, odds ratio; CI, confidence interval; IVF, *in vitro* fertilization.

Supplementary Table S11. Mediation analyses of the effect of birth defects on the association between sex (males versus females) and childhood cancer, overall and by cancer site, complete table.

Cancer site	Controlled direct effect[a] OR (95% CI)	Natural indirect effect OR (95% CI)	Natural direct effect OR (95% CI)	Marginal total effect OR (95% CI)	Percentage (%) mediated[b]
Total study population 0–19 years					
Any cancer	1.17 (1.14–1.20)	1.007 (1.005–1.008)	1.16 (1.12–1.19)	1.16 (1.13–1.20)	4.80
I Leukaemia, myeloproliferative, and myelodysplastic diseases	1.19 (1.12–1.25)	1.009 (1.006–1.012)	1.16 (1.10–1.22)	1.17 (1.11–1.24)	5.95
(a) Lymphoid leukaemia	1.19 (1.12–1.27)	1.005 (1.003–1.008)	1.18 (1.11–1.25)	1.18 (1.11–1.26)	3.42
(b) Acute myeloid leukaemia	1.06 (0.92–1.23)	1.028 (1.018–1.038)	1.00 (0.88–1.15)	1.03 (0.90–1.18)	85.44
Other leukaemia	1.33 (1.11–1.60)	1.008 (1.001–1.015)	1.32 (1.11–1.57)	1.33 (1.11–1.58)	3.16
II Lymphomas and reticuloendothelial neoplasms	1.53 (1.42–1.66)	1.002 (1.000–1.004)	1.52 (1.41–1.63)	1.52 (1.41–1.64)	..
(a) Hodgkin lymphomas	1.09 (0.98–1.22)	0.998 (0.996–1.001)	1.08 (0.97–1.20)	1.08 (0.97–1.20)	..
(b) Non–Hodgkin lymphomas	1.95 (1.71–2.24)	1.004 (1.000–1.009)	1.92 (1.68–2.19)	1.93 (1.69–2.20)	0.92
Other lymphomas	2.92 (2.37–3.61)	1.003 (0.998–1.009)	2.88 (2.34–3.54)	2.89 (2.35–3.55)	..
III CNS and miscellaneous intracranial and intraspinal neoplasms	1.14 (1.08–1.21)	1.007 (1.004–1.010)	1.13 (1.08–1.21)	1.14 (1.08–1.20)	5.69
(a.1) Ependymomas	1.30 (1.06–1.59)	1.000 (0.995–1.006)	1.29 (1.06–1.58)	1.29 (1.06–1.58)	..
(b) Astrocytoma	1.05 (0.96–1.15)	1.005 (1.001–1.008)	1.04 (0.95–1.13)	1.04 (0.95–1.14)	12.27
(c.1) Medulloblastomas	1.70 (1.44–2.00)	1.000 (0.996–1.004)	1.64 (1.40–1.93)	1.64 (1.40–1.93)	..
(c.2) Primitive neuroectodermal tumour	1.36 (1.06–1.74)	1.003 (0.995–1.011)	1.31 (1.03–1.68)	1.32 (1.03–1.68)	..
Other CNS	1.03 (0.94–1.14)	1.014 (1.009–1.019)	1.04 (0.95–1.14)	1.06 (0.97–1.16)	24.79
IV Neuroblastoma and other peripheral nervous cell tumours	1.16 (1.03–1.31)	1.009 (1.004–1.014)	1.15 (1.02–1.29)	1.16 (1.03–1.30)	6.52
(a) Neuroblastoma	1.14 (1.01–1.29)	1.009 (1.004–1.014)	1.13 (1.01–1.27)	1.14 (1.01–1.29)	7.08
(b) Other peripheral nervous cell tumours	2.25 (0.93–5.47)	1.010 (0.978–1.042)	2.05 (0.88–4.77)	2.07 (0.89–4.81)	..
V Retinoblastoma	1.12 (0.93–1.36)	1.002 (0.996–1.009)	1.12 (0.93–1.35)	1.12 (0.93–1.35)	..
VI Renal tumours	0.90 (0.79–1.02)	1.013 (1.006–1.020)	0.88 (0.77–0.99)	0.89 (0.78–1.00)	..
(a.1) Nephroblastoma	0.90 (0.78–1.02)	1.013 (1.006–1.021)	0.87 (0.77–0.99)	0.88 (0.78–1.00)	..
Other renal	0.93 (0.57–1.51)	1.003 (0.990–1.016)	0.93 (0.57–1.51)	0.93 (0.57–1.51)	..
VII Hepatic tumours	1.44 (1.13–1.84)	1.009 (0.999–1.018)	1.40 (1.11–1.77)	1.41 (1.12–1.78)	2.94
(a.1) Hepatoblastoma	1.69 (1.25–2.29)	1.006 (0.996–1.017)	1.59 (1.19–2.13)	1.60 (1.19–2.14)	..
Other hepatic	1.09 (0.73–1.65)	1.014 (0.994–1.035)	1.11 (0.73–1.65)	1.13 (0.76–1.68)	..
VIII Malignant bone tumours	1.16 (1.02–1.32)	1.002 (0.999–1.006)	1.16 (1.02–1.32)	1.17 (1.03–1.33)	..
(a) Osteosarcoma	1.25 (1.05–1.49)	1.002 (0.996–1.007)	1.23 (1.04–1.47)	1.24 (1.04–1.47)	..
(c.1) Ewing tumour and Askin tumour of bone	1.12 (0.90–1.41)	1.003 (0.996–1.011)	1.14 (0.91–1.43)	1.15 (0.92–1.44)	..
Other bone	0.93 (0.65–1.35)	1.003 (0.992–1.013)	0.93 (0.65–1.35)	0.93 (0.65–1.35)	..
IX Soft tissue and other extraosseous sarcomas	1.22 (1.09–1.36)	1.008 (1.003–1.013)	1.22 (1.10–1.37)	1.23 (1.11–1.38)	4.18
(a) Rhabdomyosarcoma	1.31 (1.11–1.56)	1.005 (0.999–1.011)	1.31 (1.11–1.55)	1.32 (1.12–1.56)	..
Other soft tissue	1.16 (1.00–1.34)	1.010 (1.003–1.017)	1.16 (1.01–1.34)	1.18 (1.02–1.36)	6.68
X Germ cell tumours, trophoblastic tumours and neoplasms of gonads	2.30 (2.04–2.60)	1.007 (1.003–1.012)	2.21 (1.96–2.48)	2.22 (1.97–2.50)	1.33
(a) Intracranial germ cell tumours	2.09 (1.53–2.84)	1.015 (1.002–1.029)	1.95 (1.45–2.61)	1.98 (1.48–2.65)	3.08
(b) Extracranial germ cell tumours	0.68 (0.48–0.97)	1.025 (1.002–1.048)	0.64 (0.46–0.90)	0.66 (0.47–0.92)	..
(c), (d), and (e) Gonadal germ cell tumours	2.86 (2.47–3.32)	1.004 (1.000–1.009)	2.83 (2.45–3.28)	2.85 (2.46–3.29)	0.67
XI Other malignant epithelial neoplasms and malignant melanomas	0.53 (0.48–0.59)	1.004 (1.000–1.009)	0.53 (0.48–0.59)	0.53 (0.48–0.59)	..
XII Other and unspecified malignant neoplasms	0.68 (0.47–0.97)	1.016 (0.996–1.036)	0.67 (0.48–0.95)	0.68 (0.48–0.97)	..
Children younger than 5 years at time of diagnosis					
Any cancer	1.13 (1.08–1.18)	1.011 (1.008–1.014)	1.10 (1.05–1.15)	1.11 (1.06–1.16)	10.69
I Leukaemia, myeloproliferative, and myelodysplastic diseases	1.02 (0.95–1.10)	1.012 (1.008–1.017)	1.00 (0.93–1.07)	1.01 (0.94–1.09)	..

Cancer site	Controlled direct effect[a] OR (95% CI)	Natural indirect effect OR (95% CI)	Natural direct effect OR (95% CI)	Marginal total effect OR (95% CI)	Percentage (%) mediated[b]
II Lymphomas and reticuloendothelial neoplasms	2.28 (1.82–2.85)	1.006 (0.999–1.013)	2.27 (1.82–2.83)	2.28 (1.83–2.84)	..
III CNS and miscellaneous intracranial and intraspinal neoplasms	1.16 (1.05–1.28)	1.013 (1.008–1.018)	1.16 (1.05–1.27)	1.17 (1.07–1.29)	8.21
IV Neuroblastoma and other peripheral nervous cell tumours	1.11 (0.97–1.26)	1.010 (1.004–1.016)	1.09 (0.96–1.24)	1.10 (0.97–1.25)	10.51
V Retinoblastoma	1.12 (0.92–1.36)	1.003 (0.996–1.010)	1.11 (0.92–1.35)	1.12 (0.92–1.35)	..
VI Renal tumours	0.89 (0.77–1.04)	1.015 (1.007–1.023)	0.87 (0.75–1.00)	0.88 (0.76–1.02)	..
VII Hepatic tumours	1.78 (1.31–2.41)	1.004 (0.995–1.013)	1.64 (1.22–2.19)	1.64 (1.23–2.20)	..
VIII Malignant bone tumours	1.00 (0.58–1.71)	1.000 (0.987–1.012)	1.00 (0.99–1.01)	1.00 (0.58–1.71)	..
IX Soft tissue and other extraosseous sarcomas	1.29 (1.07–1.56)	1.009 (1.001–1.017)	1.27 (1.06–1.53)	1.28 (1.07–1.54)	4.14
X Germ cell tumours, trophoblastic tumours and neoplasms of gonads	1.58 (1.22–2.04)	1.007 (0.998–1.017)	1.38 (1.09–1.75)	1.39 (1.09–1.77)	..
XI Other malignant epithelial neoplasms and malignant melanomas	0.61 (0.34–1.08)	1.030 (0.990–1.073)	0.62 (0.36–1.07)	0.64 (0.37–1.10)	..
XII Other and unspecified malignant neoplasms	0.56 (0.35–0.91)	1.025 (0.995–1.057)	0.57 (0.36–0.89)	0.58 (0.37–0.91)	..
Children younger than 1 year at time of diagnosis					
Any cancer	1.10 (0.99–1.21)	1.025 (1.018–1.033)	1.06 (0.97–1.17)	1.09 (0.99–1.20)	28.15
I Leukaemia, myeloproliferative and myelodysplastic diseases	0.67 (0.53–0.86)	1.043 (1.023–1.063)	0.70 (0.56–0.88)	0.73 (0.59–0.91)	..
II Lymphomas and reticuloendothelial neoplasms	1.13 (0.67–1.88)	1.025 (0.997–1.053)	1.14 (0.70–1.86)	1.17 (0.72–1.90)	..
III CNS and miscellaneous intracranial and intraspinal neoplasms	1.19 (0.94–1.50)	1.037 (1.020–1.053)	1.15 (0.93–1.43)	1.20 (0.97–1.48)	21.56
IV Neuroblastoma and other peripheral nervous cell tumours	1.40 (1.14–1.73)	1.020 (1.009–1.031)	1.36 (1.12–1.66)	1.39 (1.14–1.70)	6.85
V Retinoblastoma	1.00 (0.73–1.39)	1.000 (0.991–1.009)	0.96 (0.70–1.32)	0.96 (0.70–1.32)	..
VI Renal tumours	1.22 (0.85–1.76)	1.024 (1.004–1.045)	1.18 (0.84–1.66)	1.21 (0.86–1.70)	13.90
VII Hepatic tumours	1.60 (0.95–2.72)	1.013 (0.991–1.036)	1.45 (0.88–2.37)	1.47 (0.89–2.40)	..
VIII Malignant bone tumours[†]	..	..	..	..	..
IX Soft tissue and other extraosseous sarcomas	1.42 (0.99–2.05)	1.019 (1.001–1.038)	1.36 (0.96–1.92)	1.38 (0.98–1.95)	6.89
X Germ cell tumours, trophoblastic tumours and neoplasms of gonads	1.07 (0.70–1.63)	1.018 (0.997–1.040)	0.88 (0.60–1.29)	0.90 (0.61–1.32)	..
XI Other malignant epithelial neoplasms and malignant melanomas	1.83 (0.46–7.33)	1.058 (0.976–1.147)	1.83 (0.46–7.33)	1.93 (0.48–7.74)	..
XII Other and unspecified malignant neoplasms	0.45 (0.23–0.91)	1.044 (0.990–1.102)	0.47 (0.25–0.88)	0.49 (0.26–0.91)	..

[a]Estimated for no birth defect. [b]Proportion mediated not calculated when the NDE and NIE were in opposite directions or when the CI for NIE contained the null effect. [†]Less than 5 cases, results not included. Abbreviations: OR; odds ratio; CI, confidence interval; CNS, central nervous system.

Supplementary Table S12. Risk of specific cancers in individuals with selected specific birth defects.

Exposure	Outcome	N cases with BD (%)	OR (95% CI)
Nervous system defects			
Spina bifida without anencephaly	Any cancer	25 (0.1%)	4.3 (2.7–6.9)
	III CNS	11 (0.2%)	7.9 (4.1–15)
	III f) CNS unspecified	11 (2.5%)	84 (44–164)
	X Germ cell tumours. trophoblastic tumours and neoplasms of gonads	7 (0.6%)	21 (9.6–47)
	X a) Intracranial and intraspinal germ cell tumours	5 (2.6%)	97 (38–247)
	X b) Malignant extracranial and extragonadal germ cell tumours	<5 (1.6%)	58 (14–239)
Hydrocephaly without spina bifida	Any cancer	32 (0.2%)	10 (6.0–16)
	III CNS	27 (0.6%)	35 (21–59)
	III a) Ependymomas and choroid plexus tumour	<5 (0.6%)	36 (11–118)
	III b) Astrocytoma	<5 (0.2%)	10 (3.2–34)
	III c) Intracranial and intraspinal embryonal tumours	8 (0.9%)	53 (24–115)
	III d) Other gliomas	<5 (0.7%)	46 (14–152)
	III e) CNS Other specified	<5 (0.4%)	26 (8.0–86)
	III f) CNS unspecified	7 (1.6%)	129 (55–304)
	X a) Intracranial and intraspinal germ cell tumours	<5 (1.1%)	56 (13–239)
Microencephaly	Any cancer	<5 (0.0%)	1.7 (0.5–5.6)
Digestive system			
Biliary atresia	Any cancer	5 (0.0%)	26 (5.0–134)
	II Lymphomas	<5 (0.1%)	180 (32–1011)
	II b) Non–Hodgkin lymphomas	<5 (0.3%)	394 (62–2501)
Other			
Craniosynostosis	Any cancer	5 (0.0%)	1.2 (0.5–3.0)
Single–gene disorders			
Neurofibromatosis	Any cancer	36 (0.2%)	38 (19–77)

Exposure	Outcome	N cases with BD (%)	OR (95% CI)
Neurofibromatosis cont.	III CNS	26 (0.5%)	121 (58–252)
	III b) Astrocytoma	11 (0.6%)	129 (54–305)
	III d) Other gliomas	5 (1.1%)	238 (79–718)
	III d2) Mixed and unspecified gliomas	<5 (1.3%)	227 (69–744)
	III e) Other specified	<5 (0.3%)	50 (11–230)
	III f) CNS unspecified	8 (1.8%)	1169 (431–3173)
	IV Neuroblastoma (a)	<5 (0.3%)	59 (16–216)
	IX Soft tissue	6 (0.5%)	109 (39–304)
	IX b2) Nerve sheath tumours	5 (5.8%)	2288 (643–8135)
Tuberous sclerosis	Any cancer	26 (0.1%)	67 (24–193)
	III CNS	24 (0.5%)	269 (93–775)
	III b) Astrocytoma	19 (1.0%)	551 (187–1624)
	III d2) Mixed and unspecified gliomas	<5 (0.6%)	303 (54–1689)
	III f) CNS unspecified	<5 (0.5%)	418 (67–2593)
Genitourinary system			
Obstructive genitourinary defects	Any cancer	29 (0.1%)	1.6 (1.1–2.3)
	I Leukaemia	5 (0.1%)	0.9 (0.4–2.3)
	I a) Lymphoid Leukaemia	<5 (0.1%)	0.7 (0.2–2.3)
	I b) Acute myeloid leukaemia	<5 (0.3%)	2.8 (0.7–11)
	II Lymphomas	<5 (0.1%)	1.3 (0.4–4.1)
	III CNS	<5 (0.4%)	0.5 (0.1–1.8)
	III e) CNS Other specified	<5 (0.3%)	2.9 (0.7–12)
	VI Renal tumours	5 (0.5%)	5.4 (2.2–13)
	VI a1) Nephroblastoma	<5 (0.5%)	4.6 (1.7–12)
	IX Soft tissue	<5 (0.3%)	3.6 (1.3–9.8)
	IX a) Rhabdomyosarcomas	<5 (0.7%)	7.3 (2.7–20)
	X Germ cell tumours. trophoblastic tumours, and neoplasms of gonads	<5 (0.3%)	4.2 (1.5–11)
	X b) Malignant extracranial and extragonadal germ cell tumours	<5 (2.3%)	26 (8.2–84)

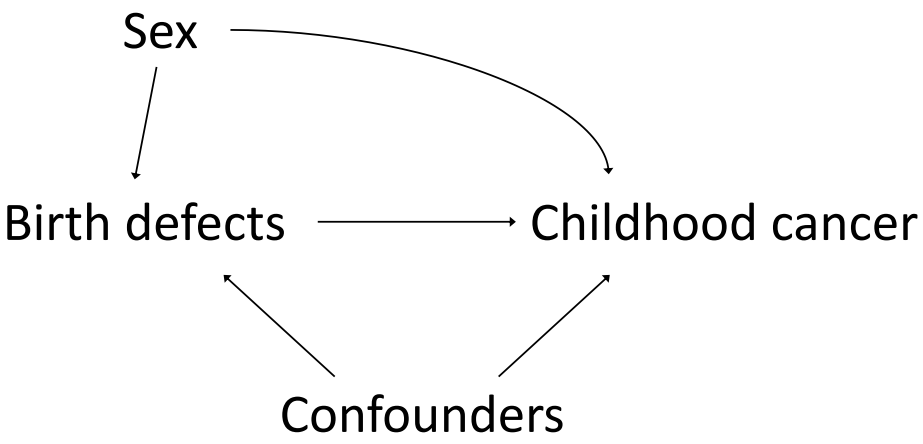
Exposure	Outcome	N cases with BD (%)	OR (95% CI)
Obstructive genitourinary defects cont.	*X b2) Malignant teratomas of extracranial and extragonadal sites*	<5 (2.5%)	25 (6.1–105)
	XI Other malignant epithelial neoplasms and malignant melanoma	<5 (0.1%)	2.1 (0.5–8.5)
	XII Other and unspecified malignant neoplasms	<5 (1.6%)	18 (4.3–73)
Hypospadias	Any cancer	26 (0.1%)	1.0 (0.7–1.5)
	I Leukaemia	8 (0.2%)	1.2 (0.6–2.4)
	II Lymphomas	<5 (0.1%)	0.8 (0.3–2.6)
	III CNS	<5 (0.1%)	0.5 (0.2–1.5)
	VI Renal tumours	<5 (0.4%)	3.7 (1.4–10)
Hypospadias/ epispadias	Any cancer	38 (0.2%)	1.1 (0.8–1.6)
	I Leukaemia	11 (0.2%)	1.3 (0.7–2.3)
	II Lymphomas	5 (0.2%)	1.1 (0.4–2.6)
	III CNS	6 (0.1%)	0.8 (0.3–1.7)
	VI Renal tumours	5 (0.5%)	3.7 (1.5–9.0)
	XI Other malignant epithelial neoplasms and malignant melanoma	<5 (0.2%)	2.0 (0.6–6.2)
Eye			
Congenital cataract	Any cancer	7 (0.0%)	1.4 (0.6–3.1)
	VI Renal tumours	<5 (0.3%)	16 (4.8–51)
Limb			
Clubfoot	Any cancer[a]	48 (0.2%)	0.9 (0.7–1.3)
Congenital hip dislocation	Any cancer	34 (0.2%)	1.2 (0.8–1.7)
	VI Renal tumours[a]	<5 (0.4%)	3.2 (1.2–8.5)
Heart			
Pulmonary artery anomalies	Any cancer	<5 (0.0%)	1.4 (0.4–4.7)
Pulmonary valve atresia and stenosis	Any cancer	<5 (0.0%)	0.9 (0.2–3.9)
Septal defects	Any cancer	97 (0.5%)	1.4 (1.1–1.7)
	I Leukaemia[a]	22 (0.4%)	1.1 (0.7–1.6)

Exposure	Outcome	N cases with BD (%)	OR (95% CI)
Septal defects cont.	II Lymphomas	18 (0.6%)	2.1 (1.3–3.4)
	II a) Hodgkin lymphoma	8 (0.6%)	2.0 (1.0–4.1)
	II b) Non–Hodgkin lymphomas	7 (0.7%)	2.3 (1.1–4.9)
	II b2) Mature B–cell lymphoma (except Burkitt)	<5 (1.5%)	4.9 (1.8–13)
	II b4) Non–Hodgkin NOS	<5 (0.6%)	1.9 (0.5–7.9)
	II d) Miscellaneous lymphoreticular neoplasms	<5 (1.6%)	3.4 (0.8–14)
	III CNS	15 (0.3%)	0.9 (0.5–1.5)
	III c) Intracranial and intraspinal embryonal tumours	<5 (0.4%)	1.2 (0.5–3.3)
	III d2) Mixed and unspecified gliomas	<5 (1.0%)	3.6 (1.2–11)
	III e) CNS Other specified	<5 (0.5%)	1.4 (0.5–3.8)
	III f) CNS unspecified	<5 (0.5%)	1.3 (0.3–5.3)
	IV Neuroblastoma	6 (0.6%)	1.5 (0.6–3.3)
	IV a) Neuroblastoma and ganglioneuroblastoma	6 (0.6%)	1.5 (0.7–3.3)
	VI Renal tumours	6 (0.6%)	1.6 (0.7–3.7)
	VI a1) Nephroblastoma	6 (0.7%)	1.7 (0.8–3.9)
	VII Hepatic tumours	<5 (1.5%)	4.0 (1.5–11)
	VII a1) Hepatoblastoma	<5 (1.6%)	4.2 (1.3–13)
	VIII Malignant bone tumours	<5 (0.4%)	1.6 (0.6–4.4)
	VIII a) Osteosarcomas	<5 (0.6%)	2.3 (0.7–7.1)
	IX Soft tissue[a]	6 (0.5%)	1.4 (0.6–3.2)
	X Germ cell tumours. trophoblastic tumours and neoplasms of gonads	9 (0.7%)	2.8 (1.4–5.4)
	X b2) Malignant teratomas of extracranial and extragonadal sites	<5 (3.8%)	8.6 (2.7–28)
	X c) Malignant gonadal germ cell tumour	5 (0.6%)	2.4 (1.0–5.9)
	X c1) Malignant gonadal germinomas	<5 (1.8%)	7.6 (1.8–31)
	X c4) Gonadal yolk sac tumour	<5 (1.6%)	4.5 (1.1–18)
	XI Other malignant epithelial neoplasms and malignant melanoma*	6 (0.4%)	1.3 (0.6–2.9)
Ventricular Septal defects	Any cancer	72 (0.4%)	1.2 (1.0–1.6)
	I Leukaemia[a]	16 (0.3%)	0.9 (0.6–1.6)
	II Lymphomas	11 (0.4%)	1.6 (0.9–2.9)

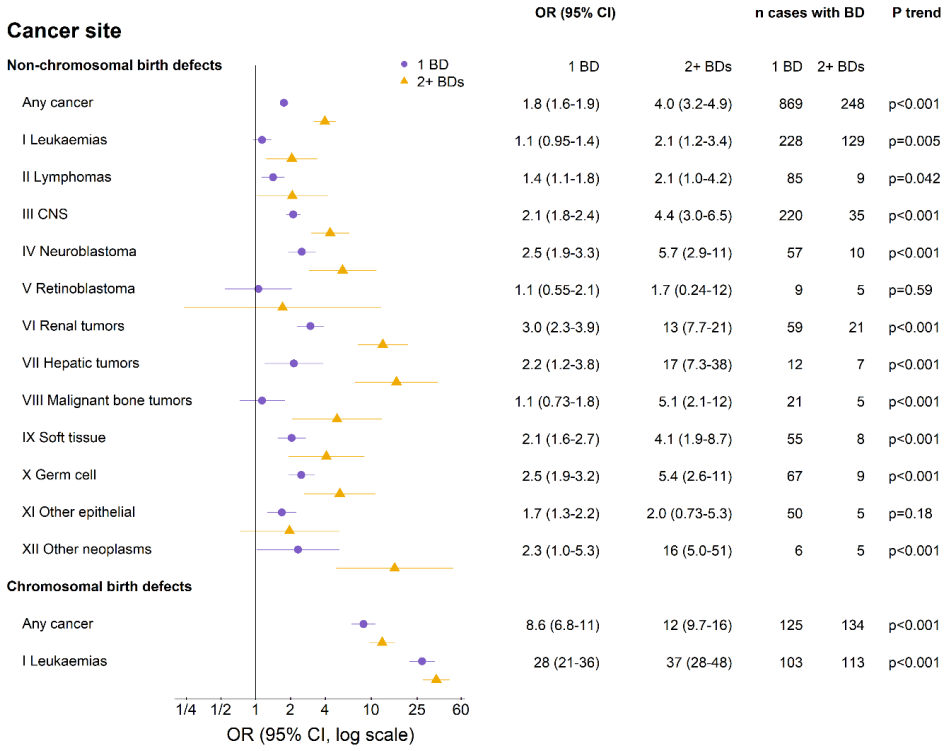
Exposure	Outcome	N cases with BD (%)	OR (95% CI)
Ventricular Septal defects cont.	*II a) Hodgkin lymphoma*	5 (0.4%)	1.6 (0.6–3.8)
	II b) Non–Hodgkin lymphomas	<5 (0.4%)	1.6 (0.6–4.4)
	II b2) Mature B–cell lymphoma (except Burkitt)	<5 (1.1%)	4.5 (1.4–14)
	II d) Miscellaneous lymphoreticular neoplasms	<5 (1.6%)	4.3 (1.1–18)
	III CNS[a]	12 (0.2%)	0.9 (0.5–1.5)
	IV Neuroblastoma[a]	6 (0.6%)	1.8 (0.8–4.1)
	VI Renal tumours	<5 (0.4%)	1.4 (0.5–3.7)
	VI a1) Nephroblastoma	<5 (0.5%)	1.5 (0.5–3.9)
	VII Hepatic tumours	<5 (0.7%)	2.5 (0.6–10)
	VII a1) Hepatoblastoma	<5 (1.1%)	3.5 (0.9–14)
	VIII Malignant bone tumours	<5 (0.2%)	1.0 (0.2–4.0)
	VIII a) Osteosarcomas	<5 (0.4%)	1.9 (0.5–7.5)
	IX Soft tissue[a]	6 (0.5%)	1.8 (0.8–4.0)
	X Germ cell tumours, trophoblastic tumours and neoplasms of gonads	7 (0.6%)	2.6 (1.2–5.6)
	X b2) Malignant teratomas of extracranial and extragonadal sites	<5 (2.5%)	7.3 (1.8–30)
	X c) Malignant gonadal germ cell tumour	<5 (0.5%)	2.4 (0.9–6.3)
	X c1) Malignant gonadal germinomas	<5 (1.8%)	9.1 (2.2–37)
	XI Other malignant epithelial neoplasms and malignant melanoma[a]	5 (0.3%)	1.3 (0.5–3.2)
Atrial Septal defects	Any cancer	35 (0.2%)	1.7 (1.2–2.5)
	I Leukaemia	7 (0.1%)	1.2 (0.6–2.5)
	I a1) Precursor cell leukaemia	7 (0.2%)	1.5 (0.7–3.2)
	II Lymphomas	10 (0.4%)	4.3 (2.3–8.1)
	II a) Hodgkin lymphoma	<5 (0.3%)	3.9 (1.4–10)
	II b) Non–Hodgkin lymphomas	5 (0.5%)	6.0 (2.5–15)
	II b2) Mature B–cell lymphoma (except Burkitt)	<5 (1.1%)	13 (4.2–42)
	II b4) Non–Hodgkin NOS	<5 (0.6%)	7.3 (1.8–30)
	III CNS	5 (0.1%)	1.0 (0.4–2.5)
	III f) CNS unspecified	<5 (0.5%)	4.9 (1.2–20)
	IV Neuroblastoma	<5 (0.2%)	1.6 (0.4–6.6)

Exposure	Outcome	N cases with BD (%)	OR (95% CI)
Atrial Septal defects cont.	*IV a) Neuroblastoma and ganglioneuroblastoma*	<5 (0.2%)	1.7 (0.4–6.7)
	VI a) Nephroblastoma and other non–epithelial renal tumours	<5 (0.3%)	3.0 (1.0–9.4)
	VII Hepatic tumours	<5 (0.7%)	6.8 (1.7–28)
	VIII Malignant bone tumours	<5 (0.2%)	2.8 (0.7–11)
	X Germ cell tumours. trophoblastic tumours and neoplasms of gonads	<5 (0.2%)	3.4 (1.1–11)
	X b2) Malignant teratomas of extracranial and extragonadal sites	<5 (2.5%)	20 (4.7–81)
Patent ductus arteriosus	Any cancer	11 (0.1%)	1.1 (0.6–2.0)
	I Leukaemia	6 (0.1%)	2.1 (0.9–4.8)
	VI Renal tumours	<5 (0.2%)	3.9 (1.0–16)
Transposition of great vessels	Any cancer	8 (0.0%)	1.4 (0.7–3.0)
	III CNS	<5 (0.1%)	3.1 (1.1–8.5)

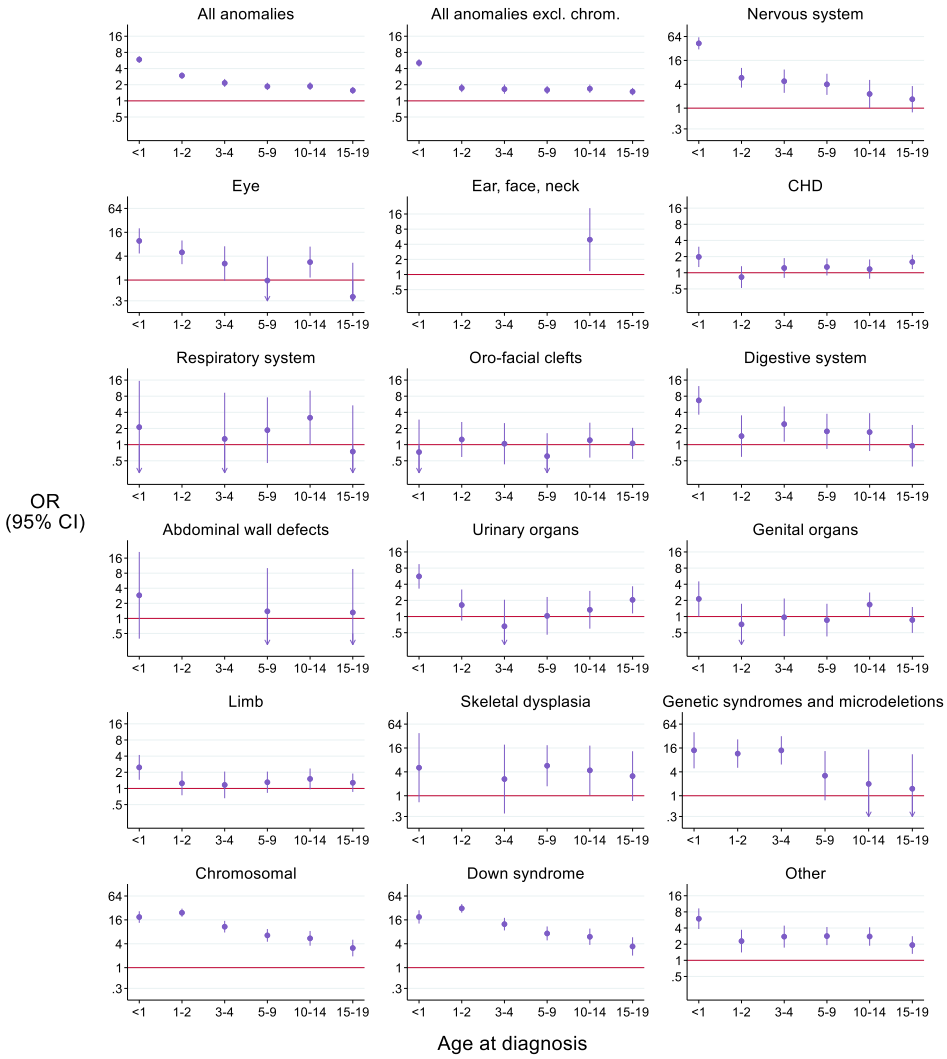
[a]No sub sites with statistically significant results. Abbreviations: BD, birth defect; OR, odds ratio; CI, confidence interval; CNS, central nervous system; NOS, not otherwise specified.



Supplementary Figure S1. A simplified illustration of the assumed causal relationship between sex, birth defects and childhood cancer



Supplementary Figure S2. Risk of cancer according to number of major birth defects (1, 2 or more) in different anatomical subgroups.
Results are presented separately for children with non–chromosomal defects only and those with chromosomal birth defects (and additional non–chromosomal defects). ORs are adjusted for matching variables (birth year and country) and sex. Orthogonal polynomial contrasts were used to test for linear trends. Abbreviations: BD, birth defect; OR, odds ratio; CI, confidence interval; CNS, central nervous system.



Supplementary Figure S3. Risk of cancer in children with major birth defects, stratified by age at cancer diagnosis.

Some age groups have no co–occurring birth defects and cancer cases. Note that scales differ. ORs are adjusted for matching variables (birth year and country) and sex. Abbreviations: CHD, congenital heart defect; OR, odds ratio; CI, confidence interval.

Supplementary sensitivity analyses – Description of results

When leaving out one country at a time we observed small differences from the results displayed in Figures 1 and 2, and Tables 2-4. Leaving out Finland, resulted in slightly reduced odds ratios (ORs) as expected due to the younger population. The OR for any cancer in children with non-chromosomal birth defects was 1.9 in our main analysis (Figure 1), while leaving out Finland the OR was 1.7. Leaving out Denmark, Norway and Sweden hardly changed the ORs. In Finland, 47% of the children were below the age of five at cancer diagnosis, compared to 35% in Denmark, 38% in Norway, and 34% in Sweden. The only noticeable difference we observed was among children with non-chromosomal birth defects, where the OR of lymphoma was reduced from 1.5 (Figure 2) to 1.1 when excluding Finland and to 1.3 when excluding Sweden, whereas excluding Norway or Denmark increased the OR to 1.7. A total of 26 out of 84 children with both lymphomas and a birth defect had a congenital heart defect. Norway and Denmark had lower numbers of registered heart defects compared to Sweden and Finland, which could explain the reduced association with lymphomas when these countries were included.

Investigating the association between birth defects and cancer stratified by sex when leaving out one country at a time also gave similar results as those found in the main analyses. The ORs of any cancer ranged between 1.8-2.2 among males and 2.6-3.0 among females. Overall, the pattern of greater effect sizes among females than males was observed as in the main results (Tables 2 and 3). For the mediation analyses (Table 4), the overall percentage mediated ranged between 3.4% to 5.7 % when leaving out one country at a time (4.8% in the overall analysis)..

Additional sensitivity analyses including only children born 1990 onwards yielded similar results (slightly higher ORs due to the younger population). Results were similar to those presented in Figures 1-2 and Tables 2-3. The percentage mediated was slightly higher than in Table 4 (from 4.8% to 7.0%). The sex-cancer association (Supplementary Table S2) was slightly reduced (from 1.16 to 1.12 overall), and similarly, the male-to-female sex ratio for birth defects was lower (from 1.30 to 1.23).

Since the germ cell tumour (GCT) group was heterogeneous and types differed in males and females, we did sensitivity analyses for the results presented in Table 2 in which we excluded GCTs. The overall risk of cancer among children with BDs stratified by sex were similar when excluding germ cell tumours. Including GCT: OR_{Males}=2.1 vs. $OR_{Females}$=2.8, excluding GCT: OR_{Males}=2.0 vs. $OR_{Females}$=2.8.

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Original article

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Cancer risk in the siblings of individuals with major birth defects: a large Nordic population-based case-control study

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Abstract

Background: Individuals with major birth defects are at increased risk of developing cancer, indicating a common aetiology. However, whether the siblings of individuals with birth defects are also at an increased risk of cancer is unclear.

Methods: We used nationwide health registries in four Nordic countries and conducted a nested case-control study. We included 40 538 cancer cases (aged 0–46 years) and 481 945 population controls (matched by birth year and country), born between 1967 and 2014. The relative risk of cancer among individuals whose siblings had birth defects was computed with odds ratios (OR) and 95% confidence intervals (CIs), using logistic regression models.

Results: In the total study population (aged 0–46 years), we observed no overall difference in cancer risk between individuals whose siblings had birth defects and those who had unaffected siblings (OR 1.02; 95% CI 0.97–1.08); however, the risk of lymphoid and haematopoietic malignancies was elevated (1.16; 1.05–1.28). The overall risk of childhood cancer (0–19 years) was increased for siblings of individuals who had birth defects (1.09; 1.00–1.19), which was mainly driven by lymphoma (1.35; 1.09–1.66), neuroblastoma (1.51; 1.11–2.05) and renal carcinoma (5.03; 1.73–14.6). The risk of cancer also increased with the number of siblings with birth defects ($P_{trend} = 0.008$).

Conclusion: Overall risk of cancer among individuals (aged 0–46 years) whose siblings had birth defects was not elevated, but the risk of childhood cancer (ages 0–19 years) was increased. Our novel findings are consistent with the common aetiologies of birth defects and cancer, such as shared genetic predisposition and environmental factors.

Keywords: Neoplasms, abnormalities, epidemiology, aetiology, risk, sibling

Key Messages

- The overall cancer risk for individuals (ages 0 to 46 years) whose siblings have a birth defect is not increased.
- The risk of childhood cancer (ages 0–19 years) is elevated among individuals whose siblings have a birth defect.
- Risks vary by age at cancer diagnosis, type of birth defect and type of cancer.
- There is a dose-response relationship between the number of siblings with birth defects and the risk of developing cancer.
- These findings provide evidence consistent with common aetiologies of birth defects and cancer.

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Introduction

The causes of both childhood cancer and birth defects are largely unknown.[1,2] However, individuals with major birth defects are at an increased risk of cancer, particularly during childhood, indicating a possible common aetiology.[3–6] A common aetiology may also imply that relatives of individuals with birth defects are at an increased cancer risk. Indeed, birth defects are known to have an increased recurrence risk in first-degree relatives.[7–9] Moreover, a history of cancer among first-degree family members is associated with increased risk of some childhood cancers.[10] However, whether the siblings of individuals with birth defects are also at increased risk of cancer is not well understood.[11–13]

Previous studies on the association between birth defects and cancer risk among siblings are mostly inconclusive and underpowered; nevertheless, these studies suggest a lack of an overall association.[11–18] There is, however, more evidence for a link between specific birth defects in individuals and cancer development in their siblings. For instance, the following associations have been reported: (i) cancer development in siblings of individuals affected by defects of the nervous system, or the ear, face, and neck [hazard ratio (HR) = 2.61; 95% confidence interval (CI): 1.60–4.27, and 2.47; 1.46–4.18, respectively][11]; (ii) congenital heart defects in siblings and acute lymphatic leukaemia (odds ratio OR = 2.49; 95% CI: 1.23–5.04)[16]; and (iii) any birth defect in siblings and central nervous system (CNS) tumours (OR = 1.82; 95% CI: 1.25–2.65).[17]

In this population-based case-control study conducted in four Nordic countries, we examined the risk of cancer (from childhood to adulthood) in individuals whose siblings had birth defects, and compared it with the risk of cancer in individuals whose siblings did not have birth defects.

Methods

Data sources

We performed a nested case-control study that combined data from the national population-based health registries of four Nordic countries.[19] The use of unique identifiers made an accurate linkage between the registries of the Nordic countries possible. Information on cancer was retrieved from the cancer registries, and information on emigration and deaths was retrieved from the population registries. Information on birth defects among siblings was obtained from the medical birth registries (all countries) and supplemented with information from the patient registries (inpatient diagnoses during the first year of life in Denmark and Sweden), the Register of Congenital Malformations (in Finland) and the Norwegian Cause of Death Registry; see Supplementary Table S1 (available as Supplementary data at *IJE* online) for additional descriptions of the registries accessed in this study. Information on the identity of fathers was only available in Norway.

Source populations

Cases were defined as individuals recorded in the birth registries from 1977 to 2013 in Denmark, from 1994 to 2013 in Finland, from 1967 to 2013 in Norway and from 1973 to 2014 in Sweden, who had a cancer diagnosis recorded in the cancer registries. Only primary cancer diagnoses were included. Controls were frequency matched (case-control ratio 1:10) by country and birth year; individuals who were alive, residing in the country of birth, and with no cancer diagnosis by the end of follow-up were selected as controls. Cases and controls without siblings or with incomplete sibling records (i.e. those with siblings who were born prior to the establishment of the birth registry), and individuals with a major birth defect, were excluded. We know from previous studies that having a birth defect is a risk factor for cancer, and to be able to separate that effect from the effect of having a sibling with a major birth defect, we included only cases and controls without birth defects.

Classification of cancer

Within the total study population, comprising individuals aged 0–46 years, most cancer cases were classified according to the *International Statistical Classification of Diseases and Related Health Conditions*, 10th Revision (ICD-10).[20] Leukaemia and lymphoma cases were classified according to the *International Classification of Diseases for Oncology*, Third edition (ICD-O-3) morphology codes.[21] Cases with non-malignant neoplasms (except for urinary tract tumours, CNS tumours and other intracranial tumours), without verified morphology (except for CNS and other intracranial tumours), or with basal cell carcinomas, were excluded (see Supplementary Table A in Daltveit *et al.*[3] for details).

In the childhood cancer subpopulation (aged 0–19 years), the cancer cases were additionally grouped according to the *International Classification of Childhood Cancer*, Third edition (ICCC-3) [International Agency for Research on Cancer (IARC) 2017].[22,23] Cases with non-malignant neoplasms (except for groups III and Xa), without verified morphology, or those who were not classified by the ICCC-3, were excluded.

Classification of exposure

The exposure of interest was having a sibling(s) with a birth defect(s). Siblings were defined as individuals sharing the same biological mother. For Norway, analyses for individuals sharing the same mother and father were also carried out. Major birth defects among siblings were classified using ICD-10 codes, according to the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT).[24] Minor congenital anomalies, according to EUROCAT Guide 1.4, Section 3.2, were excluded.[24]

Statistical analysis

We computed ORs with 95% CIs using unconditional logistic regression models. All models were adjusted for the matching factors (i.e. country and birth year). We performed sensitivity analyses adjusting for maternal smoking (information that was not available at the beginning of the study period) and maternal age, using a complete case approach for handling missing data. In addition, cancer risk was evaluated in relation to age at diagnosis, sex and the number of siblings with birth defects (i.e. 0, 1 or ≥2). Tests for linear trends were performed using orthogonal polynomial contrasts.[25] Sensitivity analyses of cancer risk among only full siblings were performed using the Norwegian dataset. All analyses were performed using Stata version 17 software (StataCorp LLC, College Station, TX, USA).

Results

During the study period, we identified 40 538 cancer cases (aged 0–46 years) and 481 945 matched controls (Table 1). The median age at cancer diagnosis was 22 years. The proportions of individuals who had siblings with birth defects was equal between the cases and controls (3.7% in both groups). The most common malignancies in the total study population were lymphoid and haematopoietic malignancies ($n = 9864$), genitourinary cancers ($n = 8112$) and CNS tumours ($n = 7082$) (Figure 1).

A total of 38% ($n = 15\,458$) of the cancer cases were childhood cancers, affecting individuals aged 0–19 years, which were classified using ICCC-3 (Table 1). For this subpopulation, the median age at cancer diagnosis was 8 years; 4% of the childhood cancer cases had siblings with birth defects, versus 3.6% of the controls. The primary childhood cancers were leukaemia ($n = 3962$), CNS tumours (n = 3742) and lymphomas ($n = 1997$) (Figure 2).

Risk of any and specific cancers

Using the ICD-10 classification within the total study population, we observed no overall cancer risk between individuals whose siblings had birth defects and individuals whose siblings did not have birth defects (OR = 1.02; 95% CI: 0.97–1.08) (Figure 1). However, we detected an increased risk of lymphoid and haematopoietic malignancies (1.16; 1.05–1.28), specifically, acute lymphatic leukaemia (1.17; 1.00–1.37), among individuals whose siblings had birth defects.

Using the ICCC-3 classification within the subpopulation of children and adolescents with childhood cancer, we found an overall increased cancer risk for individuals whose siblings had birth defects (1.09; 1.00–1.19), compared with matched controls (Figure 2). In addition, we observed increased risks of lymphoma (1.35; 1.09–1.66), neuroblastoma (1.51; 1.11–2.05), neuroblastoma in combination with ganglioneuroblastoma (1.43; 1.04–1.96) or with other peripheral nervous cell tumours (5.93; 1.70–20.7), and renal carcinoma (5.03; 1.73–14.6); the two latter groups had few exposed cases (<5).

We observed no strong sex differences in the association between having siblings with birth defects and overall cancer risk (Supplementary Tables S2 and S3, available as Supplementary data at *IJE* online). Moreover, adjusting for maternal age and maternal smoking did not impact on the results (data not shown).

Risk of cancer by age at diagnosis

Using the ICD-10 classification within the total study population revealed that the overall association between having a sibling with birth defects and cancer risk was 1.15 (0.99–1.34) in adolescents (aged 15–19 years), 1.07 (0.98–1.17) in children (aged 0–14 years) and 1.00 (0.93–1.08) in adults (aged ≥20 years) (Table 2). Among adults, having a sibling with birth defects was associated with an increased risk of CNS tumours (1.29; 1.05–1.57) and kidney cancer (1.90; 1.10–3.27).

In the subpopulation with childhood cancer classified by ICCC-3, the OR for the development of any cancer was 1.19 (1.01–1.39) among adolescents and 1.06 (0.96–1.17) among children (Table 3). The adolescents had the highest risk of developing neuroblastoma (6.50; 1.84–22.9), renal tumours (4.17; 1.23–14.1) and leukaemia (1.61; 1.08–2.42), specifically acute myeloid leukaemia (2.38; 1.20–4.72). The risk of gonadal tumours was also increased for adolescents who had siblings with birth defects (1.56; 1.03–2.35). Children who had siblings with birth defects were most at risk of developing lymphomas (1.44; 1.09–1.89) and neuroblastomas (1.42; 1.03–1.96). The subgroup of adolescents had higher ORs for most cancers than the subpopulation of children, except for lymphomas (excluding non-Hodgkin lymphoma), malignant melanomas and CNS tumours.

Risk of cancer by the number of siblings with birth defects

Among individuals aged 0–46 years with two or more siblings, the OR for cancer development increased with the number of siblings with birth defects ($P_{trend} = 0.008$) (Table 4). The OR for cancer development in individuals with one sibling with birth defects was 1.02 (95% CI: 0.96–1.09) and was1.42 (1.10–1.86) for individuals with two or more siblings with birth defects, compared with individuals with two or more siblings with no birth defects. A similar trend was observed for lymphoid and haematopoietic malignancies, in particular acute lymphatic leukaemia. For cases with at least two siblings with birth defects, the most common defect among siblings was congenital heart defects (40%), followed by limb defects (32%) (Supplementary Table S4, available as Supplementary data at *IJE* online).

Using the ICCC-3 classification in the subpopulation of children and adolescents revealed that the OR for cancer development in individuals with one sibling with birth defects was 1.06 (95% CI: 0.96–1.17) and 1.38 (0.91–2.11) for individuals with two or more affected siblings ($P_{trend} = 0.13$). Moreover, the OR for leukaemia development increased with number of affected siblings ($P_{trend} = 0.009$).

Risk of cancer and specific birth defects among siblings

Using the ICD-10 classification in the total study population showed that no single specific birth defect was associated with overall cancer risk (Supplementary Table S5, available as Supplementary data at *IJE* online).

The use of the ICCC-3 classification in the subgroup of children and adolescents revealed an increased cancer risk for individuals whose sibling had birth defects affecting the nervous system (1.40; 1.03–1.91) (Supplementary Table S6, available as Supplementary data at *IJE* online). We next investigated the link between the risk of developing childhood cancer and having a sibling with a specific birth defect, and found the following associations: nervous system defects and risk of lymphoma (2.16; 1.11–4.20), genital or urinary defects and germ cell tumours (2.28; 1.13–4.59 and 2.83; 1.17–6.88, respectively) and limb defects and neuroblastoma (1.99; 1.03–3.86) (Supplementary Tables S7 and S8, available as Supplementary data at *IJE* online).

Risk of cancer among full siblings

Sensitivity analyses performed in the Norwegian study population did not indicate large differences in cancer risk between individuals who had maternal siblings with birth defects (n cases with affected siblings = 568) or those who had full siblings with birth defects ($n = 481$). The relative risk of cancer among all Norwegians with maternal siblings with birth defects was 1.07 (0.98–1.17) and 1.13 (1.03–1.24), after exclusion of half-siblings. The same was observed for the childhood cancer cases [maternal siblings ($n = 216$): 1.07 (0.96–1.28) and full siblings ($n = 194$): 1.08 (0.93–1.25)].

Table 1. Population characteristics of the total study population (aged 0–46 years) and the subpopulation of children and adolescents (aged 0–19 years)

	Subpopulation of children and adolescents (aged 0–19 years)		Total study population (aged 0–46 years)	
	Cases[a]	Controls	Cases[b]	Controls
Study population	15 458 (8.9%)	157 329 (91.1%)	40 538 (7.8%)	481 945 (92.2%)
Sibling with major birth defects	612 (4.0%)	5738 (3.6%)	1509 (3.7%)	18 022 (3.7%)
Number of siblings with birth defects				
0	14 846 (96.0%)	151 591 (96.4%)	39 029 (96.3%)	463 923 (96.3%)
1	587 (3.8%)	5552 (3.5%)	1447 (3.6%)	17 490 (3.6%)
≥2	25 (0.2%)	186 (0.1%)	62 (0.2%)	532 (0.1%)
Sex[c]				
Males	8433 (54.6%)	80 934 (51.4%)	19 987 (49.3%)	248 682 (51.6%)
Females	7025 (45.4%)	76 395 (48.6%)	20 551 (50.7%)	233 263 (48.4%)
Birthweight (g)				
<2500	572 (3.7%)	6175 (3.9%)	1530 (3.8%)	18 547 (3.8%)
2500–3999	11 526 (74.6%)	121 921 (77.5%)	31 544 (77.8%)	381 257 (79.1%)
≥4000	3313 (21.4%)	28 863 (18.3%)	7368 (18.2%)	81 059 (16.8%)
Missing	47 (0.3%)	370 (0.2%)	96 (0.2%)	1082 (0.2%)
Gestational age (weeks)				
<37	829 (5.4%)	8100 (5.1%)	2014 (5.0%)	23 675 (4.9%)
37–41	12 869 (83.3%)	131 183 (83.4%)	32 831 (81.0%)	395 167 (82.0%)
≥42	1356 (8.8%)	13 960 (8.9%)	4419 (10.9%)	49 889 (10.4%)
Missing	404 (2.6%)	4086 (2.6%)	1274 (3.1%)	13 214 (2.7%)
In vitro fertilization[d]				
No	7291 (47.2%)	74 669 (47.5%)	8754 (21.6%)	89 553 (18.6%)
Yes	103 (0.7%)	851 (0.5%)	108 (0.3%)	911 (0.2%)
Not collected	8064 (52.2%)	81 809 (52.0%)	31 676 (78.1%)	391 481 (81.2%)
Maternal smoking[e]				
No	7262 (76.0%)	73 728 (75.6%)	10 125 (72.0%)	139 943 (70.3%)
Yes	1587 (16.6%)	16 633 (17.1%)	2647 (18.8%)	40 592 (20.4%)
Missing[f]	711 (7.4%)	7151 (7.3%)	1281 (9.1%)	18 453 (9.3%)
Not collected	6609 (42.8%)	66 968 (42.6%)	27 766 (68.5%)	301 410 (62.5%)
Maternal age (years)				
<25	3996 (25.9%)	44 563 (28.3%)	15 733 (38.8%)	182 548 (37.9%)
25–29	5747 (37.2%)	58 323 (37.1%)	14 685 (36.2%)	177 359 (36.8%)
30–34	4089 (26.5%)	39 617 (25.2%)	7657 (18.9%)	93 408 (19.4%)
≥35	1626 (10.5%)	14 826 (9.4%)	2463 (6.1%)	28 630 (5.9%)
Paternal age (years)[g]				
<25	1063 (6.9%)	11 216 (7.1%)	4725 (11.7%)	43 868 (9.1%)
25–29	2226 (14.4%)	22 886 (14.5%)	6726 (16.6%)	64 168 (13.3%)
30–34	2065 (13.4%)	21 417 (13.6%)	4389 (10.8%)	43 900 (9.1%)
≥35	1511 (9.8%)	15 093 (9.6%)	2540 (6.3%)	26 344 (5.5%)
Missing	8593 (55.6%)	86 717 (55.1%)	22 158 (54.7%)	303 665 (63.0%)
Year of birth				
<1970	215 (1.4%)	2044 (1.3%)	2185 (5.4%)	19 001 (3.9%)
1970–79	1724 (11.2%)	17 863 (11.4%)	14 609 (36.0%)	154 014 (32.0%)
1980–89	3822 (24.7%)	38 277 (24.3%)	12 694 (31.3%)	183 756 (38.1%)
1990–99	5868 (38.0%)	59 135 (37.6%)	7061 (17.4%)	81 841 (17.0%)
2000–09	3408 (22.0%)	35 276 (22.4%)	3558 (8.8%)	38 134 (7.9%)
≥2010	421 (2.7%)	4734 (3.0%)	431 (1.1%)	5199 (1.1%)
Age at cancer diagnosis (years)[h]				
0–4	5755 (37.2%)	–	7188 (17.7%)	–
5–9	2982 (19.3%)	–	3637 (9.0%)	–
10–14	2723 (17.6%)	–	3133 (7.7%)	–
15–19	3998 (25.9%)	–	4345 (10.7%)	–
20–29	–	–	11 385 (28.1%)	–
30–39	–	–	9356 (23.1%)	–
≥40	–	–	1494 (3.7%)	–
Year of cancer diagnosis[h]				
<1980	448 (2.9%)	–	700 (1.7%)	–
1980–89	1343 (8.7%)	–	2630 (6.5%)	–
1990–99	4170 (27.0%)	–	6608 (16.3%)	–
2000–09	6265 (40.5%)	–	16 471 (40.6%)	–
≥2010	3232 (20.9%)	–	14 129 (34.9%)	–

[a] Classified according to the International Classification of Childhood Cancer. Third edition (ICCC-3).
[b] Classified according to the International Statistical Classification of Diseases and Related Health Conditions, 10th Revision (ICD-10).
[c] Differences between cases and controls caused by birth sex ratio and differences in cancer risk for males and females in the study population.
[d] Reported from 1984 onwards in Norway, and from 1995 onwards in Sweden; not included for Denmark.
[e] Information recorded from 1991 onwards in Denmark, from 1998 onwards in Norway and from 1982 onwards in Sweden.
[f] Percentage missing during the time period that this information was available.
[g] Not reported in Sweden.
[h] Only reported for cases.

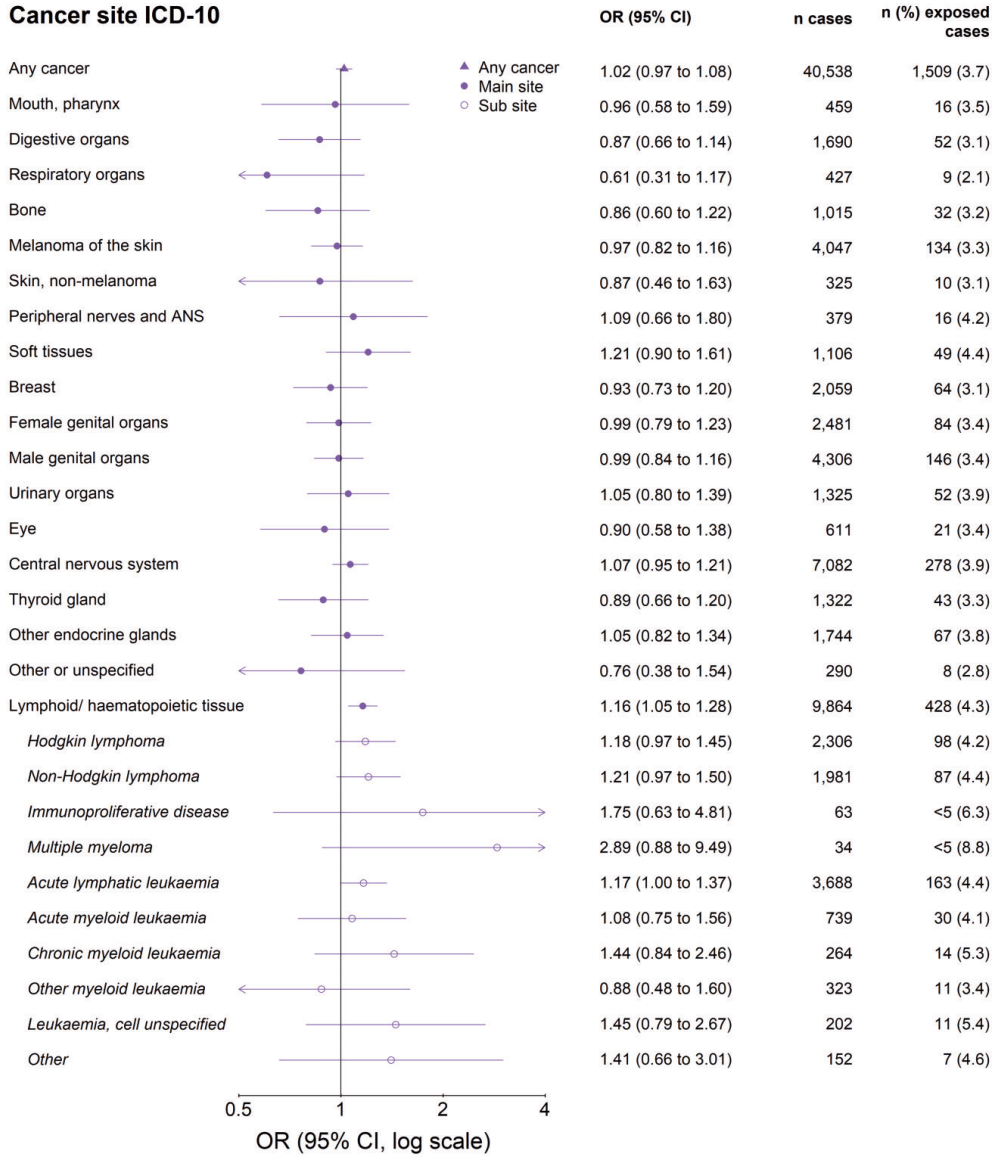

Figure 1. Total or specific cancer risk (according to ICD-10) for individuals (aged 0–46 years) with siblings who had any major birth defect. ORs were adjusted for matching variables (i.e. birth year and country). ICD-10, International Statistical Classification of Diseases and Related Health Conditions, Tenth edition; OR, odds ratio; CI, confidence interval; ANS, autonomic nervous system

Discussion

In this population-based nested case control study, using data from national health registries in four Nordic countries, we observed a 7% and a 15% increase in overall cancer risk among children and adolescents, respectively, whose siblings had birth defects. However, in the total study population of individuals aged 0–46 years, having a sibling with a birth defect did not increase overall cancer risk. Having a sibling with birth defects was instead associated with an increased risk of developing specific malignancies. Individuals whose siblings had birth defects had a 16% increased risk of lymphoid and haematopoietic malignancies. This was observed across all ages (i.e. children, adolescents and adults). In addition, we detected an increased risk of CNS tumours and kidney cancer among adults; an increased risk of neuroblastoma, renal tumours, leukaemia and gonadal tumours among adolescents;

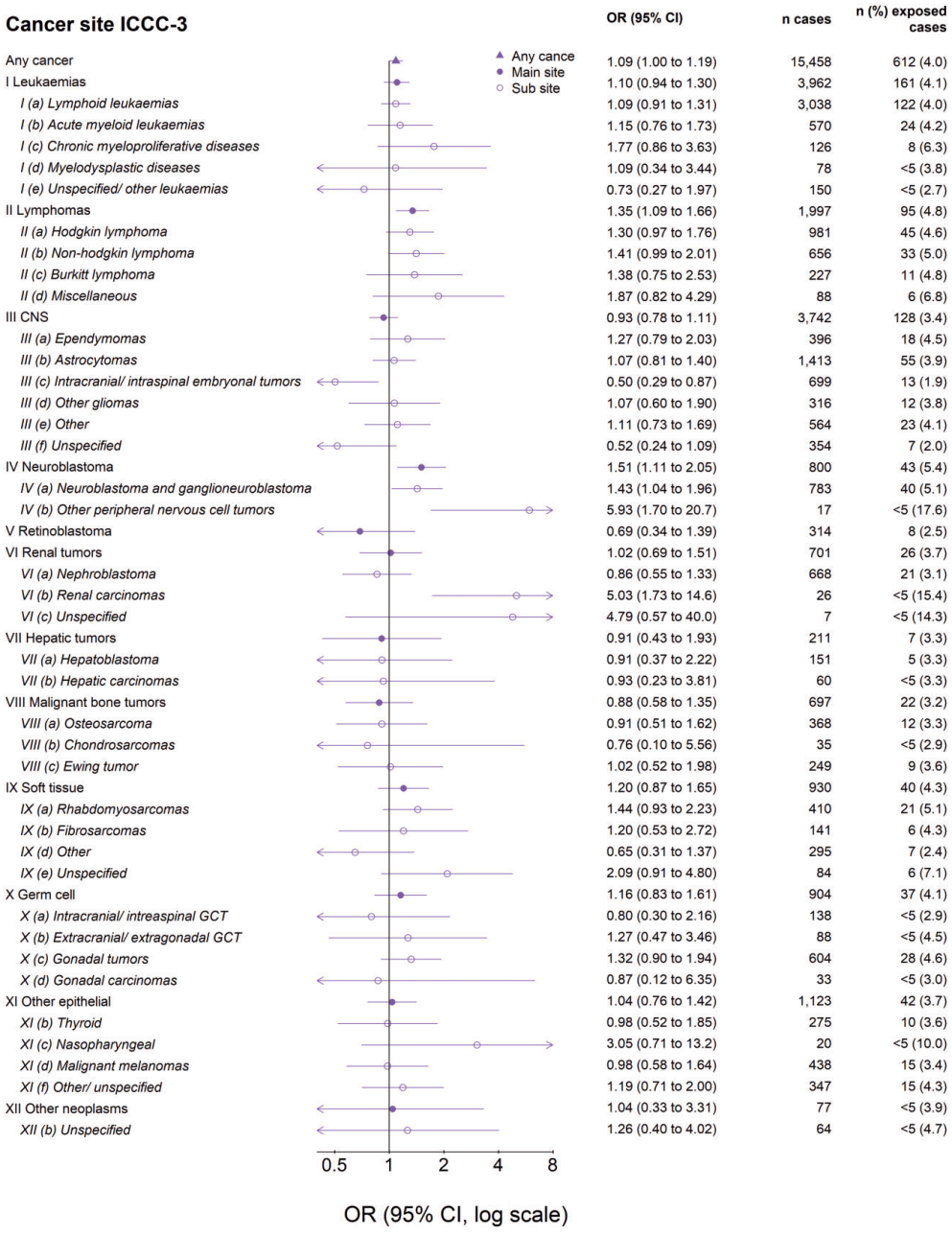

Figure 2. Total or specific childhood cancer risk (according to ICCC-3) for children and adolescents (aged 0–19 years) with siblings who had any major birth defect. ORs adjusted for matching variables (i.e. birth year and country). ICCC-3, International Classification of Childhood Cancer, Third edition; OR, odds ratio; CI, confidence interval; CNS, central nervous system; GCT, germ cell tumour

and an increased risk of lymphomas and neuroblastomas among children. In addition, cancer risk increased with the number of siblings with birth defects. In the total study population, individuals with one sibling with a birth defect had no increase in cancer risk whereass individuals with two or more siblings with birth defects had a 42% increase in

Table 2 Total or specific cancer risk (using the ICD-10 classification) for individuals (aged 0–46 years) with siblings who had any major birth defect, stratified by age at diagnosis

Cancer site (ICD-10[a])	Children (aged 0–14 years)			Adolescents (aged 15–19 years)			Adults (aged ≥ 20 years)		
	Cases	Exposed cases	OR[b] (95% CI)	Cases	Exposed cases	OR[b] (95% CI)	Cases	Exposed cases	OR[b] (95% CI)
Any cancer	13 958	561 (4.0%)	1.07 (0.98–1.17)	4345	183 (4.2%)	1.15 (0.99–1.34)	22 235	765 (3.4%)	1.00 (0.93–1.08)
Mouth, pharynx	100	7 (7.0%)	1.95 (0.90–4.21)	69	5 (7.2%)	2.02 (0.81–5.03)	290	<5 (1.4%)	0.39 (0.14–1.04)
Digestive organs	318	12 (3.8%)	1.01 (0.57–1.80)	132	5 (3.8%)	1.01 (0.41–2.46)	1240	35 (2.8%)	0.83 (0.59–1.16)
Colon	66	5 (7.6%)	2.01 (0.81–5.01)	80	<5 (3.8%)	1.00 (0.31–3.17)	562	20 (3.6%)	1.04 (0.66–1.62)
Rectum, rectosigmoid	<5	0	–	9	0	–	275	8 (2.9%)	0.89 (0.44–1.81)
Liver	234	7 (3.0%)	0.80 (0.38–1.70)	20	<5 (5.0%)	1.42 (0.19–10.6)	81	<5 (2.5%)	0.66 (0.16–2.69)
Respiratory organs	75	0	–	43	<5 (9.3%)	2.84 (1.01–7.97)	309	5 (1.6%)	0.48 (0.20–1.16)
Lung, trachea	25	0	–	26	<5 (11.5%)	3.53 (1.06–11.8)	233	5 (2.1%)	0.63 (0.26–1.52)
Bone	523	16 (3.1%)	0.82 (0.50–1.34)	264	9 (3.4%)	0.92 (0.47–1.79)	228	7 (3.1%)	0.91 (0.43–1.93)
Melanoma of the skin	100	<5 (4.0%)	1.12 (0.41–3.05)	326	11 (3.4%)	0.94 (0.51–1.71)	3621	119 (3.3%)	0.98 (0.81–1.17)
Skin, non-melanoma	44	0	–	39	0	–	242	10 (4.1%)	1.22 (0.65–2.31)
Peripheral nerves and ANS	322	14 (4.3%)	1.13 (0.66–1.94)	24	<5 (4.2%)	1.14 (0.15–8.46)	33	<5 (3.0%)	0.78 (0.11–5.72)
Soft tissues	550	24 (4.4%)	1.16 (0.77–1.75)	177	11 (6.2%)	1.74 (0.94–3.20)	379	14 (3.7%)	1.07 (0.63–1.83)
Breast	<5	0	–	<5	0	–	2055	64 (3.1%)	0.94 (0.73–1.20)
Female genital organs	110	<5 (3.6%)	0.98 (0.36–2.65)	115	<5 (2.6%)	0.70 (0.22–2.21)	2256	77 (3.4%)	1.01 (0.80–1.27)
Cervix, uterus	<5	0	–	5	0	–	1746	58 (3.3%)	0.98 (0.76–1.28)
Ovary etc.	90	<5 (4.4%)	1.19 (0.44–3.25)	102	<5 (2.9%)	0.79 (0.25–2.49)	348	13 (3.7%)	1.08 (0.62–1.88)
Male genital organs	154	<5 (1.9%)	0.52 (0.16–1.62)	414	21 (5.1%)	1.44 (0.93–2.24)	3738	122 (3.3%)	0.96 (0.80–1.15)
Testicular	137	<5 (2.2%)	0.58 (0.19–1.83)	409	21 (5.1%)	1.46 (0.94–2.27)	3703	121 (3.3%)	0.96 (0.80–1.15)
Urinary organs	890	31 (3.5%)	0.92 (0.64–1.32)	43	<5 (7.0%)	1.90 (0.59–6.14)	392	18 (4.6%)	1.37 (0.85–2.20)
Kidney (excluding renal pelvis)	844	27 (3.2%)	0.84 (0.58–1.24)	26	<5 (11.5%)	3.32 (0.99–11.1)	231	14 (6.1%)	1.90 (1.10–3.27)
Eye	532	17 (3.2%)	0.83 (0.51–1.35)	17	0	–	62	<5 (6.5%)	1.84 (0.67–5.07)
Central nervous system	3930	150 (3.8%)	1.02 (0.86–1.20)	836	28 (3.3%)	0.91 (0.63–1.33)	2316	100 (4.3%)	1.29 (1.05–1.57)
Thyroid gland	95	<5 (4.2%)	1.10 (0.40–2.98)	189	8 (4.2%)	1.12 (0.55–2.28)	1038	31 (3.0%)	0.83 (0.58–1.19)
Other endocrine glands	642	28 (4.4%)	1.20 (0.82–1.75)	230	8 (3.5%)	0.92 (0.45–1.86)	872	31 (3.6%)	0.97 (0.68–1.39)
Lymphoid/haematopoietic tissue	5459	243 (4.5%)	1.18 (1.04–1.35)	1403	64 (4.6%)	1.26 (0.98–1.62)	3002	121 (4.0%)	1.15 (0.96–1.38)
Hodgkin lymphoma	370	19 (5.1%)	1.41 (0.89–2.23)	663	28 (4.2%)	1.16 (0.79–1.70)	1273	51 (4.0%)	1.14 (0.86–1.50)
Non-Hodgkin lymphoma	909	46 (5.1%)	1.37 (1.01–1.84)	275	11 (4.0%)	1.13 (0.62–2.06)	797	30 (3.8%)	1.09 (0.76–1.57)
Acute lymphocytic leukaemia	3241	139 (4.3%)	1.13 (0.95–1.34)	256	12 (4.7%)	1.29 (0.72–2.31)	191	12 (6.3%)	1.76 (0.98–3.16)
Acute myeloid leukaemia	453	18 (4.0%)	1.05 (0.66–1.69)	85	5 (5.9%)	1.61 (0.65–3.98)	201	7 (3.5%)	0.97 (0.46–2.07)
Chronic myeloid leukaemia	71	<5 (5.6%)	1.53 (0.56–4.19)	37	<5 (5.4%)	1.40 (0.34–5.82)	156	8 (5.1%)	1.42 (0.70–2.90)
Other myeloid leukaemia	128	<5 (1.6%)	0.41 (0.10–1.67)	44	<5 (9.1%)	2.51 (0.90–7.01)	151	5 (3.3%)	0.85 (0.35–2.07)
Leukaemia, unspecified cell type	164	10 (6.1%)	1.64 (0.86–3.10)	8	0	–	30	<5 (3.3%)	0.88 (0.12–6.45)

ANS, autonomic nervous system; CI, confidence interval; ICD-10, International Statistical Classification of Diseases and Related Health Conditions, Tenth edition; OR, odds ratio.

[a] Subsites with less than five cases in all age groups were excluded.

[b] Adjusted for matching variables (i.e. birth year and country).

cancer risk, indicating a dose-response relationship. Together, these findings provide evidence consistent with common aetiologies of birth defects and cancer, such as a shared genetic predisposition and/or shared environmental factors. Both (epi)genetic and environmental factors have been suggested as common causes of birth defects and cancer, by previous research.[26]

Strengths and limitations

Our study had several strengths, including the use of nationwide population-based registries, with accurate information and close to complete coverage.[19] The study also included a larger sample size than previous studies, which allowed us to investigate relations between specific birth defects and specific cancer types. Moreover, the study included individuals born over a 46-year period, enabling us to investigate cancer risk among children, adolescents and adults.

Our study also had several limitations, such as differences in birth defect ascertainment, which occurred both over time and between countries. In addition, despite the large sample size, investigation of specific combinations of birth defects and cancer types had limited statistical power and multiple comparisons could have yielded spurious associations. We also had limited information on possible confounding factors or common causes other than maternal smoking and maternal age. We excluded cases and controls who themselves had a record of a major birth defect; it is possible that misclassification could have occurred and thus distorted the associations. However, this is unlikely to fully explain the observed associations. In addition, the main analyses were performed for maternal siblings, possibly underestimating the risks we observed. However, sensitivity analyses in the Norwegian dataset revealed no discernible differences between cancer risk associated with birth defects in full siblings and cancer risk associated with birth defects in maternal siblings.

Comparison with other studies

Previous studies have reported no association between having a sibling with a birth defect and overall cancer risk, with two of the studies based on data overlapping with our data.[11,12,14] Our findings for the total study population are consistent with these conclusions. However, we did observe a small increase in overall childhood cancer risk. Increased risk of overall childhood cancer has been suggested previously in a small study by Savitz *et al.*[13]

Table 3 Total and specific childhood cancer risk (calculated using the ICCC-3 classification) in children and adolescents (aged 0–19 years) who had siblings with any major birth defect, stratified by age at diagnosis

Cancer site (ICCC-3)	Children (aged 0–14 years)			Adolescents (aged 15–19 years)		
	Cases	Exposed cases	OR[a] (95% CI)	Cases	Exposed cases	OR[a] (95% CI)
Any cancer	11 460	444 (3.9%)	1.06 (0.96–1.17)	3998	168 (4.2%)	1.19 (1.01–1.39)
I Leukaemia	3523	136 (3.9%)	1.04 (0.88–1.24)	439	25 (5.7%)	1.61 (1.08–2.42)
I (a) Lymphoid leukaemia	2782	110 (4.0%)	1.07 (0.88–1.30)	256	12 (4.7%)	1.33 (0.74–2.37)
I (b) Acute myeloid leukaemia	460	15 (3.3%)	0.88 (0.53–1.48)	110	9 (8.2%)	2.38 (1.20–4.72)
II Lymphomas	1068	55 (5.1%)	1.44 (1.09–1.89)	929	40 (4.3%)	1.23 (0.90–1.69)
II (a) Hodgkin lymphoma	332	17 (5.1%)	1.45 (0.89–2.36)	649	28 (4.3%)	1.23 (0.84–1.79)
II (b) Non-Hodgkin lymphoma	441	22 (5.0%)	1.38 (0.89–2.11)	215	11 (5.1%)	1.50 (0.82–2.75)
II (c) Burkitt lymphoma	180	10 (5.6%)	1.57 (0.83–2.97)	47	<5 (2.1%)	0.59 (0.08–4.26)
II (d) Miscellaneous	79	6 (7.6%)	2.09 (0.91–4.81)	9	0	–
III CNS	3008	108 (3.6%)	0.98 (0.81–1.19)	734	20 (2.7%)	0.74 (0.48–1.16)
III (a) Ependymomas	342	16 (4.7%)	1.30 (0.78–2.14)	54	<5 (3.7%)	1.05 (0.26–4.31)
III (b) Astrocytoma	1166	49 (4.2%)	1.15 (0.86–1.53)	247	6 (2.4%)	0.67 (0.30–1.50)
III (c) Intracranial/intraspinal embryonal tumours	628	12 (1.9%)	0.51 (0.29–0.91)	71	<5 (1.4%)	0.39 (0.05–2.79)
III (d) Other gliomas	231	9 (3.9%)	1.09 (0.56–2.13)	85	<5 (3.5%)	1.00 (0.32–3.17)
III (e) Other	396	15 (3.8%)	1.03 (0.61–1.72)	168	8 (4.8%)	1.31 (0.64–2.67)
III (f) Unspecified	245	7 (2.9%)	0.76 (0.36–1.61)	109	0	–
IV Neuroblastoma	784	40 (5.1%)	1.42 (1.03–1.96)	16	<5 (18.8%)	6.50 (1.84–22.9)
IV (a) Neuroblastoma and ganglioneuroblastoma	773	39 (5.0%)	1.41 (1.02–1.94)	10	<5 (10.0%)	3.19 (0.40–25.3)
V Retinoblastoma	314	8 (2.5%)	0.69 (0.34–1.39)	0	–	–
VI Renal tumours	679	23 (3.4%)	0.93 (0.61–1.41)	22	<5 (13.6%)	4.17 (1.23–14.1)
VI (a) Nephroblastoma	659	20 (3.0%)	0.83 (0.53–1.29)	9	<5 (11.1%)	2.73 (0.34–22.0)
VII Hepatic tumours	191	6 (3.1%)	0.85 (0.38–1.93)	20	<5 (5.0%)	1.45 (0.19–10.8)
VII (a) Hepatoblastoma	150	5 (3.3%)	0.91 (0.37–2.23)	<5	0	–
VIII Malignant bone tumours	443	12 (2.7%)	0.75 (0.42–1.33)	254	10 (3.9%)	1.11 (0.59–2.10)
VIII (a) Osteosarcoma	225	5 (2.2%)	0.61 (0.25–1.48)	143	7 (4.9%)	1.41 (0.66–3.03)
VIII (c) Ewing tumour	171	6 (3.5%)	0.98 (0.43–2.22)	78	<5 (3.8%)	1.08 (0.34–3.43)
IX Soft tissue	676	28 (4.1%)	1.15 (0.79–1.68)	254	12 (4.7%)	1.36 (0.76–2.43)
IX (a) Rhabdomyosarcomas	358	18 (5.0%)	1.41 (0.87–2.26)	52	<5 (5.8%)	1.65 (0.52–5.32)
X Germ cell	344	12 (3.5%)	0.96 (0.54–1.70)	560	25 (4.5%)	1.28 (0.86–1.92)
X (c) Gonadal tumours	157	<5 (2.5%)	0.69 (0.26–1.87)	447	24 (5.4%)	1.56 (1.03–2.35)
XI Other epithelial	366	13 (3.6%)	0.98 (0.56–1.70)	757	29 (3.8%)	1.07 (0.74–1.56)
XI (b) Thyroid	90	<5 (3.3%)	0.89 (0.28–2.82)	185	7 (3.8%)	1.03 (0.48–2.19)
XI (d) Malignant melanomas	103	<5 (3.9%)	1.10 (0.40–2.98)	335	11 (3.3%)	0.94 (0.52–1.72)
XI (f) Other/unspecified	145	6 (4.1%)	1.14 (0.50–2.59)	202	9 (4.5%)	1.23 (0.63–2.40)

CI, confidence interval; CNS, central nervous system; ICCC-3, International Classification of Childhood Cancer, Third edition; OR, odds ratio.
[a] Adjusted for matching variables (i.e. birth year and country).

Table 4 Number of siblings with birth defects and risk of cancer[a]

Cancer site (ICD-10/ICCC-3)	One sibling with birth defects		Two or more siblings with birth defects		
	Cases	OR[b] (95% CI)	Cases	OR[b] (95% CI)	P_{trend}
Total study population (aged 0–46 years)[c]					
Any cancer	1091	1.02 (0.96–1.09)	62	1.42 (1.10–1.86)	0.008
Melanoma of the skin	97	1.04 (0.85–1.28)	6	1.65 (0.73–3.69)	0.23
Female genital organs	67	1.11 (0.86–1.42)	5	2.10 (0.87–5.09)	0.10
Male genital organs	104	0.98 (0.80–1.19)	7	1.65 (0.78–3.48)	0.19
Central nervous system	200	1.02 (0.89–1.18)	8	0.99 (0.49–2.00)	0.99
Lymphoid/haematopoietic tissue	309	1.14 (1.01–1.28)	20	1.76 (1.13–2.76)	0.01
Hodgkin lymphoma	70	1.18 (0.93–1.51)	5	2.09 (0.87–5.06)	0.10
Acute lymphocytic leukaemia	113	1.08 (0.89–1.31)	10	2.26 (1.21–4.26)	0.01
Children and adolescents (aged 0–19 years)[d]					
Any cancer	446	1.06 (0.96–1.17)	25	1.38 (0.91–2.11)	0.13
Leukaemia (ICCC-3 group I)	109	0.99 (0.81–1.20)	11	2.27 (1.23–4.18)	0.009

CI, confidence interval; ICCC-3, International Classification of Childhood Cancer, Third edition; ICD-10, International Statistical Classification of Diseases and Related Health Conditions, 10th Revision; OR, odds ratio.
[a] The reference category is an individual with two or more siblings with no birth defects.
[b] Adjusted for matching variables (i.e. birth year and country).
[c] ICD-10 classification.
[d] ICCC-3 classification. Sites with less than five cases in any of the exposure categories are not included in the table.

Using Danish data, Sun *et al.*[11] reported a 2.6-fold increase in cancer risk for individuals who had a full sibling with a nervous system birth defect. Combining data from four Nordic countries, we observed a 1.4-fold increase in childhood cancer risk for individuals whose maternal siblings were affected by birth defects in the nervous system. Sun *et al.*[11] also reported

a 2.5-fold increase in the risk of developing any cancer for individuals who had a sibling with ear, face and neck birth defects, which was not supported by our data (0.76; 0.28–2.10). Infante-Rivard *et al.*[16] reported a 2.5-fold increase in the risk of developing acute lymphatic leukaemia for children who had siblings with congenital heart defects, but we observed no increase in this risk (0.98; 0.71–1.36). Partap *et al.*[17] observed a 1.8-fold increased risk of childhood CNS tumour among children who had siblings with birth defects, which was also not observed in our study (0.93; 0.78–1.11). Mertens *et al.*[18] found no association between having siblings with birth defects and the risk of acute leukaemia in childhood, consistent with our findings.

The cancer risk associated with having a sibling with birth defects in our study was lower than that of having one's own birth defect observed in the same source population previously (children: OR = 1.1 versus 1.9, adults: OR = 1.0 versus 1.2).[3,6] Having any major birth defect of one's own was associated with an increased risk of several specific cancers,[3,6] but having a sibling with any birth defect was only associated with an increased risk of lymphoid and haematopoietic malignancies (with similar effect estimates: own birth defect: OR = 1.2,[3] sibling with birth defects: OR = 1.16). For childhood cancer, we observed increased risk in three combinations of birth defects and cancers that were present for both own and sibling's birth defects: (i) nervous system defects and any childhood cancer (own: OR = 6.1[3], sibling's: OR = 1.4); (ii) urinary system defects and germ cell tumours (own: OR = 3.9[3], sibling's: OR = 2.8); and (iii) limb defects and neuroblastoma (own: OR = 2.5,[3] sibling's: OR = 2.0). If the common causes of both birth defects and cancer are mostly genetic/environmental risk factors, we would have expected the same association for one's own birth defects as for siblings' birth defects. However, we observed far fewer birth defect-cancer associations between siblings' birth defects compared with one's own defects, and having a birth defect was a stronger risk factor for cancer than having a sibling with a birth defect. This could indicate that many birth defect-cancer associations are linked to prenatal developmental errors, but not all. Assuming that a higher number of siblings with birth defects indicate a higher burden of genetic or persistent environmental risk factors, the observation of increased cancer risk by the number of siblings with birth defects could be compatible with some birth defect-cancer associations being linked to genetic/shared environmental factors. Together, these findings reflect the heterogeneity of both the exposure (birth defect) and outcome (cancer) and the complexity of the relationships that likely involve multiple different combinations of embryonic, genetic/epigenetic and/or persistent environmental risk factors.

Conclusion

We found that although having a sibling with birth defects did not raise the overall cancer risk, the risk of childhood cancer was slightly elevated. In addition, we revealed the existence of a dose-response relationship between the number of siblings with birth defects and the OR for developing cancer. Our novel findings provide evidence consistent with common aetiologies of birth defects and cancer, such as shared genetic predisposition and environmental factors. Further research into possible mechanisms should be pursued.

Ethics approval

The study was approved by the Ethics Committees of Norway (2015/317/REK vest) and Stockholm, Sweden (2015/1642–31/2) and by the Data Protection Agency of Denmark (2015–57-0002). Permission to use health register data in Finland was granted by the Finnish Institute of Health and Welfare after consultation with the Data Protection Authority (THL/68/5.05/2014 and THL/909/5.05/2015).

Data availability

The datasets analysed during the current study cannot be shared because of national data sharing regulations; however, the raw data can be obtained directly from the relevant registries.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

T.B., A.E. and K.K. designed and planned the study. T.B., I.G., M.G. and H.T.S. gained access to the data. D.S.D. performed data analysis and drafted the manuscript with support from T.B., A.E. and K.K. All authors were involved in the interpretation of results, manuscript revision, and approval of the final version.

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Conflict of interest

None declared.

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Supplementary materials

Supplementary Table S1. Description of the registries accessed in this study

Registry	Country	Description	Coding	Supporting references
The Medical Birth Registries	All countries	Contains information on all births in Denmark, Finland, Norway, and Sweden since 1973, 1987, 1967, and 1973, respectively.	Denmark: 1973–1993: ICD-8, since 1994: ICD-10. Finland:1987–1995: ICD-9, since 1996: ICD-10. Norway: 1967–1998: ICD-8 (with some internally generated codes), since 1999: ICD-10. Sweden: 1973–1986: the Swedish versions of ICD-8, 1987–1996: ICD-9, since 1997: ICD-10.	Langhoff-Roos J, Krebs L, Klungsoyr K, *et al*. The Nordic medical birth registers-a potential goldmine for clinical research. *Acta Obstetricia et Gynecologica Scandinavica*. 2014;93(2):132-7.
The National Patient Registries	Denmark and Sweden	Administrative nationwide registries on inpatient care since 1978 in Denmark and 1987 in Sweden.	Corresponding to the Birth Registries.	Ludvigsson JF, Andersson E, Ekbom A, *et al*. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;11:450. Schmidt M, Schmidt SA, Sandegaard JL, *et al*. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:449-90.
The Register of Congenital Malformations	Finland	Contains information on birth defects among live and stillborn infants since 1963.	Since 1986: ICD-9 Atlanta modification. Retrospective inclusion of ICD-10 codes since 2014.	Kiuru-Kuhlefelt S: 2018. Statistical report 36/2021. Finnish Institute for Health and Welfare in Finland, 2021.
The Norwegian Cause of Death Registry	Norway	Contains information on all deaths among Norwegian residents, electronically available since 1951. Available for non-residents since 2012.	ICD-6 1951–1957, ICD-7 1958–1968, ICD-8 1969–1985, ICD-9 1986–1995, ICD-10 onwards.	Pedersen AG, Ellingsen CL. Data quality in the Causes of Death Registry. *Tidsskr Nor Laegeforen*. 2015;135(8):768-770. Published 2015 May 5. doi:10.4045/tidsskr.14.1065
The Cancer Registries	All countries	Covers the entire populations of Denmark, Finland, Norway, and Sweden since 1943, 1953, 1953, and 1958, respectively.	Current coding: ICD-O-3 codes. Previous cancer cases coded with earlier ICD versions (Pukkala *et al*. 2018).	Pukkala E, Engholm G, Hojsgaard Schmidt LK *et al*. Nordic Cancer Registries – an overview of their procedures and data comparability. *Acta Oncologica* (Stockholm, Sweden). 2018;57(4):440-55.
The National Population Registries.	All countries	Administrative registry of the populations of Denmark, Finland, Norway, and Sweden since 1968, 1971, 1964, and 1968, respectively. Contains information on deaths and emigration.	NA	Laugesen K, Ludvigsson JF, Schmidt M, *et al*. Nordic Health Registry-Based Research: A Review of Health Care Systems and Key Registries. *Clinical Epidemiology* 2021; 13: 533-54.

Abbreviations: ICD, International Statistical Classification of Diseases and Related Health Conditions; NA, Not Applicable.

Supplementary Table S2. Relative risk of any and specific cancers (ICD-10) in individuals (ages 0-46 years) with siblings with major birth defects, stratified by sex.

	Males			Females		
Cancer site (ICD-10 main groups)	n cases	n exposed cases	OR (95% CI)	n cases	n exposed cases	OR (95% CI)
Any cancer	19,987	761 (3.8)	1.04 (0.97–1.13)	20,551	748 (3.6)	1.00 (0.93–1.08)
Mouth, pharynx	206	7 (3.4)	0.96 (0.45–2.04)	253	9 (3.6)	0.97 (0.50–1.88)
Digestive organs	859	25 (2.9)	0.82 (0.55–1.22)	831	27 (3.2)	0.91 (0.62–1.34)
Respiratory organs	214	5 (2.3)	0.67 (0.28–1.64)	213	< 5 (1.9)	0.54 (0.20–1.45)
Bone	550	17 (3.1)	0.84 (0.52–1.36)	465	15 (3.2)	0.88 (0.52–1.47)
Melanoma of the skin	1,321	41 (3.1)	0.89 (0.65–1.22)	2,726	93 (3.4)	1.01 (0.82–1.25)
Skin, non-melanoma	169	6 (3.6)	1.01 (0.45–2.29)	156	< 5 (2.6)	0.72 (0.26–1.93)
Peripheral nerves and ANS	196	10 (5.1)	1.33 (0.70–2.52)	183	6 (3.3)	0.84 (0.37–1.89)
Soft tissues	610	26 (4.3)	1.16 (0.78–1.71)	496	23 (4.6)	1.27 (0.83–1.93)
Urinary organs	725	29 (4.0)	1.08 (0.74–1.56)	600	23 (3.8)	1.02 (0.67–1.56)
Eye	313	11 (3.5)	0.92 (0.51–1.68)	298	10 (3.4)	0.87 (0.46–1.63)
Central nervous system	3,745	155 (4.1)	1.12 (0.95–1.32)	3,337	123 (3.7)	1.01 (0.84–1.21)
Thyroid gland	307	10 (3.3)	0.89 (0.47–1.67)	1,015	33 (3.3)	0.89 (0.63–1.26)
Other endocrine glands	717	24 (3.3)	0.92 (0.61–1.39)	1,027	43 (4.2)	1.13 (0.83–1.53)
Other or unspecified	144	5 (3.5)	0.97 (0.40–2.37)	146	< 5 (2.1)	0.56 (0.18–1.77)
Lymphoid/ haematopoietic tissue	5,592	244 (4.4)	1.17 (1.03–1.33)	4,272	184 (4.3)	1.15 (0.99–1.34)

Abbreviations: ICD, International Statistical Classification of Diseases and Related Health Conditions; OR, odds ratio; ANS, autonomic nervous system.

Supplementary Table S3. Relative risk of any or specific childhood cancers (ICCC-3) in children (ages 0-19 years) who had siblings with major birth defects, stratified by sex

	Males			Females		
Cancer site (ICCC-3 main groups)	n cases	n exposed cases	OR (95% CI)	n cases	n exposed cases	OR (95% CI)
Any cancer	8,433	334 (4.0)	1.08 (0.96–1.21)	7,025	278 (4.0)	1.10 (0.97–1.25)
I Leukaemia	2,194	89 (4.1)	1.09 (0.88–1.35)	1,768	72 (4.1)	1.12 (0.88–1.42)
II Lymphomas	1,235	61 (4.9)	1.39 (1.07–1.80)	762	34 (4.5)	1.27 (0.90–1.79)
III CNS	2,009	70 (3.5)	0.94 (0.74–1.20)	1,733	58 (3.3)	0.92 (0.71–1.20)
IV Neuroblastoma	431	26 (6.0)	1.68 (1.13–2.50)	369	17 (4.6)	1.29 (0.79–2.11)
V Retinoblastoma	167	5 (3.0)	0.80 (0.33–1.96)	147	< 5 (2.0)	0.55 (0.18–1.74)
VI Renal tumors	338	10 (3.0)	0.80 (0.42–1.49)	363	16 (4.4)	1.24 (0.75–2.05)
VII Hepatic tumors	127	5 (3.9)	1.07 (0.44–2.61)	84	< 5 (2.4)	0.66 (0.16–2.70)
VIII Malignant bone tumors	367	11 (3.0)	0.83 (0.45–1.51)	330	11 (3.3)	0.95 (0.52–1.73)
IX Soft tissue	513	20 (3.9)	1.08 (0.69–1.68)	417	20 (4.8)	1.36 (0.86–2.13)
X Germ cell	627	26 (4.1)	1.17 (0.79–1.73)	277	11 (4.0)	1.12 (0.61–2.05)
XI Other epithelial	393	10 (2.5)	0.69 (0.37–1.30)	730	32 (4.4)	1.23 (0.86–1.76)
XII Other neoplasms	32	<5 (3.1)	0.82 (0.11–6.04)	45	< 5 (4.4)	1.20 (0.29–4.94)

Abbreviations: ICCC-3, International Classification of Childhood Cancer, 3rd edition; OR, odds ratio; CI, confidence interval; CNS, central nervous system.

Supplementary Table S4. Siblings' specific birth defect among cancer cases with at least two siblings with birth defects.

Siblings' birth defects	All cases (n=62) n (%)	Lymphoid/ hematopoietic tissue cancer cases (n=20) n (%)
Nervous system defects	9 (15)	<5
Neural tube defects	5 (8)	<5
Eye	<5	0
Head	0	0
CHD	25 (40)	9 (45)
Respiratory	<5	0
Oro-facial clefts	5 (8)	<5
CPO	<5	0
CL/P	<5	<5
Digestive system	<5	<5
Abd. wall	<5	<5
Urinary	7 (11)	<5
Genital	11 (18)	6 (30)
Limb	20 (32)	6 (30)
Skeletal dysplasia	0	0
Genetic	0	0
Chromosomal	7 (11)	<5
Down syndrome	5 (8)	<5
Other	16 (26)	8 (40)

Abbreviations: CHD, congenital heart disease; CPO, cleft palate only; CL/P, cleft lip with/ without cleft palate.

Supplementary Table S5. Relative risk of overall cancer (using ICD-10 classification) in individuals with siblings with specific birth defects.

Birth defects[a] among siblings	Total study population (aged 0–46 years)		
	n cases	n controls	OR (95% CI)
Nervous system defects	114 (0.3)	1,181 (0.3)	1.14 (0.95–1.38)
Neural tube defects	61 (0.2)	664 (0.1)	1.09 (0.85–1.41)
Eye defects	24 (0.1)	248 (0.1)	1.16 (0.76–1.76)
Ear, face, and neck	<5 (0.0)	65 (0.0)	0.76 (0.28–2.10)
CHD	421 (1.1)	4,766 (1.0)	1.10 (1.00–1.21)
Respiratory	28 (0.1)	375 (0.1)	0.90 (0.62–1.32)
Oro-facial clefts	109 (0.3)	1,382 (0.3)	0.93 (0.76–1.12)
CPO	29 (0.1)	401 (0.1)	0.86 (0.59–1.25)
CL/P	81 (0.2)	990 (0.2)	0.96 (0.76–1.20)
Digestive system	75 (0.2)	839 (0.2)	1.05 (0.84–1.32)
Abdominal wall defects	20 (0.1)	176 (0.0)	1.25 (0.80–1.97)
Urinary	63 (0.2)	776 (0.2)	0.98 (0.76–1.26)
Genital	169 (0.4)	2,474 (0.5)	0.89 (0.76–1.05)
Limb	242 (0.6)	2,954 (0.6)	0.98 (0.86–1.12)
Skeletal dysplasia	11 (0.0)	110 (0.0)	1.18 (0.63–2.20)
Genetic syndromes and microdeletions	8 (0.0)	108 (0.0)	0.92 (0.52–1.63)
Chromosomal anomalies	109 (0.3)	1,254 (0.3)	1.02 (0.84–1.25)
Down syndrome	87 (0.2)	953 (0.2)	1.07 (0.86–1.33)
Other anomalies/ syndromes	238 (0.6)	2,904 (0.6)	1.01 (0.88–1.15)

[a]Classified by EUROCAT. Abbreviations: CHD, congenital heart disease; CPO, cleft palate only; CL/P, cleft lip with/ without cleft palate.

Supplementary Table S6. Relative risk of overall childhood cancer (using ICCC-3 classification) in individuals with siblings with specific birth defects.

Birth defects[a] among siblings	Childhood cancer (ICCC-3) study population (aged 0–19 years)		
	n cases	n controls	OR (95% CI)
Nervous system defects	36 (0.2)	254 (0.2)	1.40 (1.03-1.91)
Neural tube defects	21 (0.1)	149 (0.1)	1.48 (0.98-2.24)
Eye defects	10 (0.1)	57 (0.0)	1.32 (0.70-2.47)
Ear, face, and neck	< 5 (0.0)	19 (0.0)	0.39 (0.05-2.88)
CHD	164 (1.1)	1,555 (1.0)	1.06 (0.92-1.23)
Respiratory	7 (0.0)	79 (0.1)	0.65 (0.32-1.34)
Oro-facial clefts	35 (0.2)	367 (0.2)	0.92 (0.67-1.26)
CPO	9 (0.1)	114 (0.1)	0.89 (0.50-1.57)
CL/P	27 (0.2)	256 (0.2)	0.95 (0.66-1.39)
Digestive system	27 (0.2)	229 (0.2)	0.96 (0.67-1.39)
Abdominal wall defects	< 5 (0.0)	43 (0.0)	1.33 (0.66-2.66)
Urinary	29 (0.2)	276 (0.2)	0.96 (0.67-1.38)
Genital	55 (0.4)	554 (0.4)	1.06 (0.82-1.37)
Limb	87 (0.6)	804 (0.5)	1.09 (0.89-1.35)
Skeletal dysplasia	< 5 (0.0)	20 (0.0)	1.42 (0.56-3.62)
Genetic syndromes and microdeletions	< 5 (0.0)	26 (0.0)	0.67 (0.27-1.67)
Chromosomal anomalies	51 (0.3)	457 (0.3)	1.14 (0.86-1.53)
Down syndrome	39 (0.3)	330 (0.2)	1.21 (0.87-1.69)
Other anomalies/syndromes	67 (0.4)	612 (0.4)	1.09 (0.87-1.38)

[a]Classified by EUROCAT. Abbreviations: CHD, congenital heart disease; CPO, cleft palate only; CL/P, cleft lip with/ without cleft palate.

Supplementary Table S7. Relative risk of any or specific childhood cancers (ICCC-3 groups) in children who had siblings with any major birth defects, stratified by type of defect among siblings.

Cancer site	OR (95% CI)							
	CHD	Limb defects	Genital defects	Chromosomal anomalies	Orofacial clefts	Urinary system defects	Nervous system defects	Digestive system defects
I Leukaemia	1.00 (0.76 to 1.33)	1.32 (0.92 to 1.89)	1.29 (0.83 to 2.02)	0.95 (0.52 to 1.72)	1.21 (0.71 to 2.06)	1.07 (0.57 to 2.02)	1.19 (0.63 to 2.24)	0.70 (0.31 to 1.57)
a) Lymphoid leukaemia	0.98 (0.71 to 1.36)	1.22 (0.80 to 1.86)	1.36 (0.82 to 2.23)	0.78 (0.37 to 1.65)	1.24 (0.68 to 2.26)	0.97 (0.46 to 2.05)	1.24 (0.61 to 2.50)	0.61 (0.23 to 1.63)
b) Acute myeloid leukaemia	1.30 (0.67 to 2.51)	1.48 (0.61 to 3.58)	0.90 (0.22 to 3.61)	1.20 (0.30 to 4.82)	1.20 (0.30 to 4.83)	1.52 (0.38 to 6.13)	0.82 (0.12 to 5.88)	0.82 (0.11 to 5.84)
II Lymphomas	1.40 (0.98 to 2.00)	1.22 (0.72 to 2.07)	1.45 (0.80 to 2.64)	1.08 (0.48 to 2.42)	0.86 (0.35 to 2.07)	0.49 (0.12 to 1.97)	2.16 (1.11 to 4.20)	1.19 (0.49 to 2.88)
a) Hodgkin lymphoma	1.22 (0.71 to 2.12)	1.77 (0.95 to 3.32)	1.52 (0.68 to 3.42)	1.11 (0.36 to 3.47)	0.70 (0.17 to 2.82)	0.53 (0.07 to 3.79)	1.99 (0.74 to 5.36)	1.00 (0.25 to 4.04)
b) Non-Hodgkin lymphoma	1.20 (0.62 to 2.32)	0.79 (0.25 to 2.47)	1.97 (0.82 to 4.78)	1.10 (0.27 to 4.42)	1.04 (0.26 to 4.19)	0.74 (0.10 to 5.26)	2.99 (1.11 to 8.04)	1.44 (0.36 to 5.80)
c) Burkitt lymphoma	1.97 (0.81 to 4.78)	0.78 (0.11 to 5.60)	-	1.54 (0.22 to 11.0)	1.54 (0.21 to 11.0)	-	-	-
III CNS	0.94 (0.69 to 1.28)	0.98 (0.64 to 1.50)	0.74 (0.41 to 1.34)	1.37 (0.82 to 2.29)	0.72 (0.36 to 1.44)	0.84 (0.40 to 1.77)	1.36 (0.75 to 2.48)	0.62 (0.26 to 1.51)
b) Astrocytoma	1.01 (0.62 to 1.63)	1.07 (0.55 to 2.07)	1.08 (0.48 to 2.41)	1.46 (0.65 to 3.28)	1.42 (0.63 to 3.19)	0.64 (0.16 to 2.59)	1.64 (0.68 to 3.98)	0.99 (0.32 to 3.09)
c) Intracranial/intraspinal embryonal tumors	0.58 (0.24 to 1.41)	0.48 (0.12 to 1.92)	0.37 (0.05 to 2.63)	0.48 (0.07 to 3.44)	-	0.59 (0.08 to 4.21)	1.34 (0.33 to 5.38)	0.64 (0.09 to 4.56)
e) Other	1.17 (0.58 to 2.36)	0.89 (0.28 to 2.77)	0.87 (0.22 to 3.48)	2.47 (0.92 to 6.63)	0.60 (0.08 to 4.31)	0.81 (0.11 to 5.77)	1.72 (0.43 to 6.93)	
IV Neuroblastoma	1.25 (0.71 to 2.22)	1.99 (1.03 to 3.86)	1.06 (0.34 to 3.32)	1.74 (0.65 to 4.67)	1.31 (0.42 to 4.08)	1.57 (0.50 to 4.89)	2.35 (0.87 to 6.33)	1.67 (0.53 to 5.22)
a) Neuroblastoma and ganglioneuroblastoma	1.28 (0.72 to 2.26)	2.03 (1.05 to 3.93)	1.08 (0.35 to 3.38)	1.77 (0.66 to 4.75)	1.33 (0.43 to 4.15)	1.06 (0.26 to 4.26)	2.39 (0.89 to 6.44)	1.13 (0.28 to 4.56)
VI Renal tumors	0.70 (0.31 to 1.56)	0.49 (0.12 to 1.96)	1.14 (0.37 to 3.55)	0.98 (0.24 to 3.94)	0.99 (0.25 to 3.99)	-	1.36 (0.34 to 5.49)	1.93 (0.62 to 6.02)
VIII Malignant bone tumors	1.18 (0.61 to 2.29)	0.73 (0.23 to 2.28)	1.07 (0.34 to 3.33)	1.01 (0.25 to 4.06)	1.46 (0.47 to 4.55)	1.43 (0.36 to 5.76)	-	-
a) Osteosarcoma	1.25 (0.52 to 3.04)	1.39 (0.44 to 4.33)	1.33 (0.33 to 5.36)	0.96 (0.13 to 6.85)	0.91 (0.13 to 6.53)	1.39 (0.20 to 9.96)	-	-
IX Soft tissue	1.51 (0.92 to 2.48)	1.29 (0.61 to 2.72)	0.55 (0.14 to 2.20)	0.38 (0.05 to 2.70)	0.37 (0.05 to 2.64)	1.00 (0.25 to 4.04)	1.04 (0.26 to 4.16)	0.51 (0.07 to 3.64)
a) Rhabdomyosarcoma	1.25 (0.56 to 2.80)	1.69 (0.63 to 4.54)	-	0.86 (0.12 to 6.14)	-	1.07 (0.15 to 7.65)	1.20 (0.17 to 8.56)	-
X Germ cell	0.93 (0.48 to 1.80)	0.95 (0.39 to 2.29)	2.28 (1.13 to 4.59)	0.78 (0.19 to 3.14)	0.37 (0.05 to 2.63)	2.83 (1.17 to 6.88)	2.02 (0.75 to 5.43)	0.54 (0.08 to 3.84)
c) Gonadal tumors	1.27 (0.63 to 2.55)	0.86 (0.28 to 2.68)	2.55 (1.14 to 5.74)	1.18 (0.29 to 4.76)	0.56 (0.08 to 3.97)	3.50 (1.30 to 9.44)	3.06 (1.14 to 8.24)	-
XI Other epithelial	1.11 (0.65 to 1.89)	1.06 (0.50 to 2.23)	0.42 (0.10 to 1.69)	1.91 (0.85 to 4.29)	0.60 (0.15 to 2.41)	0.94 (0.23 to 3.77)	0.87 (0.22 to 3.49)	1.30 (0.42 to 4.07)
f) Other/ unspecified	1.48 (0.66 to 3.32)	0.49 (0.07 to 3.47)	1.39 (0.35 to 5.61)	4.14 (1.54 to 11.1)	-	2.91 (0.72 to 11.7)	-	-

Sites with less than five cases were not included in the table. Sample sizes are shown in Supplementary Table 7. Abbreviations: ICCC-3, International Classification of Childhood Cancer, 3rd edition; OR, odds ratio; CI, confidence interval; CHD, congenital heart disease; CNS, central nervous system

Supplementary Table S8. Number of cases (ICCC-3 groups) with siblings with specific birth defects in the childhood cancer study population.

Cancer site	n (%) exposed cases							
	CHD	Limb defects	Genital defects	Chromosomal anomalies	Orofacial clefts	Urinary system defects	Nervous system defects	Digestive system defects
I Leukaemia	50 (1.3)	31 (0.8)	20 (0.5)	11 (0.3)	14 (0.4)	10 (0.3)	10 (0.3)	6 (0.2)
a) Lymphoid leukaemia	38 (1.3)	22 (0.7)	16 (0.5)	7 (0.2)	11 (0.4)	7 (0.2)	8 (0.3)	< 5 (0.1)
b) Acute myeloid leukaemia	9 (1.6)	5 (0.9)	< 5 (0.4)	< 5 (0.4)	< 5 (0.4)	< 5 (0.4)	< 5 (0.2)	< 5 (0.2)
II Lymphomas	31 (1.6)	14 (0.7)	11 (0.6)	6 (0.3)	5 (0.3)	< 5 (0.1)	9 (0.5)	5 (0.3)
a) Hodgkin lymphoma	13 (1.4)	10 (1.1)	6 (0.6)	< 5 (0.3)	< 5 (0.2)	< 5 (0.1)	< 5 (0.4)	< 5 (0.2)
b) Non-Hodgkin lymphoma	9 (1.4)	< 5 (0.5)	5 (0.8)	< 5 (0.3)	< 5 (0.3)	< 5 (0.2)	< 5 (0.6)	< 5 (0.3)
c) Burkitt lymphoma	5 (2.3)	< 5 (0.5)	0	< 5 (0.5)	< 5 (0.5)	0	0	0
III CNS	42 (1.1)	22 (0.6)	11 (0.3)	15 (0.4)	8 (0.2)	7 (0.2)	11 (0.3)	5 (0.1)
b) Astrocytoma	17 (1.2)	9 (0.7)	6 (0.4)	6 (0.4)	6 (0.4)	< 5 (0.1)	5 (0.4)	< 5 (0.2)
c) Intracranial/intraspinal embryonal tumors	5 (0.7)	< 5 (0.3)	< 5 (0.1)	< 5 (0.1)	0	< 5 (0.1)	< 5 (0.3)	< 5 (0.1)
e) Other	8 (1.5)	< 5 (0.6)	< 5 (0.4)	< 5 (0.7)	< 5 (0.2)	< 5 (0.2)	< 5 (0.4)	0
IV Neuroblastoma	12 (1.6)	9 (1.2)	< 5 (0.4)	< 5 (0.5)	< 5 (0.4)	< 5 (0.4)	< 5 (0.5)	< 5 (0.4)
a) Neuroblastoma and ganglioneuroblastoma	12 (1.6)	9 (1.2)	< 5 (0.4)	< 5 (0.5)	< 5 (0.4)	< 5 (0.3)	< 5 (0.5)	< 5 (0.3)
VI Renal tumors	6 (0.9)	< 5 (0.3)	< 5 (0.4)	< 5 (0.3)	< 5 (0.3)	0	< 5 (0.3)	< 5 (0.4)
VIII Malignant bone tumors	9 (1.3)	< 5 (0.4)	< 5 (0.4)	< 5 (0.3)	< 5 (0.4)	< 5 (0.3)	0	0
a) Osteosarcoma	5 (1.4)	< 5 (0.8)	< 5 (0.6)	< 5 (0.3)	< 5 (0.3)	< 5 (0.3)	0	0
IX Soft tissue	16 (1.8)	7 (0.8)	< 5 (0.2)	< 5 (0.1)	< 5 (0.1)	< 5 (0.2)	< 5 (0.2)	< 5 (0.1)
a) Rhabdomyosarcomas	6 (1.5)	< 5 (1.0)	0	< 5 (0.3)	0	< 5 (0.3)	< 5 (0.3)	0
X Germ cell	9 (1.0)	5 (0.6)	8 (0.9)	< 5 (0.2)	< 5 (0.1)	5 (0.6)	< 5 (0.5)	< 5 (0.1)
c) Gonadal tumors	8 (1.4)	< 5 (0.5)	6 (1.0)	< 5 (0.3)	< 5 (0.2)	< 5 (0.7)	< 5 (0.7)	0
XI Other epithelial	14 (1.3)	7 (0.6)	< 5 (0.2)	6 (0.6)	< 5 (0.2)	< 5 (0.2)	< 5 (0.2)	< 5 (0.3)
f) Other/unspecified	6 (1.8)	< 5 (0.3)	< 5 (0.6)	< 5 (1.2)	0	< 5 (0.6)	0	0

Abbreviations: ICCC-3, International Classification of Childhood Cancer, 3rd edition; CHD, congenital heart disease; CNS, central nervous system

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