Preterm birth, neonatal therapies and the risk of childhood cancer

Seppala, Laura K.

2021-05

Seppala , L K , Vettenranta , K , Leinonen , M K , Tommiska , V & Madanat-Harjuoja , L-M 2021 , ' Preterm birth, neonatal therapies and the risk of childhood cancer ' , International Journal of Cancer , vol. 148 , no. 9 , pp. 2139-2147 . https://doi.org/10.1002/ijc.33376

http://hdl.handle.net/10138/353247
https://doi.org/10.1002/ijc.33376

acceptedVersion

Research article:

Preterm birth, neonatal therapies and the risk of childhood cancer

Authors: Laura K Seppälä

Kim Vettenranta

Maarit K Leinonen

Viena Tommiska

Laura-Maria Madanat-Harjuoja

Corresponding author: Laura K Seppälä, MD, University of Helsinki, Children´s Hospital, Pediatric Research Center, Helsinki, Finland

laura.k.seppala@fimnet.fi

ORCiD ID: https://orcid.org/0000-0003-3028-9127

Twitter account: @LauraSaari

Key words: preterm birth, gestational age, neonatal therapies, childhood cancer, cancer risk

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ijc.33376

Abbreviations:

ADJ= Adjusted

AGA= Appropriate for gestational age

ALL= Acute lymphoblastic leukemia

AML= Acute myeloid leukemia

CNS= Central nervous system

FCR= Finnish Cancer Registry

LGA= Large for gestational age

MBR= Medical Birth Registry

OR= Odds ratio

SGA= Small for gestational age

THL= Finnish Institute for Health and Welfare

Novelty and impact

In this study we show an association with preterm, especially early preterm, birth, and childhood cancer, especially germ cell tumors and retinoblastoma. Neonatal therapies given and/or perinatal hypoxia also seem to be associated with an increased risk of childhood cancer.

Abstract

Our aim was to study the impact of preterm birth and neonatal therapies on the risk of childhood cancer using a nationwide, registry-based, case-control design.

Combining population-based data from Finnish Medical Birth Registry (MBR) and Finnish Cancer Registry (FCR), we identified a total of 2,029 patients diagnosed with cancer under the age of 20 years and 10,103 age- and sex-matched controls over the years 1996-2014. Information on the pre- and perinatal conditions was obtained from the MBR. Gestational age was categorized into early (<32) and late preterm (32-36) and term (≥37 weeks). Cancer risk among the preterm compared to term neonates was evaluated using conditional logistic regression.

We identified 141 cancers among the preterm (20.8% of 678) vs. 1888 cancers in the term children (16.5% of 11,454). The risk of any cancer was increased for the preterm (OR 1.28, 95% CI 1.06- 1.57), especially for the early preterm (OR 1.84, 95% CI 1.16-2.92).

The risk of AML (OR 2.33, 95% CI 1.25-4.37), retinoblastoma (OR 3.21, 95% CI 1.22-8.41) and germ cell tumors (OR 5.89, 95% CI 2.29-15.18) was increased among the preterm compared to term. Germ cell tumors were diagnosed at a significantly younger age among the preterm. Neonatal therapies, e.g. mechanical ventilation, were associated with an increased risk of childhood cancer independent of gestational age.

Preterm, especially early preterm birth is associated with an increased risk of childhood cancer, especially germ cell tumors and AML. Respiratory distress requiring neonatal intervention also appears to be associated with an increased risk.

Introduction

Both the morbidity and mortality among preterm infants have decreased due to advances in therapies such as ventilatory support, antenatal steroids and surfactant.[1,2] Although many of the long-term effects of preterm birth and the respective treatments have been explored, the risk of malignancy remains poorly delineated. Oxidative stress inflicted early on in life has been shown to cause bronchopulmonary dysplasia and retinopathy[3–7] and be potentially carcinogenic.[8] Preterm infants are also exposed to diagnostic x-rays during the first weeks of life,[9,10] a well-established risk factor for cancer.[11,12] Furthermore, there is also evidence that preterm children have more complications, such as neurological adverse outcomes, later in life.[13–15]

Aside from ionizing radiation and a high birth weight,[16] the etiology of childhood cancer remains enigmatic. Hereditary cancer predisposition syndromes are estimated to account only for up to 5-10% of all childhood cancers [17–19] with an accelerated pace of malignant development.[20,21]

The risk of developing childhood cancer after having been born preterm has been studied previously.[22–28] Certain subtypes of childhood cancer, i.e. hepatoblastoma[27–30] and AML,[31,32] have been found to be associated with preterm birth. The possible association between other childhood cancers and preterm birth, however, remains inconclusive.[28] Yet, most studies have been limited by sample size and unable to differentiate impacts rendered by early or late preterm birth. Neither has the possible impact of perinatal interventions and conventional therapies been fully explored in a registry-based setting.[23]

Using a case-control design in a population-based, nationwide registry setting, we aimed to study the relationship between a preterm birth, neonatal therapies, and the risk of childhood cancer.

aterials and methods

The use of a unique personal identity code, given to each Finnish citizen since 1967, allows for the compilation of data from a host of health registries.

The Finnish Cancer Registry (FCR) commenced the systematic, nationwide registration of cancer in 1953 and includes comprehensive data on the patients, cancer, possible date and cause of death

(all causes) of all cancer cases diagnosed in individuals living in Finland at the time of diagnosis. The FCR has a 95% coverage for all cancers,[33] and the respective completeness of data for childhood cancer is 92% for solid tumors and 97% for leukemia.[34]

The Finnish Medical Birth Registry (MBR), maintained by the Finnish Institute for Health and Welfare (THL), includes information on all babies born in Finland from 1987 onwards. It also includes information on the pregnancies, pre- and perinatal conditions, neonatal therapies (mechanical ventilation, resuscitation right after birth, phototherapy, antibiotics and antenatal steroids) and diagnoses set by the age of seven days. Data are reported to THL directly from all delivery units or by the midwife or physician assisting in the delivery. The data provided by hospitals are checked and any missing or seemingly incorrect entries are confirmed by contacting the respective unit. The MBR has been validated earlier and the quality of the data considered, depending on the variable, good or satisfactory (over 95% agreement with information from the medical records)[35,36] with those for under 1% of all births missing.[35,37] Data is further supplemented by the Population Register Center on live births and Statistics Finland on stillbirths and deaths during the first year of life.[38]

The relevant research permits were obtained from the THL and Helsinki University Hospital. No ethical board approval was required for this registry-based study.

Study population

We identified all cases, defined as individuals diagnosed with their first malignancy under the age of 20 years between the years 1996 and 2014 (n=2,037) from the FCR. The MBR was used to identify

all births during the aforementioned years (n=1 108 754) including five sex- and birth year-matched controls for each case (1:5) (n=10,185). Data on the perinatal conditions, neonatal therapies and diagnoses up to seven days of age or at hospital discharge were obtained from the MBR for both the cases and controls. For detailed information on the data linkage, see *Figure 1.* The cases and controls are described in *Table 1*.

Exposure definition and classification

In this study, the exposure, i.e. preterm birth, was defined as one occurring before 37 gestational weeks (WHO definition).[39] We further defined an early preterm birth as one occurring before 32 and a late preterm birth as one occurring between 32+0 and 36+6 gestational weeks according to the most common definition.[40] The gestational age was thus categorized into three groups: early (<32 weeks) and late preterm (32-36 weeks) and term (≥37 weeks). The reference group, or the unexposed, were pregnancies resulting in a term birth (≥37 gestational weeks). The gestational age was defined by the best clinical estimate, primarily by ultrasound or the last menstrual period recorded in the MBR. The duration of pregnancy ranged from 24 to 43 gestational weeks.

Outcome definition and classification

The outcome, a primary diagnosis of cancer under the age of 20 years, was defined as a malignant neoplasm, but also included benign or borderline tumors of the central nervous system (CNS). The FCR uses both the ICD-O-3 and ICCC3 to classify childhood cancers.[41] In this study, malignancies were classified using the ICCC3-codes 011 for ALL, 011-015 for all leukemias, 021-025 for

lymphomas, 031-036 for CNS tumors and 041-122 for the other cancers further categorized using the codes 041-042 for neuroblastomas, 050 for retinoblastoma, 061-063 for renal tumors, 071-073 for hepatic tumors, 081-085 for bone tumors, 091-095 for soft tissue sarcomas, 101-105 for germ cell tumors and 111 and above for other, non-specified solid tumors.

Statistical analysis

Analyses were performed with the Stata MP14 (StataCorp LLC) using conditional logistic regression modelling to estimate the risk of childhood cancer. We compared the preterm births to those at term and estimated the odds ratios (ORs) for childhood cancer using crude and adjusted models. For the latter we adjusted for the maternal age (<25, 25-29, ≥30 years), parity (1^{st}, $\geq 2^{nd}$), and smoking status during pregnancy (yes/no). The cases and controls with missing data on smoking were omitted from the adjusted analyses (2.9% and 2.5%, respectively). Since both a low and high birth weight have been considered risk factors for childhood cancer, but with the birth weight in the preterm and term groups being differently distributed, it was not included in the adjusted model. Instead, one sensitivity analysis adjusting for the birth weight for gestational age, and a second one for birth weight only, were conducted *(Appendix 1).* SGA was defined as having a birth weight below the 10^{th} percentile, AGA as a birth weight between the 10^{th} and 90^{th} percentile, and LGA as a birth weight above the 90^{th} percentile compared with infants of the same sex and of the same gestational age at birth using national birth weight statistics.[42] We also analyzed the risk by cancer subtype and used the Mann-Whitney t-test to study the calendar age at cancer diagnosis.

Furthermore, as secondary exposures of interest, we included key perinatal conditions and therapies, namely, asphyxia during delivery (low umbilical vein pH during delivery, pathological cardiotocography, ICD-10-code O68 indicating compromised fetal acid-base balance during delivery) or after birth (low umbilical artery pH, ICD-10 code P20 until 2012, P21 thereafter, indicating neonatal asphyxia), a low Apgar-score (less than 7 at 1 or 5 minutes), and mechanical ventilation, resuscitation, phototherapy, antibiotic therapy given to child until 7 days of age and administration of antenatal steroids, in our analyses. Information on the Apgar score at 5 minutes was missing for the majority (67%) of cases and controls and was more likely to be missing if the 1 min Apgar score was high (68% missing if ≥7 vs 57% missing if <7), and thus this variable was omitted from the subgroup analysis.

Results

A total of 141 cancers were identified among the preterm (20.8% of 678) vs. 1888 in the control group born at term (16.5% of 11,454).

We found the crude OR for childhood cancer for the preterm compared to term to be significantly increased up to 1.33 (95% CI 1.10-1.61). The risk remained elevated even after adjusting for maternal age, parity and smoking status (adjusted OR 1.28, 95% CI 1.06-1.57) *(Table 2).*

The risk of childhood cancer was even higher for the preterm children born before 32 gestational weeks. The crude OR for an early preterm birth was 1.79 (95% CI 1.15-2.77) compared to term children and remained elevated even after adjustment (1.84, 95% CI 1.16-2.92). For the late preterm

children, a seemingly elevated risk was observed, but, after adjustment, it no longer remained significant *(Table 2).*

In a sensitivity analysis also adjusting for the birth weight for gestational age (SGA, AGA or LGA), the OR remained increased in each group for the preterm compared to term (adjusted OR 1.29, 95% CI 1.06-1.57) and adjusting with birth weight the risk estimates were slightly increased (adjusted OR 1.48, 95% CI 1.18-1.85) *(Appendix 1).* For the late preterm the adjusted OR was 1.20 (95%CI 0.97-1.50) and for the early preterm 1.85 (95% CI 1.16-2.93), respectively.

The risk of lymphoma, CNS tumor or any leukemia was not increased in our study. However, the risk of AML was significantly elevated among the preterm (adjusted OR 2.33, 95% CI 1.25-4.37) as shown in Table 3 and particularly among the early preterm (adjusted OR 4.47, 95% CI 1.10-18.12) *(Appendix 2).* Also, the risk of a non-CNS, solid tumor was significantly increased among the preterm compared to term (adjusted OR 1.59, 95% CI 1.16-2.19) *(Table 3),* again peaking among the early preterm (adjusted OR 4.01, 95% CI 1.97-8.16) *(Appendix 2).*

To explore solid tumors in more detail, we performed subgroup analyses for the other cancers. For the preterm, we found the overall risk of retinoblastoma to be increased compared to the term children (adjusted OR 3.21, 95% CI 1.22-8.41). Especially the risk of germ cell tumors was increased after having been born preterm (adjusted OR 5.89, 95% CI 2.29-15.18). It also appeared increased for hepatoblastoma *(Table 3).*

Among the cancer subtypes with an elevated risk, we set out to explore the calendar age at cancer diagnosis using the Mann-Whitney t-test. In our study population there were no patients with retinopathy of prematurity and retinoblastoma. The median calendar age at retinoblastoma diagnosis was 1.13 years for the preterm and 1.04 years for term children (p=0.002). As the distribution of calendar ages at diagnosis is unequal, we also reanalyzed the differences with the correct t-test and report the medians instead of means *(Table 4)*.

For the preterm, 92% (11/12) of the germ cell tumors were classified as malignant extracranial and extragonadal, with one being intracranial. For the term, the majority (58%) were classified as malignant gonadal germ cell tumors, followed by 23% extracranial and -gonadal. 11/12 of these in the preterm group were diagnosed before 1 year of age, supporting the hypothesis of a varying pathogenesis of these tumors among the term and preterm children, respectively.

Respiratory distress requiring mechanical ventilation in the neonatal period appeared to be associated with an increased risk of childhood cancer among all the neonates (adjusted OR 2.69, 95% CI 1.89-3.84) as did resuscitation at birth (adjusted OR 1.84, 95% CI 1.21-2.80) compared to those not requiring the above. Severe respiratory distress, or associated conditions, were also significantly associated with an increased risk among the term children (adjusted OR 2.99, 95% CI 1.70-5.28). The administration of antenatal steroids to the mother was also associated with an increased risk of childhood cancer (adjusted OR 2.53, 95% CI 1.64-3.88) while phototherapy was not. Antibiotic therapy given to the neonate in 7 days after birth was associated with higher

childhood cancer risk (adjusted OR 1.40, 95% CI 1.13-1.74). This association was not seen in the analyses of preterm children *(Table 5).* The subgroup analysis for neonatal therapies on early and late preterm children was only possible for late preterm, trending towards the increased cancer risk after respiratory distress and mechanical ventilation also in this group (*Appendix 3)*.

As further surrogate markers for perinatal hypoxia, we analyzed the possible association of a low 1min Apgar score (<7) compared to one above 7 at 1 min with the risk of childhood cancer for those with data available. The adjusted OR for a low Apgar score at 1 min was 1.32 (95% CI 1.07-1.61) for all the newborn compared to those with a high score *(Table 6)*.

Discussion

Our aim was to study whether preterm birth impacts the risk of childhood cancer defined as a malignant disease diagnosed prior to the age of 20 years. We also aimed at exploring if early preterm children are at an increased risk of childhood cancer. Furthermore, we wanted to investigate the potential impact of key perinatal factors and neonatal interventions.

We found the overall risk of childhood cancer to be increased among the preterm compared to term with a more pronounced risk of the early preterm children. When looking at the cancer subtypes, we found the risk of non-CNS solid tumors to be increased, in line with previous studies.[23–25,27,28,30,43,44] A few have found the risk of CNS tumors to be increased,[22,45,46] a finding our results did

not corroborate. We also found the risk of AML to be increased, again confirming results previously published.[31,32]

Yet, and unlike previous studies, we found a strong association between preterm birth and later diagnosis of a germ cell tumor or retinoblastoma. For hepatic tumors we were hampered by the low numbers with only three cases in our preterm population, but the OR was suggestive of an elevated risk. The risk of other childhood cancer subtypes was not significantly increased.

There are only a few cases published describing the development of retinoblastoma after retinopathy of prematurity.[47,48] The increased risk of retinoblastoma in our study suggests that a preterm birth per se, and/or an early exposure to high supplementary oxygen may contribute, not only to the development of retinopathy, but also that of retinoblastoma. Our results are in concordance with those of Spector et al., who also found the risk of retinoblastoma increased in a larger dataset with a very low birth weight and/or preterm birth.[27] The putative impact of germline mutations [49–51] could not be assessed in our cohort in the absence of the relevant data.

It has been postulated that early disturbances in the fetal sex hormone balance might be linked to an increased risk of germ cell tumors later in life.[52] Preterm infants, especially boys, have been shown to have altered levels of sex hormones compared to the term,[53] possibly predisposing them to tumors. Previous studies have reported varying results on preterm birth and its possible association with germ cell tumors.[54,55] Our results support those from a large Swedish registry

study,[54] linking preterm birth to germ cell tumors. The germ cell tumor subtypes differ among preterm children as opposed to term, with the majority being diagnosed before 1 year of age, raising the possibility that the malignant process may play a role in the premature birth itself by sharing the same epigenetic pathway.[56] Though, in a registry-based setting it is impossible to study this type of causality and it needs to be addressed in further studies.

We found neonatal clinical problems requiring mechanical ventilation and/or resuscitation to be associated with an increased risk of childhood cancer among all the neonates, independent of gestational age. Yet, these need to be considered only as surrogate markers of hypoxia, and supplementary oxygen only as potentially carcinogenic.[8] Our finding on the impact of a low Apgar score also supports this hypothesis with the main reason for the low scores being short- or long-term, perinatal hypoxia.[57] Mechanical ventilation can also be seen as a proxy for iatrogenic radiation, e.g. x-rays, a known carcinogenic risk factor,[11,12] as intubated neonates are subjected to diagnostic radiation.

We also found an association between the risk of childhood cancer and neonatal antibiotic therapy with the respective results having been controversial in previous studies.[58–61] To our knowledge ours is the first study looking specifically at early neonatal exposure to antibiotics in an unbiased registry-based setting with the previous studies looking at maternal antibiotic use or infections as such. The role of neonatal septic infection vs. treatment or prevention of suspected infections in the background of childhood cancer remains to be delineated.

There is one previous study exploring neonatal therapies (surfactant, nitric oxide, postnatal steroids and indomethacin) given to preterm neonates and their association with childhood cancer.[23] Our study also adds to the existing literature by exploring cancer risk after conventional neonatal therapies given to all sick neonates, and with a longer follow-up and almost double the amount of cases has more power to explore the association.

Furthermore, we found antenatal steroid treatment to be associated with an increased risk of childhood cancer. The mechanism behind this may be the same as that of prematurity itself with most of these mothers having delivered preterm babies. The background of these associations, however, remains currently unknown and the lifesaving nature of the perinatal therapies needs to be assessed when interpreting these results. Our results highlight the need to avoiding hypoxia during pregnancy and the management of deliveries according to the highest obstetric standards, and may be applied in the setting of mainly designing follow-up of these neonates.[14,57]

In addition to prematurity itself, our novel finding of an earlier age at the diagnosis of a germ cell tumor among preterm children does not exonerate the altered sex hormone levels[53] or treatments of a potential role in the pathogenesis of childhood cancer. The earlier age at the diagnosis of AML further supports our hypothesis that preterm birth itself is associated with childhood cancer and the development of cancer differs from children born at term.

Both a low and high birth weight have been considered risk factors for childhood cancer. Yet, birth weight in our term and preterm groups were differently distributed and grossly overlapping and thus birth weight was not included in the first adjusted model. Instead, we employed weight for gestational age as an improved estimate of size at birth. To avoid possible over-adjustment, we also ran a second sensitivity analysis including only birth weight, but with the birth weight and preterm birth being correlated these estimates need to be interpreted with caution.

The definitive strength of our study is the comprehensive, registry-based, nationwide dataset with a long follow-up, avoiding selection and recall bias with virtually no loss to follow-up. We also had access to details on the pre- and perinatal care as well as therapies administered allowing us to define exposures more accurately than previously reported. To our knowledge, this is the first study to demonstrate an association between neonatal hypoxia and/or use of supplementary oxygen and childhood cancer.

Our study also has some definite limitations. Due to a small sample size, our estimates on the risk of solid tumors need to be confirmed using larger datasets or, e.g., combining data from the other Nordic countries. Lack of data on the exact doses of diagnostic radiation and those on the antenatal steroids prevented the evaluation of a dose-response. Furthermore, we didn´t have information on the possible birth defects, known to be associated with both childhood cancer and preterm birth, and thus the effect of this potential confounder could not be accounted for.[62] Nor did we have relevant genetic information on germline mutations , and thus could not assess the possible

contribution of hereditary predisposition syndromes in, e.g., retinoblastoma.[63,64] Due to the obvious correlation between preterm birth and measures of neonatal intensive care, there is a risk of confounding by indication rendering it challenging to analyze causality of preterm birth and therapies in this registry-based setting.

Conclusion

The risk of childhood cancer is increased among children born prematurely, especially following an early preterm birth. The risk of AML and solid tumors, especially germ cell tumors and retinoblastoma, appears increased, but the underlying biology remains to be delineated. Our data may also implicate neonatal intensive care, including the use of supplementary oxygen, at any gestational age, in contributing to the increased risk for childhood cancer. We suggest the apparent risk to be included in planning the follow-up of these children.

Conflict of interest

Dr. Leinonen has received a grant from the Innovative Medicines Initiative (IMI ConcePTION, grant agreement number 821520) during preparation of this manuscript.

Dr. Seppälä has received a grant from the Väre Foundation, Finland, to prepare this manuscript as part of her PhD studies. The funding bodies had no role in preparation on this study.

Ethics statement

This study being fully registry-based, no ethical board approval was needed.

Data Availability Statement

According to the national data protection legislation, the permission to obtain the data must be applied for from Findata (https://www.findata.fi/en/). Further information is available from the corresponding author upon request.

Acknowledgements

We would like to thank statistician, Ms. Elli Hirvonen from the Finnish Cancer Registry (FCR) for helping us to prepare the data before analysis and PhD, Professor Janne Pitkäniemi from the FCR for statistical guidance.

References

1. Feng Y, Abdel-Latif ME, Bajuk B, Lui K, Oei JL. Causes of death in infants admitted to Australian neonatal intensive care units between 1995 and 2006. *Acta Paediatr* 2013; 102(1):e17-e23.
2. Patel RM, Kandefer S, Walsh MC, Bell EF, Carlo WA, Laptook AR, Sánchez PJ, Shankaran S, Van Meurs KP, Ball MB, Hale EC, Newman NS, et al. Causes and timing of death in extremely premature infants from 2000 through 2011. *N Engl J Med* 2015; 372(4):331-340.
3. Shahzad T, Radajewski S, Chao C-M, Bellusci S, Ehrhardt H. Pathogenesis of bronchopulmonary dysplasia: when inflammation meets organ development. *Mol Cell Pediatr* 2016; 3(1):23

4. Weinberger B, Laskin DL, Heck DE, Laskin JD. Oxygen toxicity in premature infants. *Toxicol Appl Pharmacol* 2002; 181(1):60-67.

5. Stenson BJ, Tarnow-Mordi WO, Darlow BA, Simes J, Juszczak E, Askie L, Battin M, Bowler U, Broadbent R, Cairns P, Davis PG, Deshpande S, et al. Oxygen saturation and outcomes in preterm infants. *N Engl J Med* 2013; 368(22):2094-2104.

6. Cherian S, Morris I, Evans J, Kotecha S. Oxygen therapy in preterm infants. *Paediatr Respir Rev* 2014; 15(2):135-141.

7. Cummings JJ, Lakshminrusimha S, Polin RA. Oxygen-saturation targets in preterm infants. *N Engl J Med* 2016; 375(2):186-187.

8. Naumburg E, Bellocco R, Cnattingius S, Jonzon A, Ekbom A. Supplementary oxygen and risk of childhood lymphatic leukaemia. *Acta Paediatr* 2002; 91(12):1328-1333.

9. Iyer NP, Baumann A, Rzeszotarski MS, Ferguson RD, Mhanna MJ. Radiation exposure in extremely low birth weight infants during their neonatal intensive care unit stay. *World J Pediatr* 2013; 9(2):175-178.

10. Puch-Kapst K, Juran R, Stoever B, Wauer RR. Radiation exposure in 212 very low and extremely low birth weight infants. *Pediatrics* 2009; 124(6):1556-1564.

11. Mullenders L, Atkinson M, Paretzke H, Sabatier L, Bouffler S. Assessing cancer risks of low-dose radiation. *Nat. Rev. Cancer* 2009; 9(8):596-604

12. Nikkilä A, Raitanen J, Lohi O, Auvinen A. Radiation exposure from computerized tomography and risk of childhood leukemia: Finnish register-based case-control study of childhood leukemia (FRECCLE). *Haematologica* 2018; 103(11):1873-1880.

13. Marlow N, Wolke D, Bracewell MA, Samara M. Neurologic and developmental disability at six years of age after extremely preterm birth. *N Engl J Med* 2005; 352(1):9-19.

14. Ream MA, Lehwald L. Neurologic Consequences of Preterm Birth. *Curr Neurol Neurosci Rep* 2017; 18(8):48.

15. Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. *N Engl J Med* 2008; 359(3):262-273.

16. Paltiel O, Tikellis G, Linet M, Golding J, Lemeshow S, Phillips G, Lamb K, Stoltenberg C, Håberg SE, Strøm M, Granstrøm C, Northstone K, et al. Birthweight and childhood cancer: Preliminary findings from the international childhood cancer cohort consortium (I4C). *Paediatr Perinat Epidemiol* 2015; 29(4):335-345.

17. Lichtenstein P, Holm N V., Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A, Hemminki K. Environmental and heritable factors in the causation of cancer: Analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* 2000; 343(2):78-85.

18. Narod SA, Lenoir GM, Stiller C. An estimate of the heritable fraction of childhood cancer. *Br J Cancer* 1991; 63(6):993-999.

19. Stiller CA. Epidemiology and genetics of childhood cancer. *Oncogene* 2004; 23:6429–44.

20. Bayoumy M, Wynn T, Jamil A, Kahwash S, Klopfenstein K, Ruymann F. Prenatal presentation supports the in utero development of congenital leukemia: A case report. *J Pediatr Hematol Oncol* 2003; 25(2):148-152

21. Sato Y, Izumi Y, Minegishi K, Komada M, Yamada S, Kakui K, Tatsumi K, Mikami Y, Fujiwara H, Konishi I. Prenatal findings in congenital leukemia: A case report. *Fetal Diagn Ther* 2011;

29(4):325-330.

22. Mellemkjær L, Hasle H, Gridley G, Johansen C, Kjær SK, Frederiksen K, Olsen JH. Risk of cancer in children with the diagnosis immaturity at birth. *Paediatr Perinat Epidemiol* 2006; 20(3):231-237.

23. Dixon F, Ziegler DS, Bajuk B, Wright I, Hilder L, Abdel Latif ME, Somanathan A, Oei JL. Treatment with nitric oxide in the neonatal intensive care unit is associated with increased risk of childhood cancer. *Acta Paediatr* 2018;107(12):2092–2098.

24. Sonke GS, Chang S, Strom SS, Sweeney AM, Annegers JF, Sigurdson AJ. Prenatal and perinatal risk factors and testicular cancer: a hospital-based case-control study. *Oncol Res* 2007;16(8):383-387. Available from: http://dx.doi.org/10.3727/000000006783980928

25. Lupo PJ, Luna-Gierke RE, Chambers TM, Tavelin B, Scheurer ME, Melin B, Papworth K. Perinatal and familial risk factors for soft tissue sarcomas in childhood through young adulthood: A population-based assessment in 4 million live births. *Int J Cancer* 2019; 146(3):791-802.Available from: http://dx.doi.org/10.1002/ijc.32335

26. Wang YF, Wu LQ, Liu YN, Bi YY, Wang H. Gestational age and childhood leukemia: A meta-analysis of epidemiologic studies. *Hematology* 2018;23(5):253–262.

27. Spector LG, Puumala SE, Carozza SE, Chow EJ, Fox EE, Horel S, Johnson KJ, McLaughlin CC, Reynolds P, Von Behren J, Mueller BA. Cancer risk among children with very low birth weights. *Pediatrics* 2009; 124(1):96-104.

28. Paquette K, Coltin H, Boivin A, Amre D, Nuyt AM, Luu TM. Cancer risk in children and young adults born preterm: A systematic review and meta-analysis. *PLoS One* 2019;14(1):e0210366.

29. Licht S de F, Schmidt LS, Rod NH, Schmiegelow K, Lähteenmäki PM, Kogner P, Träger C, Stokland T, Schüz J. Hepatoblastoma in the Nordic countries. *Int J Cancer* 2012;131(4):E555-E561 Available from: http://dx.doi.org/10.1002/ijc.27351

30. Heck JE, Meyers TJ, Lombardi C, Park AS, Cockburn M, Reynolds P, Ritz B. Case-control study of birth characteristics and the risk of hepatoblastoma. *Cancer Epidemiol* 2013; 37(4):390-395.

31. Huang QT, Gao YF, Zhong M, Yu YH. Preterm Birth and Subsequent Risk of Acute Childhood Leukemia: A Meta-Analysis of Observational Studies. *Cell Physiol Biochem* 2016; 39(3):1229-1238.

32. Wang YF, Wu LQ, Liu YN, Bi YY, Wang H. Gestational age and childhood leukemia: A meta-analysis of epidemiologic studies. *Hematology* 2018; 23(5):253-262.

33. Leinonen MK, Miettinen J, Heikkinen S, Pitkäniemi J, Malila N. Quality measures of the population-based Finnish Cancer Registry indicate sound data quality for solid malignant tumours. *Eur J Cancer* 2017; 77:31-39.

34. Jokela M, Leinonen MK, Malila N, Taskinen M, Madanat-Harjuoja LM. Completeness of pediatric cancer registration in the Finnish Cancer Registry. *Acta Oncol* 2019; 58(11):1577-1580. Available from: https://doi.org/10.1080/0284186X.2019.1638522

35. Gissler M, Shelley J. Quality of data on subsequent events in a routine Medical Birth Register. *Med Inform Internet Med* 2002;27(1):33-38.

36. Gissler M, Teperi J, Hemminki E, Meriläinen J. Short Communication: Data Quality after Restructuring a National Medical Registry. *Scand J Public Health* 1995;23(1):75-80.

37. Teperi J. Multi method approach to the assessment of data quality in the Finnish medical birth registry. *J Epidemiol Community Health* 1993;47(3):242-247.

38. Gissler M, Berg C, Bouvier-Colle MH, Buekens P. Methods for identifying pregnancy-associated deaths: Population-based data from Finland 1987-2000. *Paediatr Perinat Epidemiol* 2004;18(6):448-455.

39. WHO. Born too soon: the global action report on preterm birth. 2012.

40. Kramer MS, Papageorghiou A, Culhane J, Bhutta Z, Goldenberg RL, Gravett M, Iams JD, Conde-Agudelo A, Waller S, Barros F, Knight H, Villar J. Challenges in defining and classifying the preterm birth syndrome. *Am J Obstet Gynecol* 2012;206(2):108-112.

41. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International classification of childhood cancer, third edition. *Cancer* 2005; 103(7):1457-1467.

42. Pihkala J, Hakala T, Voutilainen P, Raivio K. [Characteristic of recent fetal growth curves in Finland]. *Duodecim* 1989;105:1540–6.

43. Kaijser M, Akre O, Cnattingius S, Ekbom A. Preterm birth, low birth weight, and risk for esophageal adenocarcinoma. *Gastroenterology* 2005;128(3):607-609. Available from: http://dx.doi.org/10.1053/j.gastro.2004.11.049

44. Lupo PJ, Danysh HE, Skapek SX, Hawkins DS, Spector LG, Zhou R, Okcu MF, Papworth K, Erhardt EB, Grufferman S. Maternal and birth characteristics and childhood rhabdomyosarcoma: a report from the Children's Oncology Group. *Cancer Causes Control* 2014;25:905-913–913. Available from: http://dx.doi.org/10.1007/s10552-014-0390-6

45. Buck BM, Michalek M, Chen C, Nasca N, Baptiste B. Perinatal factors and risk of

neuroblastoma. *Paediatr Perinat Epidemiol* 2001; 15(1):47-53.

46. Samsø L, Schmidt JS, Lähteenmäki P, Träger C, Tore Stokland GG, Hjalgrim L, Sehested A, Johansen C, Schmiegelow K. Fetal growth, preterm birth, neonatal stress and risk for CNS tumors in children: A nordic population and register-based case-control study. *Cancer Epidemiol Biomarkers Prev* 2010; 19(4):1042-1052.
47. Vasu U, Nithyanandam S, D'Souza S, Kamath S. Retinoblastoma in patients with regressed retinopathy of prematurity. *Indian J Ophthalmol* 2011;59:501–2.
48. Self J, Bush K, Baral VR, Puvanachandra N, Puddy VF, Hodgkins P. Bilateral retinoblastoma presenting at retinopathy of prematurity screening. *Arch Dis Child Fetal Neonatal Ed*. 2010;95(4):F292.
49. Schubert EL, Hansen MF, Strong LC. The retinoblastoma gene and its significance. *Ann Med* 1994;26:177–184.
50. Berry JL, Polski A, Cavenee WK, Dryja TP, Linn Murphree A, Gallie BL. The RB1 story: Characterization and cloning of the first tumor suppressor gene. *Genes (Basel).*2019;10(11):879.
51. Knudson Jr AG. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci U S A* 1971;68:820–823. Available from: https://www.ncbi.nlm.nih.gov/pubmed/5279523
52. Holl K, Lundin E, Surcel HM, Grankvist K, Koskela P, Dillner J, Hallmans G, Wadell G, Olafsdottir GH, Ögmundsdottir HM, Pukkala E, Lehtinen M, et al. Endogenous steroid hormone levels in early pregnancy and risk of testicular cancer in the offspring: A nested case-referent study. *Int J Cancer* 2009; 124(12):2923-2928.

53. Kuiri-Hänninen T, Seuri R, Tyrväinen E, Turpeinen U, Hämäläinen E, Stenman UH, Dunkel L, Sankilampi U. Increased activity of the hypothalamic-pituitary-testicular axis in infancy results in increased androgen action in premature boys. *J Clin Endocrinol Metab* 2011; 96(1):98-105.

54. Crump C, Sundquist K, Winkleby MA, Sieh W, Sundquist J. Gestational age at birth and risk of testicular cancer. *Int J Cancer* 2012;131:446-451. Available from: http://dx.doi.org/10.1002/ijc.26371

55. Hall C, Ritz B, Cockburn M, Davidson TB, Heck JE. Risk of malignant childhood germ cell tumors in relation to demographic, gestational, and perinatal characteristics. *Cancer Epidemiol* 2017; 46:42-49.

56. Tan Q, Li S, Frost M, Nygaard M, Soerensen M, Larsen M, Christensen K, Christiansen L. Epigenetic signature of preterm birth in adult twins. *Clin Epigenetics* 2018;10:87.

57. Hogan L, Ingemarsson I, Thorngren-Jerneck K, Herbst A. How often is a low 5-min Apgar score in term newborns due to asphyxia? *Eur J Obstet Gynecol Reprod Biol* 2007;130:169-175.

58. Bonaventure A, Simpson J, Ansell P, Roman E, Lightfoot T. Prescription drug use during pregnancy and risk of childhood cancer - Is there an association? *Cancer Epidemiol]* 2015;39:73–78. Available from: http://dx.doi.org/10.1016/j.canep.2014.10.008

59. Francis SS, Wallace AD, Wendt GA, Li L, Liu F, Riley LW, Kogan S, Walsh KM, De Smith AJ, Dahl G V., Ma X, Delwart E, et al. In utero cytomegalovirus infection and development of childhood acute lymphoblastic leukemia. *Blood* 2017;129(12):1680-1684.

60. Daniels JL, Pan I-J, Olshan AF, Breslow NE, Bunin GR, Ross JA, Group CO. Obstetric history and birth characteristics and Wilms tumor: a report from the Children's Oncology Group. *Cancer*

Causes Control 2008;19:1103-1110. Available from: http://dx.doi.org/10.1007/s10552-008-9174-1

61. Marcotte EL, Ritz B, Cockburn M, Clarke CA, Heck JE. Birth characteristics and risk of lymphoma in young children. *Cancer Epidemiol* 2014;38(1):48-55.

62. Botto LD, Flood T, Little J, Fluchel MN, Krikov S, Feldkamp ML, Wu Y, Goedken R, Puzhankara S, Romitti PA. Cancer Risk in Children and Adolescents with Birth Defects: A Population-Based Cohort Study. *PLoS One* 2013;8(7): e69077.

63. Strahm B, Malkin D. Hereditary cancer predisposition in children: Genetic basis and clinical implications. *Int J Cancer* 2006;119(9):2001–2006.

64. Madanat-Harjuoja LMS, Malila N, Lähteenmäki P, Pukkala E, Mulvihill JJ, Boice JD, Sankila R. Risk of cancer among children of cancer patients - A nationwide study in Finland. *Int J Cancer* 2010;126:1196–205.

Figure legend:

Fig. 1 Flow chart of data formation 1996-2014. 8 cases and 82 controls were excluded due to missing data on birth weight or gestational age.

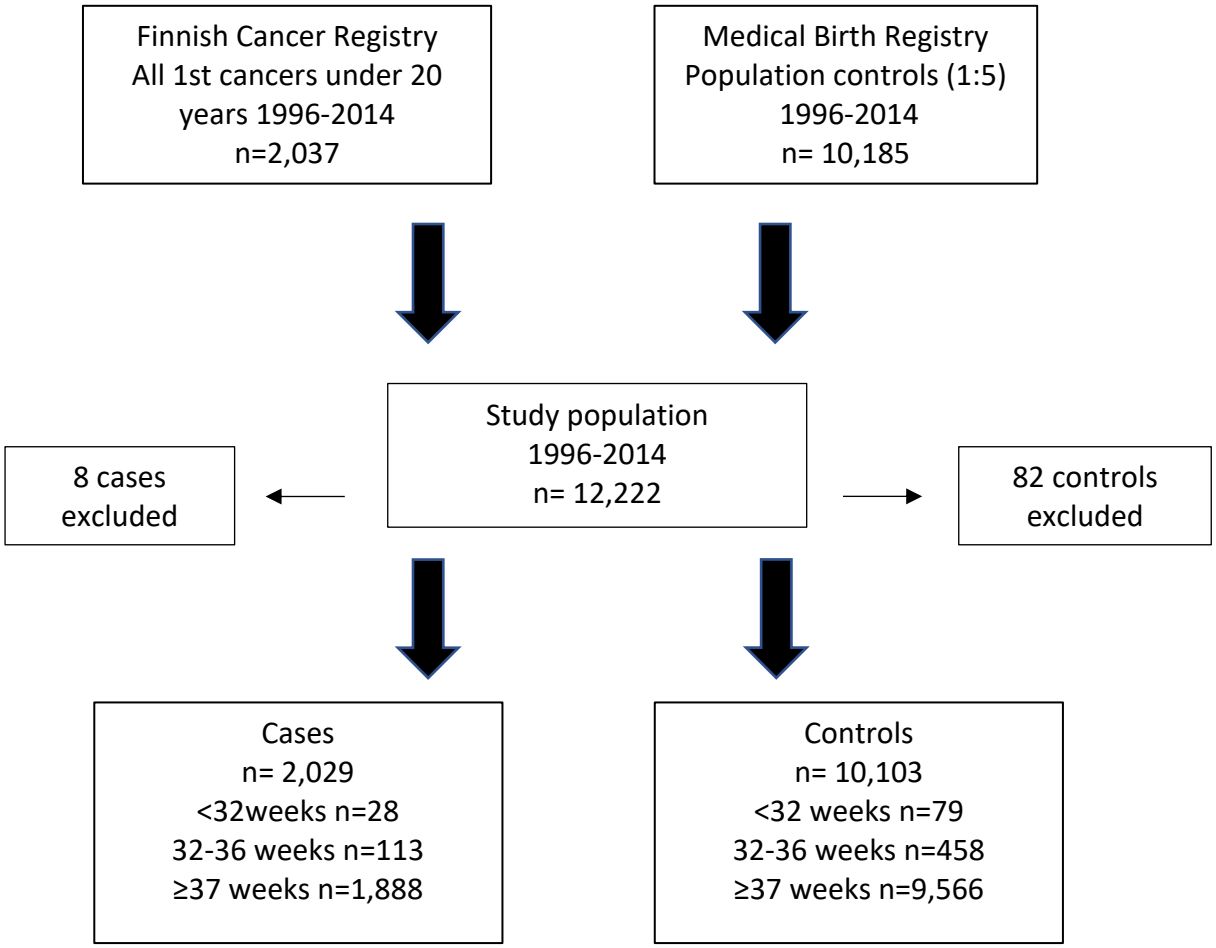

Fig.1 Flow chart of data formation 1996-2014. 8 cases and 82 controls were excluded due to missing data on birth weight or gestational age.

Preterm birth, neonatal therapies and the risk of childhood cancer - Tables

	Cases n= 2,029	Proportion (%)	Controls n= 10,103	Proportion (%)
Maternal characteristics				
Age <25 (years)	355	17.5	1,872	18.5
Age 25-29 (years)	639	31.5	3,246	32.1
Age ≥30 (years)	1,035	51.0	4,985	49.3
First child	847	41.7	4,098	40.6
Smoking				
Yes	291	14.3	1,447	14.3
No	1,680	82.3	8,404	83.2
Unknown	58	2.9	252	2.5
Offspring characteristics				
Female	937	46.2	4,672	46.2
Male	1,092	53.8	5,431	53.8
Small for gestational age (SGA)	55	2.7	217	2.1
Appropriate for gest. age (AGA)	1,881	92.7	9,587	94.9
Large for gestational age (LGA)	93	4.6	299	3.0
Twins	67	3.3	319	3.2
Born by caesarian section	354	17.4	1,627	16.1

Table 1. Descriptive statistics of study population 1996-2014.

Gestational weeks	N cases (%)	N controls (%)	Crude OR[1]	95% CI	Adj. OR[2]	95 % CI
Term birth (≥37 weeks)	1,888 (93.1)	9,566 (94.7)	**Ref.**	**Ref.**	**Ref.**	**Ref.**
Preterm birth (<37 weeks)	141 (6.9)	537 (5.3)	**1.33**	**1.10-1.61**	**1.28**	**1.06-1.57**
Late	113 (5.6)	458 (4.5)	**1.26**	**1.02-1.56**	1.21	0.97-1.50
Early	28 (1.4)	79 (0.8)	**1.79**	**1.15-2.77**	**1.84**	**1.16-2.92**

[1] Matched analysis
[2] Matched analysis adjusted for maternal age (categorized), parity and smoking status

Table 2. The risk of childhood cancer for those born preterm vs. term, measured with odds ratio (OR).

Cancer subtypes		Preterm birth <37 weeks				
	N preterm =140[1]	N term =1,888				
			Crude OR[2]	95% CI	Adjusted OR[3]	95% CI
All leukemias	42	627	1.22	0.86-1.73	1.28	0.90-1.82
ALL	25	486	0.94	0.61-1.45	1.00	0.64-1.56
AML	**17**	**141**	**2.21**	**1.21-4.02**	**2.33**	**1.25-4.37**
Lymphomas	7	140	0.94	0.41-2.15	0.64	0.25-1.68
CNS tumors	32	451	1.09	0.73-1.61	1.04	0.69-1.60
Other cancers	**59**	**667**	**1.71**	**1.26-2.32**	**1.59**	**1.16-2.19**
Neuroblastoma	9	144	1.16	0.55-2.42	0.95	0.44-2.07
Retinoblastoma	8	44	**3.26**	**1.26-8.39**	**3.21**	**1.22-8.41**
Renal tumors	9	110	1.48	0.69-3.20	1.35	0.60-3.10
Hepatic tumors	3	19	2.66	0.62-11.31	2.91	0.60-13.89
Bone tumors	2	34	1.42	0.28-7.14	1.38	0.26-7.32
Soft tissue sarcomas	10	132	1.21	0.59-2.50	1.09	0.51-2.33
Germ cell tumors	**12**	**52**	**4.32**	**1.91-9.79**	**5.89**	**2.29-15.18**
Other non-specified solid tumors	6	157	1.00	0.41-2.41	0.93	0.38-2.26

[1] 1 case omitted for missing specific information on the cancer subtype
[2] Matched analysis
[3] Matched analysis adjusted for maternal age (categorized), parity and smoking status

Table 3. Risk of childhood cancer subtypes for those born preterm vs term, measured with odds ratio (OR).

	Preterm N cases = 141	Median age	Term N cases = 1,888	Median age	p- value
All leukemias	42	3.25	627	3.67	0.41
AML	25	2.75	486	3.25	0.004
ALL	10	4.33	141	3.71	0.51
Lymphoma	7	1.5	140	8.09	0.66
CNS	32	4.92	451	5.42	0.53
Other	59	1.75	667	3.33	0.23
Neuroblastoma	9	1.7	144	1.33	0.89
Retinoblastoma	8	1.13	44	1.04	0.002
Renal tumors	9	3.17	110	3.0	0.31
Hepatic tumors	3	5.17	19	2.08	0.08
Bone tumors	2	6.42	34	11.4	0.51
Soft tissue sarcomas	10	5.93	132	5.58	0.57
Germ cell tumors	12	0.0	52	2.41	0.62
Non-specified tumors	6	7.34	157	10.92	0.17

Table 4. Median calendar age at diagnosis for the preterm and term by cancer type, difference in the distributions analyzed with the Mann-Whitney t-test.

All newborn	**N cases (%) = 2,029**	**N controls (%) = 10,103**	**Crude OR[1]**	**95% CI**	**Adj. OR[2]**	**95% CI**
Mechanical ventilation	51 (2.5)	103 (1.0)	**2.51**	**1.79-3.52**	**2.69**	**1.89-3.84**
Phototherapy	139 (6.8)	623 (6.2)	1.12	0.93-1.36	1.11	0.91-1.35
Resuscitation	31 (1.5)	87 (0.9)	**1.79**	**1.19-2.71**	**1.84**	**1.21-2.80**
Antenatal steroids	33 (1.6)	73 (0.7)	**2.34**	**1.53-3.57**	**2.53**	**1.64-3.88**
Antibiotic therapy	124(6.1)	446(4.4)	**1.42**	**1.15-1.75**	**1.40**	**1.13-1.74**
Preterm children	N= 141	N= 537				
Mechanical ventilation	30 (21.3)	62 (11.5)	2.13	0.64-7.11	3.25	0.67-15.84
Phototherapy	51 (36.1)	238 (44.3)	0.78	0.29-2.10	0.91	0.29-2.83
Resuscitation	24 (17.0)	41 (7.6)	1.36	0.44-5.11	2.48	0.52-11.73
Antenatal steroids	24 (17.0)	48 (8.9)	3.00	0.31-28.8	1.78	0.16-20.3
Antibiotic therapy	44(31.2)	138(25.6)	0.72	0.27-1.92	0.59	0.19-1.80
Term children	N=1,888	N= 9,566				
Mechanical ventilation	21 (1.1)	41 (0.4)	**2.95**	**1.70-5.10**	**2.99**	**1.70-5.28**
Phototherapy	88 (4.5)	385 (4.0)	1.17	0.92-1.49	1.17	0.91-1.49
Resuscitation	7 (0.4)	46 (0.5)	0.80	0.36-1.80	0.77	0.34-1.73
Antenatal steroids	9 (0.5)	25 (0.3)	1.94	0.89-4.22	1.93	0.89-4.20
Antibiotic therapy	80(4.2)	308(3.2)	**1.35**	**1.04-1.74**	**1.31**	**1.01-1.70**

[1] Matched analysis [2] Matched analysis adjusted for maternal age (categorized), parity and smoking status

Table 5. The risk of childhood cancer for all the newborn with neonatal interventions vs. those without, measured with odds ratio (OR).

Hypoxia-associated conditions	N cases (%)	N controls (%)	Crude OR[1]	95% CI	Adj. OR[2]	95% CI
All newborn	N=2,029	N=10,103				
Apgar < 7 (1 min)	134 (6.6)	512 (5.1)	**1.33**	**1.09-1.62**	**1.32**	**1.07-1.61**
Asphyxia	69 (3.4)	285 (2.8)	1.22	0.93-1.61	1.22	0.93-1.61
Preterm children	N=141	N=537				
Apgar < 7 (1 min)	35 (24.8)	101 (18.8)	1.15	0.33-4.00	1.14	0.27-4.91
Asphyxia	12 (8.5)	35 (6.5)	2.56	0.23-29.12	3.12	0.22-43.30
Term children	N=1,888	N=9,566				
Apgar < 7 (1 min)	99 (5.2)	411 (4.3)	1.24	0.99-1.56	1.25	0.99-1.58
Asphyxia	57 (3.0)	250 (2.6)	1.19	0.89-1.61	1.17	0.87-1.59

[1] Matched analysis

[2] Matched analysis adjusted for maternal age (categorized), parity and smoking status

Table 3. Pre- and perinatal conditions associated with hypoxia and the risk of childhood cancer, measured with odds ratio (OR).