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Childhood central nervous system tumoursand leukaemia: incidence and familial risk. A comparative population-based study in Utah and Norway

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Abstract

Background—In this study we aimed to evaluate incidence rates and family risk of the most common childhood cancers, tumours in the central nervous system (CNS) and leukaemia among individuals from Norway and individuals with Scandinavian ancestry living in Utah.

Methods—We used the Utah Population Database and the Norwegian National Population Register linked to Cancer registries to identify cancers in children born between 1966 and 2015 and their first-degree relatives. We calculated incidence rates and hazards ratios.

Results—The overall incidence of CNS tumours increased with consecutive birth cohorts similarly in Utah and Norway (both $p<0.001$). Incidence rates of leukaemia were more stable and similar in both Utah and in Norway with 4.6/100,000 person-years among children (<15 years) born in the last cohort. A family history of CNS tumours was significantly associated with risk of

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childhood CNS tumours in Utah HR= 3.05(95% CI 1.80–5.16) and Norway HR= 2.87(95% CI 2.20–3.74). In Norway, children with a first-degree relative diagnosed with leukaemia had high risk of leukaemia (HR= 2.39, 95% CI 1.61–3.55).

Conclusion—Despite geographical distance and assumed large life style differences, two genetically linked paediatric populations show similar incidences of CNS tumours and leukaemia in the period 1966–2015. CNS tumours and leukaemia aggregated in families in both countries.

Keywords

Cancer in the central nervous system (CNS); leukemia; cancer incidence; familial aggregation; family risk; family history; UPDB; children

1 Introduction

Cancer is a leading cause of death for children and adolescents worldwide, where Scandinavian countries together with North America and other European countrieshave the highest cancer incidence among children.[1] The causes of most childhood cancers are unknown. Family history of cancer, certain genetic conditions, and some environmental factors, such as exposure to radiation, account for only a small percentage of the cases.[2] Hereditary syndromes such as Li-Fraumeni syndrome, an autosomal dominant disorder caused by germline TP53 mutations, are thought to be a rare cause of paediatric cancers.[3]

Childhood cancer risk factors may be different in distinct populations, and studies carried out in migrant populations might contribute to split the role of genetic and environmental factors in cancer development. In the present study we focus on leukaemia and tumours in the central nervous system (CNS), the most common cancers in children accounting for around 60% of all cancer cases.[4] Leukaemia can occur at any age but it is most commonly diagnosed in children <4 years old.[5] Astrocytomas and embryonal tumoursare the most common types of childhood CNS tumours, followed byependymomas.[6] Younger children have a higher incidence of tumours of embryonal origin, such as medulloblastoma or atypical teratoid/rhabdoid tumour, whereas older children tend to have tumours of glial origin such as astrocytomas.[7]

Over one million Scandinavians emigrated to America throughout the 19th century; some weremembers of the Church of Jesus Christ of the Latter-Day Saints (LDS) from the Scandinavian Mission.[8,9,10,11] They had many of the same motives as other migrants, but in addition they were directly encouraged to settle in Utah where most of the population still practices the LDS religion. This population is well-known for their lifestyle characteristics including large family size, a healthy lifestyle, and proscriptions against alcoholic beverages and tobacco.[12]

The Utah Population Database (UPDB) and the Norwegian National Population Register (DSF) are well established registries that allowfor population-based analyses of the familial nature of diseases. We were able to conduct a unique comparison of incidence and family history of cancer in Utah and in Norway,considering the influence of Scandinavian

(Norwegian, Swedish and Danish) ancestry on the development and aetiology of childhood cancers.

The goals of the present study were:

i) to explore childhood CNS tumours and leukaemia incidence ratesin Norway and Utah and across Scandinavian ancestry in Utah; ii) to quantify the potentially increased risk of childhood CNS tumours and leukaemia among those with a family historyof leukaemia, CNS tumours, solid tumours and all cancers, taking intoconsideration Scandinavian ancestry in Utah;iii) to quantify the effect of family history of Li-Fraumenitumour spectrum on the risk of childhood CNS tumours and leukaemia, taking Scandinavian ancestry in Utah into account.

2 Materials and methods

2.1 Cohort Definitions

All children born in Utah and Norway between 1966 and 2015 who were also registered in UPDB or DSF were included in the study. The UPDB is one of the world's richest sources of linked population-based information and contains data for over 9 million individuals. Only those ~3 million individuals with at least 3 generations of genealogy connecting to Utah founders were analysed here to ensure consistent available genealogy data back to Utah founders. The UPDB was originally constructed of data provided by the Genealogical Society of Utah and is kept current with state vital statistics data,[13,14],84% of all individuals born in Utah in 1950 have grandparent information.[15] Approximately 60% of cancer cases registered in the Utah Cancer Registry link to genealogy data.

The UPDB includes the genealogy of the Utah founders from the mid-1800s to the present. It has been linked to the state-wide Utah Cancer Registry (UCR) from1966. The UCR has been a National Cancer Institute (NCI) Surveillance, Epidemiology, and End-Results Registry (SEER)[16] since 1973, and validates and records all independent primary cancers diagnosed or treated in Utah. The Norwegian DSF has information about the relationship between each Norwegian citizen and his/her relatives. Every person in the register has a Norwegian personal identification number which makes it possible to link the person with other registries, including the Norwegian Cancer Registry which is considered close-to-complete.[17]

The Norwegian Cancer Registry started in 1953. The overall completeness is estimated at 98.8% for the registration period 2001–2005. Several early studies conducted in the past also support the high degree of completeness of the registry.[18,19,20] In Utah approximately 60% of cancer cases registered in the Utah Cancer Registry link to genealogy data.[21]

These databases enable us to follow all individuals from birth to death, end of study, or emigration. Regarding emigration from Utah we used the last known date of residence, which is determined by when the individual had an event recorded in Utah from vital records (deaths, births, adoptions,census data and state-wide inpatient and ambulatory care).

2.2 *Cancer cases*included all children diagnosed with CNS tumours or leukaemia (all types of leukaemia) before the age of 15 between 1966 and 2015 in Norway and in Utah. Cancer cases were classified using the International Classification of Diseases for Oncology (ICDO-3).[22]

Family history of cancer for all caseswas retrieved in Utah fromthe SEER and in Norway from the Norwegian Cancer Registry,classified according to the ICD 10.The SEER codes used in the present study are based on ICD-10 codes.[23]

First-degree relatives includeparents and full siblings. Second-degree relatives included half siblings, grandparents, aunts/uncles and nieces/nephews. To identify children with a family history of the Li-Fraumeni tumour spectrum we used the Chompret's criteria, i.e. children with relativeswith a tumour belonging to the Li-Fraumeni tumour spectrum (soft tissue sarcoma, osteosarcoma, brain, premenopausal breast cancer or adrenocortical carcinoma) before the age 46 years.[24] The codes used for CNS tumours, leukaemia and the Chompret's criteria are presented in Appendix 1. Solid tumours include all cancers except leukaemia.

2.3 Scandinavian ancestry

In the UPDB we defined ancestry as an individual's place of birth, or place of birth of an individual's ancestors prior to arrival in Utah. To compare ancestry groups, we split the population in Utah into children with Scandinavian ancestry and children with non-Scandinavian ancestry. Appendix 1 gives an explanation of the method used for the identification of Scandinavian ancestry.

2.4 Statistical analyses

Incidence rates of childhood CNS tumours and leukaemiain the age groups 0–14 years and 0–4 years with 95% confidence intervals (CIs) for seven 5-year birth cohorts were calculated. For the first group we included children born between 1966 and 1999 to allow the same time frame up to 15 years for each child to develop cancer.For the youngest group we included children born up to 2009. Incidence rates were calculated by dividing the total number of CNS tumours or leukaemia cases in each cohort by the total number of follow-up years multiplied by 100,000. A Poisson model was used to establish whether changes in incidence had occurred over time.We calculated incidence rates for all children in Utah and in Norway, and separatelyfor Utah children according to Scandinavian ancestry. We also conducted a test for interaction to investigate differences in risk between individuals with and without Scandinavian ancestry. For comparison reasons incidence trends of CNS tumours and leukaemia in the general population (all ages) of Utah, Norway and United States as a whole are also presented. For this purpose data from the National Cancer Institute[25,26] and the NORDCAN project was used.[27]

Stratified Cox regression was used to analyse the association between a family history of cancerand the risk of childhood CNS tumours and leukaemia. Each birth cohort (10-year time period) was entered as a separate stratum. Using this approach, we could control for secular trends in the disease and birth-cohort effects reported in other studies. The person-time at risk was defined in both Utah and in Norway from birth to the age of a diagnosis, with censoring at the age of 15 years, death, emigration, end of study or the last known date

of residence in Utah. For the Utah population, comparisons were also made between ancestry groups according to Scandinavian ancestry. The proportional hazards assumption was verified by plotting Schoenfeld residuals. All analyses were performed using SPSS version 25.

2.4 Ethics approval and consent to participate

This study was approved by the Institutional Review Boards of the University of Utah and by the Utah Resource for Genetic and Epidemiologic Research (IRB_00090583). In Norway the project was approved by the Regional Committee for Medical and Health Research Ethics, (REK Sør-Øst: 2016/1305). As this is a register-linked study, the approval also covers exemption from informed consent because that would not be feasible to acquire.

3 Results

During the 49-year study period, a total of 1,309,797 children with genealogy data as previously described were born in Utah, and 3,835,376 children were born in Norway. Overall, 71.4% of the Utah children had ancestral roots from Scandinavia. Total numbers of cancer cases are presented in Table 1.

3.1 Childhood cancer incidence rate

CNS cancer: in Utah the incidence rate of CNS tumours(0–14 years)varied from 2.1/100,000 person-years among children born in the period 1966–1969 to 4.8/100,000person-yearsamong children born in 1995–1999. The corresponding incidence rates for Norway were 2.5/100,000 person-years and 5.3/100,000 person-years. We observed a statistically significant incidence increase in Utah and in Norway in the whole study period, $p<0.001$ for both (Figure 1 and Appendix 2). Theincidence rates in Utah and Norway, and in Utah according presence of Scandinavian ancestry or not, are similar with overlapping confidence intervals (Appendix 2 and 3)

A statistically significant increase in incidence rate of CNStumours in the youngest group (0–4 years) was observed in the study period as a whole,both in Utah ($p<0.001$) and in Norway ($p<0.001$) (Figure 3 and Appendix 3).Incidence rates in this group were 7.0/100,000 person-years in Norway and 7.6/100,000 person-years in Utah in the period 2005–2009.In Norway, the increase was remarkable for children born between 1980 and 1999, but the ratesflattened out among children born between1999 and 2009.

Leukaemia: the incidence rate of childhood leukaemia (0–14 years) in Norway was constant with an incidence rate of 3.2/100,000 person-years for children born during the period 1965–1969 to 1985–1989. The incidence rate increased slightly from 4.0/100,000 person-years for children born 1990–1994 to 4.6 per 100,000 person-years for children born 1995–1999. The trend analysis for the whole study period in Norway showed a statistically significantincrease in incidence rate ($p< 0.001$) (Figure 2).In Utah, the incidence rates for leukaemia were more stable with rates between 3.8 and 4.6/100,000 person-years. No statistically significant increase was noted ($p=0.77$).

Incidence rates of leukaemia diagnosed at young age (0–4 years) ranged between 6.8 and 10.6/100,000 person-years in Utah and between 6.0 and 8.0/100,000 person-years in Norway (Figure 3). A statistically significant increase in incidence rates was observed in bothUtah ($p=0.02$) and in Norway ($p<0.001$). Rates in Norway and Utah flattened out and remained stable at approximately 8/100,000 person-years among children born after 1999.

Appendix 4 shows incidence trends of CNS tumours and leukaemia in the general population (all ages) in Utah, Norway and United States from 1975–2015.An increase in incidence of CNS tumours in Norway in the last two decades can be noted. Incidence of CNS tumours and leukaemia in Utah and USA seem to be more stable; in addition, higher incidence of both type cancers was more pronounced among males.

3.2 Familial aggregation of cancer

Children with a first-degree relative diagnosed with CNS tumourshad a 3-fold statistically significantlyincreased risk of developingCNStumoursboth in Utah and in Norway (Table 2).Significantly 32–44% excess risk for CNS tumours was also observedin both populations when all solid tumours or all cancers in relatives were considered together.A family history of leukaemia was associated with a 2.4-fold significantlyincreased risk of childhood leukaemia in Norway. The risk was elevated, although not significantly, in Utah (Table 2). In Utah, the risk of childhood leukaemia was increased significantly when a first-degree relative was diagnosed with solid tumours and when we took into account all cancers.

Children with a first or second-degree relative diagnosed with cancers belonging to*the Li-Fraumeni tumour spectrum*hadincreased risk of developing a CNS tumour in both Utah (1.9-fold) and Norway (2.3-fold) (Table 3). The risk of CNS tumours was even higher when two or more relatives were diagnosed with cancers belonging to the Li-Fraumeni tumour spectrum,for both Utah and Norway.There was no association between cancers belonging to the Li-Fraumeni tumour spectrum in relatives and childhood leukaemia in any of the populations.

4 Discussion

To our knowledge, this study is the first comparative study to examine incidence and the familial risk of childhood CNS tumours and leukaemia among children with Scandinavian ancestry born in Utah compared with children born in a Scandinavian country (Norway).

In this study the incidence rate of CNS tumours showed a significant increase with consecutive birth cohorts in both populations. Childhood leukaemia (0–14 years) incidence rates showed more stable birth cohort trendsduring the study period, with only a slight increase in incidence rates among children born in the last periods in Norway.A family history of CNS tumours was associated with an elevated risk of childhood CNS tumours. The HR’s of CNS tumours was also elevated when family members were diagnosed with a tumour belonging to the Li-Fraumeni tumour spectrum.

The results from the present study are in accordance with previous observations of increasing incidence of childhood cancer among Scandinavian children, especially in

Denmark and Norway.[28,29,30,31] However, several studies show geographical and ethnicity differences of incidence ofcancer.[32,33] Our results show that the state of Utah has incidence rates of childhood CNS tumours and leukaemia similar to those found in Scandinavia.The high incidence rates reported here probably reflect the completeness of the registries, due to complete coverage in both populations. Incidence rates of CNS tumours in Utah and USA in the general population, regardless of age, show a stable trend from 1975–2016 (Appendix 4). By contrast,in Norway an increased incidence of CNS tumours was noted. However, a decline in the incidence rates has been observed in recent years. Incidence of leukaemia in the general population was relativelystable in the three populations from 1975 to 2016. Information on incidence rates among Utah children is scarce. The National Cancer Institute reports childhood cancer rates in a population consisting of 18 areas, including Utah, of 4.6/100,000 person-years for childhood CNS tumours and 5.4/100,000 person-years for leukaemia in the period 2011–2015, almost similar to our results.[34]

Childhood cancers, like adult cancers, may be the result of a mixture of genetic, environmental,and behavioural causes, not just one factor by itself. Norwegians descendants in Utah will share genetic makeup, but have grown up in different environments compared with their ancestors from Norway. Cancer incidence in Utah and Norway may be similar because of genetic similarities. However, the role of other factors influencing the aetiology cannot be ruled out.

Geographical and ethnic variations in incidence rates of CNS tumours and leukaemia among children have been reported around the world.[35,36] In USA, incidence rate of childhood cancer is higheramong white children (18.4/100,000 person-years)thanamong African-Americanchildren (13.3/100,000 person-years).[36] The incidence rates of CNS tumours and leukaemia found in our study are among the highest in the world and are similar to those observed in other parts of Europe and Canada.The stable incidence rate of leukaemia observed in Utah in Figure 2 might indicate that the prevalence of risk factors involved in the aetiology of the disease have been constant over time.An alternative explanation might be that the number of susceptible individuals in Utah and prevalence of risk factors are at their maximum.

The incidence of leukaemia diagnosed in children before 5 years isoverall higher than the incidence observed in older children. In England and Wales studies report an incidence of 7.9/100,000 person-years. This rate is similar to our study.[37] Lower incidence rates of paediatric CNS tumours are reported in some Southern and Eastern European countries with rates ranging from 3.1 to 5.0/100,000 person-years.[38]

We observed a change over time in the incidence of CNStumours, which may be attributable to the development of radiological imaging techniques such as CT and MRIfor the evaluation of brain tumours.[39] In 1971 a new era of imaging based diagnostics began with the creation of the first CT scanner. Later in 1977 the nuclear magnetic resonance technique (MRI) appears. In 1980, the first papers reporting CT scanner as the most accurate diagnostic test in children with brain tumours were published.[40,41] In Norway,the total number ofradiological examinationof CNS tumoursincreased by 16% from 1993 to 2002.[42] Despite the increased incidence of CNS tumoursobserved in the present study, we also noted

that the increase in the incidence of CNS tumoursin the youngest age group flattened out among children born after 1999, which may indicate that the effect of using these diagnostic techniques on the registration of new cases have ceased.The incidence of childhood leukaemia (0–14 years) was more stable in both populations. However, a significantly increased trend was observed in Norway.A similar increase is observed in data published by Cancer statistics for the Nordic countries(NORDCAN).[43] The increase in leukaemia rates may also reflect improved in diagnostics, classification and accuracy of reporting in recent years.

Our findings also confirm and strengthen the evidence of common familial risks for childhood CNS tumours and leukaemia, and are consistent with a wide range of studies[44,45,46,47] The biological mechanismsbehind the associations found in the present study might be explained by genetic and environmental factors or interaction between them. However, studies conducted in first-degree relatives suffer from inability to discern between possible environmental effects or shared genetic susceptibility.

Environmental and inherent risk factors consistently associated with childhood cancer are high-dose radiation, prior chemotherapy, birth weight, parental age, birth defects and family cancer syndromes.[48] Our findings of elevated risk of CNS tumours among children with a family history of Li-Fraumeni tumours support these remarks.We found a strong familial aggregation of CNS cancer and leukaemia which might indicate that these cancers share a heritable aetiology.Zhang et al, 2015[49] found that 8.5% of the children and young adults included in their study had a pathogenic or probably pathogenic germline mutationconferring cancer risk. Only 40% of these children had a family history of cancer.They also point out that the prevalence of these mutations might be underestimated.

The majority of childhood CNS tumours occur before the age of five, suggesting that prenatal as well as postnatal exposures must be considered as potential etiologic factors.[50] Leukaemia can occur at any age, but it is most commonly diagnosed in children <4 years old.[51] Environmental factors associated with elevated risk of childhood cancer with studies showing mixed results are background radiation, non-ionising electromagnetic fields, exposures to chemicals,pesticides, infections, parental exposures, such as parental smoking, alcohol consumption and occupational exposures.[52] Some of the chemical components of tobacco smoke have been demonstrated to be carcinogenic in animals and in humans, such as polycyclic aromatic hydrocarbons and nitrosamines. Both maternal and paternal smoking during pregnancy and before pregnancy are exposures that have been explored in numerous epidemiologic studies.[53]

Utah has the lowest proportion of smokers of any U.S. state (8.9%), also low compared to Norway (12%).[54,55] In addition,Utah is a population that excludes alcoholic beverages, coffee, tea, and other addictive substances. Similar incidence trends of CNStumours and leukaemia were observed in Utah and Norway. If some of these environmental factors are involved in the development of childhood cancer due to germline mutations and epigenetics, we would probably have expected differences in incidence rates between Utah and Norway.

Perinatal and reproductive factors have been consistently associated with both the risk of childhood CNS and leukaemia cases.[56,57] There is also a growing evidence that for the majority of childhood acute leukaemia the first genetic event occurs prenatally in the foetus.[58]

Parental age and parity have been associated with risk of childhood cancer in early studies, probably because of the possibility of associations with infections in early life,[37,38] and because maternal age might be associated with chromosomal aberrations of female germ cells.[59] Older maternal age has been associated with an increased risk of leukaemia, especially in the age group 0–4 years.[60] In the Utah population Mormon women are more likely to have more pregnancies with two children for every one mother compared to1.5 children among Norwegian women, according to statistics for 2017.[61,62] Utah women are also more likely to be younger at birth. The mean age of mothers at all births in Utah is 23.3 years in 2000,[63] compared to 29.6 among women in Norway at the same year.[64]

4.1 Strengths and limitations.

The present study uses two unique and well established National Population Registries. Our results are based on data from long-term prospective cancer registries with full coverage of the entire population in both countries. Utah's and Norway's cancer registries rank amongst the top regarding data quality and completeness.[65,66] This avoids ascertainment, referral, and recall bias.Our populations are representative ofCaucasian populations;the results may be applicable to individuals from a similar population.[67,68]

Limitations are, first that cancer cases diagnosed among relatives occurring before 1966 in Utah and 1953 in Norway were not available in the study, and could introduce bias by left truncation; the follow-up for cancer among relatives until 2015could also introduce bias. Second, parents and other first-degree relatives of children and young adults are often themselves young, and cancer may not have developed yet. However, both of these sources of bias would lead to an underestimation of the association between cancer in family and risk of childhood cancer. Although this is a large cohort study, some of these associations were based on small numbers which might lead to some false positive results. Thus, the results are best considered together with those from similar studies. Third, due to ethical considerations we were not allowed to pool data from Norway and Utah and this preventedus from direct testing of differences between the two populations. Some cancer types such as leukaemia and broncheoalveolar cancer have been included in the Chompret Criteria in recent studies.[69] Unfortunately, we didn't request the data for those cancer types and they were not included in our definition.The UPDB can identify the last date a person was observed in Utah via several vital records; individuals without this information were censored at the end of the study or <15 years.Relatives missing this information and diagnosed with cancer in other states could lead to an underestimation of the association between cancer in family and risk of childhood cancer. It is assumed that this effect would be uniform across the dataset. The Utah data included only those individuals with genealogy data in the UPDB and this may result in a potential for selection bias. However, approximately 84% of children born in Utah in 1950 had information on grandparents.[70]

The grade of completeness in later years might be higher due to link of UPDB with several registries and census.

5 Conclusion

We found a significant increase in incidence of CNS tumourswith consecutive birth cohorts in both populations, regardless of probable life style variations among generations of people living in Norway and Utah.

CNS tumours and leukaemia aggregatin families. Children with a family history of Li-Fraumeni tumours showed anincreasedrisk of developing these cancers.Given the importance of this syndrome in the risk of developing cancer at early age, more research including this risk population is needed.Our research findings may be useful for prioritizing childhood cancer research and continue monitoring changes in incidence of childhood cancers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CNS	central nervous system
LDS	the Church of Jesus Christ of the Latter-Day Saints
UPDB	Utah Population Database
DSF	the Norwegian National Population Register
UCR	the Utah Cancer Registry
NCI	National Cancer Institute
SEER	the urveillance, Epidemiology, and End Results

ICDO-3	International Classification of Diseases for Oncology
HR	hazardratios

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Key messages

- Incidence rates of CNS tumours and leukaemia in Utah were almost the same as those observed in Scandinavia, especially in the most recent birth cohorts.
- The incidence of CNS tumours showed a significant increase with consecutive birth cohorts in both Utah and Norway among children born from 1966 to 1999. Probably much of this increase is explained by improving diagnostic techniques and improvements in reporting to cancer registries.
- Among the youngest children the incidence rates of CNS tumours and leukaemiain Norway flattened out for children born between 1999 and 2009. In Utah we did not observe such change.
- CNS tumoursand leukaemia aggregated among families in both populations.
- Family history of cancers belonging to the Li-Fraumeni tumour spectrum was a predictorfor developing childhood CNS tumours.

Figure 1.

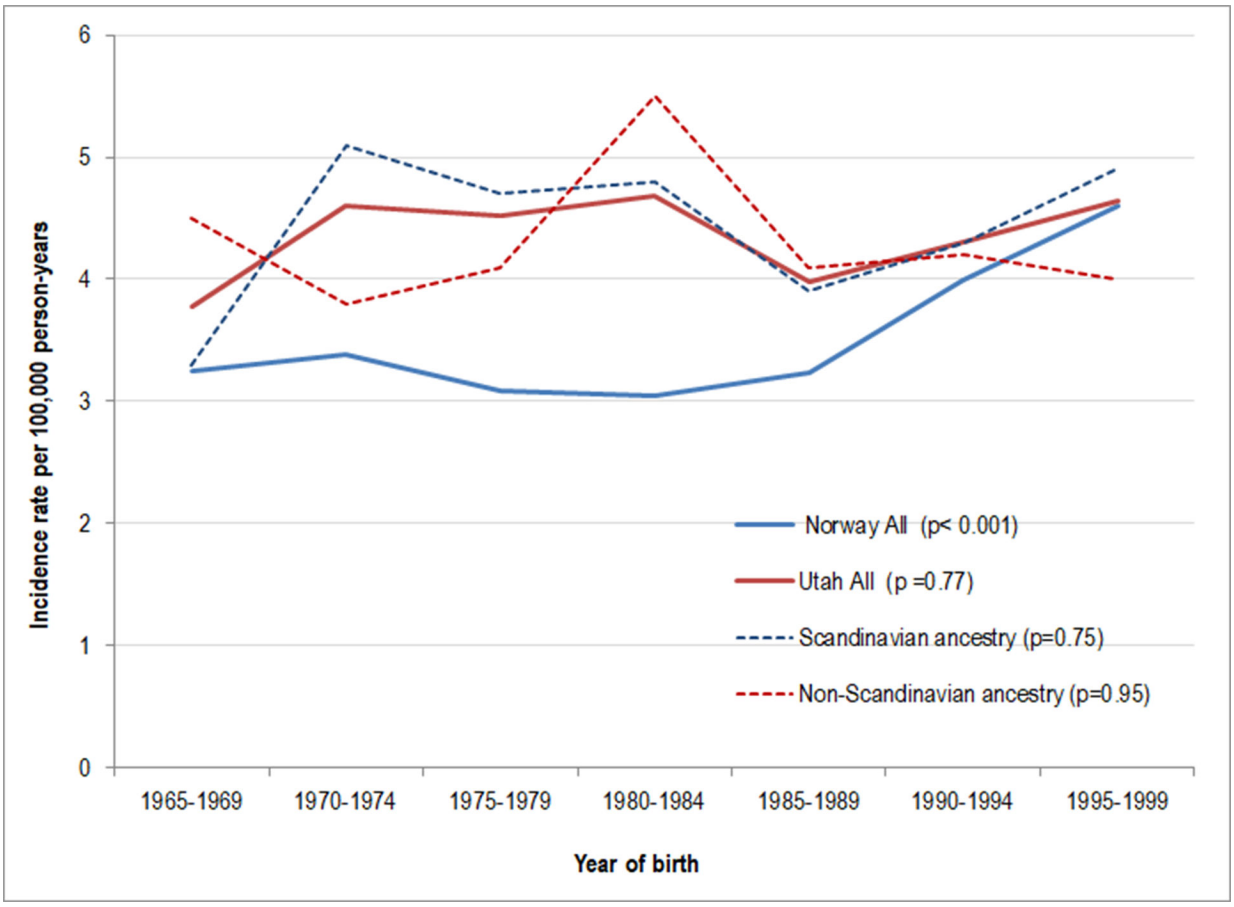

Figure 2.

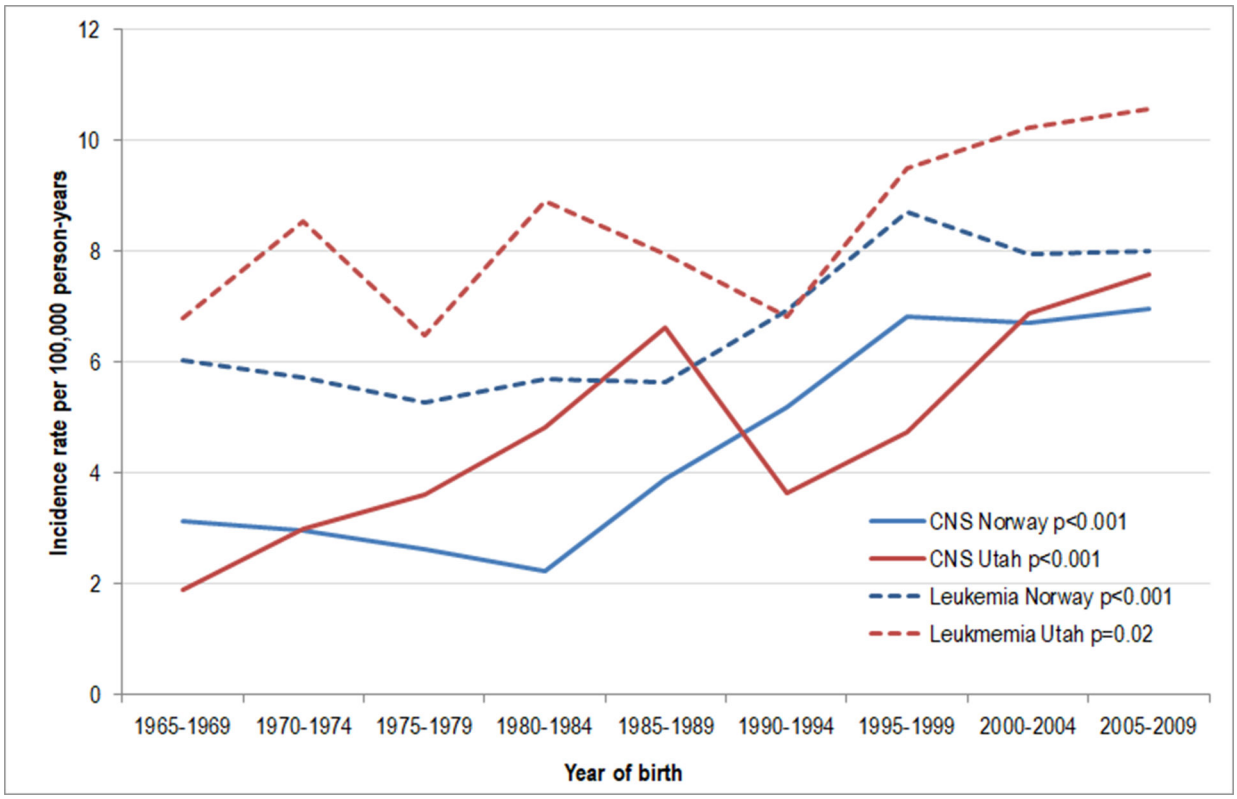

Figure 3.

TABLE 1.

Characteristics of children born in Norway and Utah in the period 1966 to 2015 across childhood cases and non-cases.

	Cases		Non-cases	
	Number	**%**	**Number**	**%**
Children born in Utah				
Tumour type and country of origin of ancestors				
Cancer in the CNS	514	100	1309283	100
Not Scandinavia	146	28.4	374309	28.6
Scandinavia	368	71.6	934974	71.4
Leukaemia	664	100	1309133	100
Not Scandinavia	189	28.5	374266	28.6
Scandinavia	475	71.5	934867	71.4
Mean age at cancer diagnosis (SD)				
Cases				
Cancer in the CNS	5.9 (4.3)			
Leukaemia	4.9 (3.8)			
Children born in Norway				
Tumour type				
Cancer in the CNS	1633		3833743	
Leukaemia	1780		3833596	
Mean age at cancer diagnosis (SD)				
Cases				
Cancer in the CNS	6.3 (4.2)			
Leukaemia	5.2 (3.6)			
Relatives				
Father	59.4 (13.6)			
Mother	54.4 (12.4)			
Siblings	32.0 (18.2)			

CNS: Central Nervous System

SD: standard deviation

TABLE 2.

Risk of childhood tumours in the central nervous system (CNS) and leukaemia according to family history of selected groups of cancers among first-degree relatives among children diagnosed in the period 1966 and 2015 in Utah and Norway. Adjusted hazard ratios (HR) with 95% confidence interval (CI) are presented separately for the whole population in Utah and Norway.

Childhood cancer		All Utah		All Norway	
	Cancer in relatives	cases	HR (95% CI)	cases	HR (95% CI)
CNS	CNS	16	3.05 (1.80–5.16)	57	2.87 (2.20–3.74)
	Leukaemia	0	NC	10	1.09 (0.59–2.03)
	Solid tumours	100	1.44 (1.13–1.85)	365	1.32 (1.16–1.50)
	All cancers	100	1.38 (1.07–1.76)	372	1.32 (1.60–1.49)
Leukaemia	Leukaemia	8	1.83 (0.89–3.76)	25	2.39 (1.61–3.55)
	Solid tumours	122	1.25 (1.00–1.56)	366	1.04 (0.92–1.18)
	All cancers	128	1.29 (1.04–1.60)	384	1.08 (0.96–1.23)

The model was adjusted for number of relatives.

Cases: number of cancer cases with relatives affected.

NC: not calculated

TABLE 3.

Risk of tumours in the central nervous system (CNS) and leukaemia among children diagnosed in the period 1966 to 2015 in Utah and Norway according to family history of tumours belonging to the Li-Fraumeni tumour spectrum and across Scandinavian ancestry. Hazard ratios (HR) with 95% confidence interval (CI) are presented separately for the whole population in Utah and for Norway.

Childhood cancer	**Family history of tumours belonging to the Li-Fraumeni tumour spectrum**		**All children in Utah**		**All children in Norway**
		cases	HR (95% CI)	cases	HR (95% CI)
CNS	One relative affected	44	1.96 (1.44–2.68)	45	2,32 (1.72–3.12)
	Two or more relatives affected	7	7.44 (3.53–15.71)	1	8.98 (1.26–63.74)
	*Scandinavian ancestry p=0.81 HR=1.08 (95% CI 0.55–2.13)				
Leukaemia	One relative affected	31	1.00 (0.70–1.44)	16	0.74 (0.45–1.21)
	Two or more relatives affected	0	NC	0	NC
	*Scandinavian ancestry p=0.99 HR=1.00 (95% CI 0.44–2.28)				

Cases: number of cancer cases with relatives affected.

*Scandinavian ancestry * Family history of tumours belonging to the Li-Fraumeni tumour spectrum

NC: not calculated