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Parental age and risk of childhood cancers: a population-based cohort study from Sweden

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Background Frequent germ line cells mutations were previously demonstrated to be associated with aging. This suggests a higher incidence of childhood cancer among children of older parents. A population-based cohort study of parental ages and other prenatal risk factors for five main childhood cancers was performed with the use of a linkage between several national-based registries.

Methods In total, about 4.3 million children with their parents, born between 1961 and 2000, were included in the study. Multivariate Poisson regression was used to obtain the incidence rate ratios (IRR) and 95% confidence interval (CI). Children <5 years of age and children 5–14 years of age were analysed independently.

Results There was no significant result for children 5–14 years of age. For children <5 years of age, maternal age were associated with elevated risk of retinoblastoma (oldest age group's IRR = 2.39, 95%CI = 1.17–4.85) and leukaemia (oldest age group's IRR = 1.44, 95%CI = 1.01–2.05). Paternal age was significantly associated with leukaemia (oldest age group's IRR = 1.31, 95%CI = 1.04–1.66). For central nervous system cancer, the effect of paternal age was found to be significant (oldest age group's IRR = 1.69, 95%CI = 1.21–2.35) when maternal age was included in the analysis.

Conclusion Our findings indicate that advanced parental age might be associated with an increased risk of early childhood cancers.

Keywords childhood cancer, relative risk, paternal age, maternal age, incidence

In recent years, several studies have shown increased incidence of childhood cancer in western industrialized countries,[1–4] particularly in children <5 years of age. Besides improvement in diagnostic/registration, the increment in childhood cancers may correspond to an increased exposure to risk factors. Epidemiological studies of childhood cancers have evaluated several birth characteristics as postulated risk factors.[5–7] One of the suggested risk factors of childhood malignancies is parental age.[8–9]

Leukaemia and central nervous system (CNS) cancers are two most common childhood cancers. They constitute almost 60% of all childhood cancer cases.[5,6] Other common childhood cancers are non-Hodgkin lymphoma, retinoblastoma of the eye, and Wilm's tumour. In earlier studies,[4,10–20] advanced maternal age was observed to be associated with retinoblastoma, leukaemia, and astrocytoma, while paternal age was associated with CNS cancer, but with conflicting results. This may ascribe to the fact that studies addressing risks factors, for example retinoblastoma, non-Hodgkin's lymphoma, and Wilm's tumours, have been limited by their small sample sizes and only a few population-based cohort studies have been done so far.[14,21–23] For the studies of CNS cancer, such disagreement might be due to the diverse histological types and the possibility of incomplete diagnosis.[5,6]

The aim of the present study was to investigate the association of the prenatal risk factors, mainly the parental age, with childhood cancer. Since prenatal factors might have various importance for early and later childhood cancers, diagnostic age groups <5 and 5–14 years were analysed separately. The time trends in the five most common childhood cancers during 1961–2000 were also studied. We also analysed other known potential risk factors such as familial cancer and birth order.

Materials and methods

Subjects

Our database is a linked product of four registries: the Multi-Generation Register (MGR), the Swedish Cancer Registry

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(SCR), national census data, and death notification. In the early 1990s, Statistics Sweden created the MGR by linking data from several different population-based registers. About 7 million children born in Sweden in the year 1932 and later are registered with their biological parents as families in MGR.[24] The population-based SCR, established in 1958, contains individual data on all newly diagnosed malignant tumours within Sweden (Swedish Cancer Registry 2000, http://www.sos.se/epc/cancereng.html). Tumours were reported to the SCR separately by both the diagnosing clinician and the responsible pathologist or cytologist. Nearly 100% of all diagnosed cancers were reported, with histological verification of 97% of the tumours. For malignant tumours, the registration rate has always been high; for benign and *in situ* conditions, there was underreporting in the beginning, but reporting improved after the 1960s. A 4-digit diagnostic code according to the 7th revision of the International Classification of Disease (ICD-7) and pathological anatomic diagnosis (PAD) was used to define the histological classification of cancer for the study. There were five main childhood cancers with sufficient numbers of cases: leukaemia (ICD-7 204–209), retinoblastoma of the eye (ICD-7 192 and PAD 436), non-Hodgkin's lymphoma (ICD-7 200,202), Wilm's tumour (ICD-7 180 and PAD 886), and CNS (ICD-7 193). Regarded as a diverse histological type of CNS, astrocytoma (ICD-7 1930 and PAD 475–476), the main childhood brain cancer, was also analysed separately.

As there were some inaccuracies in the vital status determinations in the first years of cancer registration, childhood cancer in the study was diagnosed between years 1961 and 2000. Children were followed up for their first primary cancer at age <5 or 5–14 years. Out of 6 776 313 pairs of parents and children, we included all children born since 1961. Children were included only if age data for both parents were available. Only biological parents were considered. In addition, all twins were excluded leaving ~4.3 million children for the analysis. No families with more then one child with childhood cancer were identified.

Statistical methods

We calculated incidence rates of five main childhood cancers for 10-year periods (1961–2000) in two age groups: all childhood cancers (<15 years) and early childhood cancers (<5 years). Person-years at risk were accumulated for each offspring beginning with 1 January 1961 or the date of birth and ending with the date of diagnosis of a first primary cancer, date of death, date of emigration, or 31 December 2000. Poisson regression models were used to compare incidence rates in parental age groups at birth. Parental age was grouped into 5-years group, except for the lowest (<25 years) and highest (>40 years) age group. Separate models were used to study the age effect of, either father or mother, and after adjustment for the age effects of the spouse. Likelihood ratio was used to obtain the *P*-value of the test for linear trends in rates by parental age. We performed an additional analysis where birth order and familial history of cancer were included as covariates in Poisson regression. Familial cancers were defined as those for which the parents had a concordant cancer as the children. The reference group for all risk factors were selected to group that was hypothetically unexposed. 95% confidence intervals (CI) were assessed by the likelihood ratio statistics. Variables for which 95% CI excluded 1.0 were statistically significant. *P*-value of Chi-square distribution was used as the main criterion for the goodness-of-fit for the regression model.

Results

Descriptive analysis

During the period 1961–2000 there were 7844 childhood cancer cases where the individuals were <15 years of age. Leukaemia (33.61%), CNS cancer (27.09%), non-Hodgkin's lymphoma (7.56%), Wilm's tumour (9.91%), and retinoblastoma (4.65%) corresponded to almost 85% of all cases. Generally, these cancers occurred in early childhood, peaking between 2 and 3 years of age. Retinoblastoma peaked at 1, Wilm's tumour at 1.5, and leukaemia at 2.5 years of age, whereas CNS cancer and non-Hodgkin's lymphoma had more than one peak, as shown in Figure 1. Except for CNS cancer and non-Hodgkin's lymphoma, the incidence rates decreased dramatically for children older than 5 years. Incidence in leukaemia decreased from 9 to 3 cases per 100 000 person-years and for retinoblastoma there were almost no cases since 95% of the cases occurred before 5 years of age. For cancer of children <5 years of age, there were 1234 leukaemia, 977 CNS cancer, 218 non-Hodgkin's lymphoma, 348 Wilm's tumour, and 226 retinoblastoma cases. However, irrespective of age at diagnosis, the incidence rate of childhood leukaemia, CNS cancer, and non-Hodgkin's lymphoma showed a modest increase approximately to year 1986 and after that the rates of CNS cancer had apparently stayed constant, whereas rates of leukaemia and non-Hodgkin's lymphoma increased steeply (Figure 2a and b).

The present analysis included 4.3 million pairs of parents and their children. The overall mean of the parental age at birth had increased during the period 1961–2000. Mean of maternal age at birth increased from 27.0 to 29.6 and mean of paternal age from 30.6 to 32.6. In 1996–2000, more than 50% of pregnant women were at age 30 or older, while during period 1961–1965, same groups of age category were only ~30% (Figure 3b). The distribution of paternal age had similar development (Figure 3a). Maternal age and paternal age were strongly correlated (correlation = 0.74 and *P*-value <0.001). However, the differences (paternal minus maternal age) in age were highly right skewed distributed, with only 25% of children having the mother older than the father (data not shown).

Poisson modelling

Multivariate Poisson regression was used to obtain the incidence rate ratios (IRR) and 95% confidence intervals (CI). Children <5 years of age and children 5–14 years of age were analysed independently. Incidence rates of childhood cancers were analysed in maternal age groups >40, 35–39, 30–34, 25–29, as compared with those <25 years of age. Since the incidence rate of all cancers changed along with time and age of the children (Figures 1 and 2), period and age were included as the covariates in the regression models.

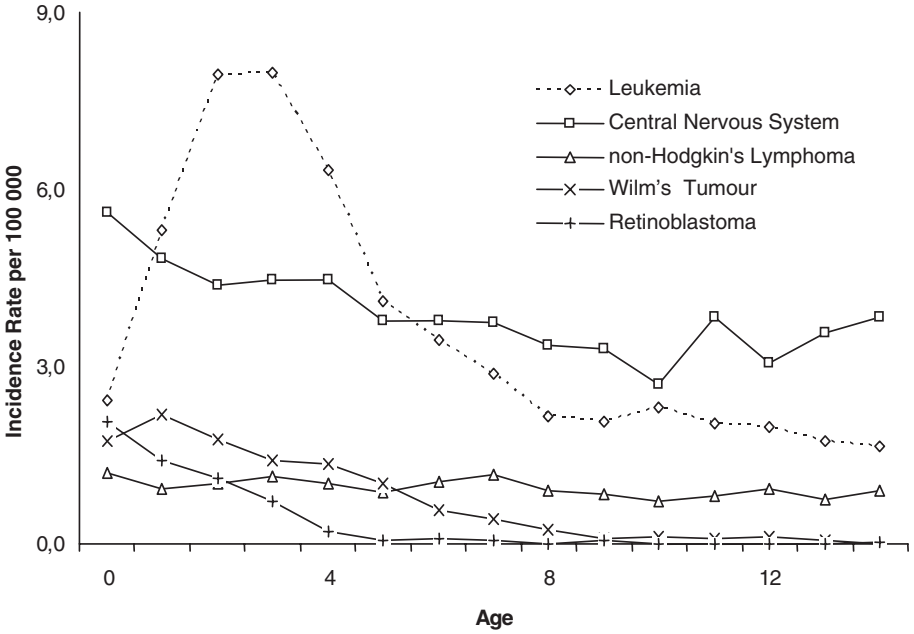

Figure 1 Age-specific incidence rates of five main childhood cancers in Sweden, 1961–2000

Maternal age effect

Table 1 shows the IRRs for maternal age effect in the studied cancers, with and without adjustment of paternal age. For retinoblastoma, the IRR was highest in maternal age group >40 years (IRR = 2.39; 95% CI = 1.17–4.85), regardless of paternal age. For leukaemia, maternal age groups 35–39 and >40 showed increased risk and also had a positive trend (*P*-value < 0.01). However, the maternal-age effect became statistically non-significant when paternal age was taken into account. Maternal age had no association with CNS cancer; however, significantly decreased risk of maternal age was observed in the age category 35–39 years after adjusting for paternal age (Table 1). Maternal age was not associated with an increased risk of Wilm's tumour and NHL.

Paternal age effect

Paternal age was not associated with the risk of developing retinoblastoma, irrespective of maternal age (Table 2). For leukaemia, without considering the effect of maternal age, the oldest paternal age group showed an increased risk (IRR = 1.31; 95% CI 1.04–1.66). After adjustment for maternal age, the effect receded. There were no significant paternal age effects in childhood CNS cancer, before adjustment of the mother age effect. Noteworthy, with adjustment of maternal age, there was a positive trend (*P*-value <0.01) for increasing risk in CNS cancer. The risk in CNS cancer for all age groups >30 years increased, with highest risk (IRR = 1.69; 95% CI 1.21–2.35) in the age group >40 years. The results of astrocytoma were similar to those of all CNS cancer. No significant association was found between paternal age and NHL or Wilm's tumour.

To confirm the increased risk of CNS cancer due to higher age of father, an additional Poisson regression model was performed where the maternal age was kept constant in age group <25 years of age (Table 3). Paternal age group >40 years of age had strong positive association with the risk of CNS cancer (IRR = 2.69; 95% CI 1.25–5.79) and the trend remained positive (*P*-value = 0.04). It was impossible to imply this method for astrycytoma, due to the limited number of cases. Use of the same method to confirm the maternal age effect in leukaemia was not feasible because there were few cases where women were older than men.

Period effect

The effect of calendar period (1961–1980 vs 1981–2000) of diagnosis of childhood cancer was also studied (data not shown). There were no apparent differences in association between parental age and risk for childhood cancer related to calendar period except for CNS. For CNS cancer, the significant results were confined to the period 1981–2000, the period with complete diagnostics/reporting. Even without adjustment for maternal age, there was a clear trend of paternal age effect (*P*-value <0.05) and the oldest age group showed an IRR of 1.52 (95% CI 1.05–2.19). After adjustment for the maternal age, the IRR increased for all paternal age groups and the oldest two age groups became significant (IRR 1.62 with 95 % CI 1.09–2.41 and IRR 2.15 with 95% CI 1.39–3.33) with a stronger trend (*P*-value <0.01). Still, the second oldest maternal age group showed an IRR <1 (IRR 0.67, 95% CI 0.48–0.94).

Other risk factors

Models with birth order and familial history of cancer were studied separately in both diagnostic age groups of childhood cancer, since some previous reports have found associations for these variables. However, birth order had no association with any childhood cancer that we studied. There were no concordant cases where parent and child had leukaemia. Noteworthy, family history increased risk of retinoblastoma in

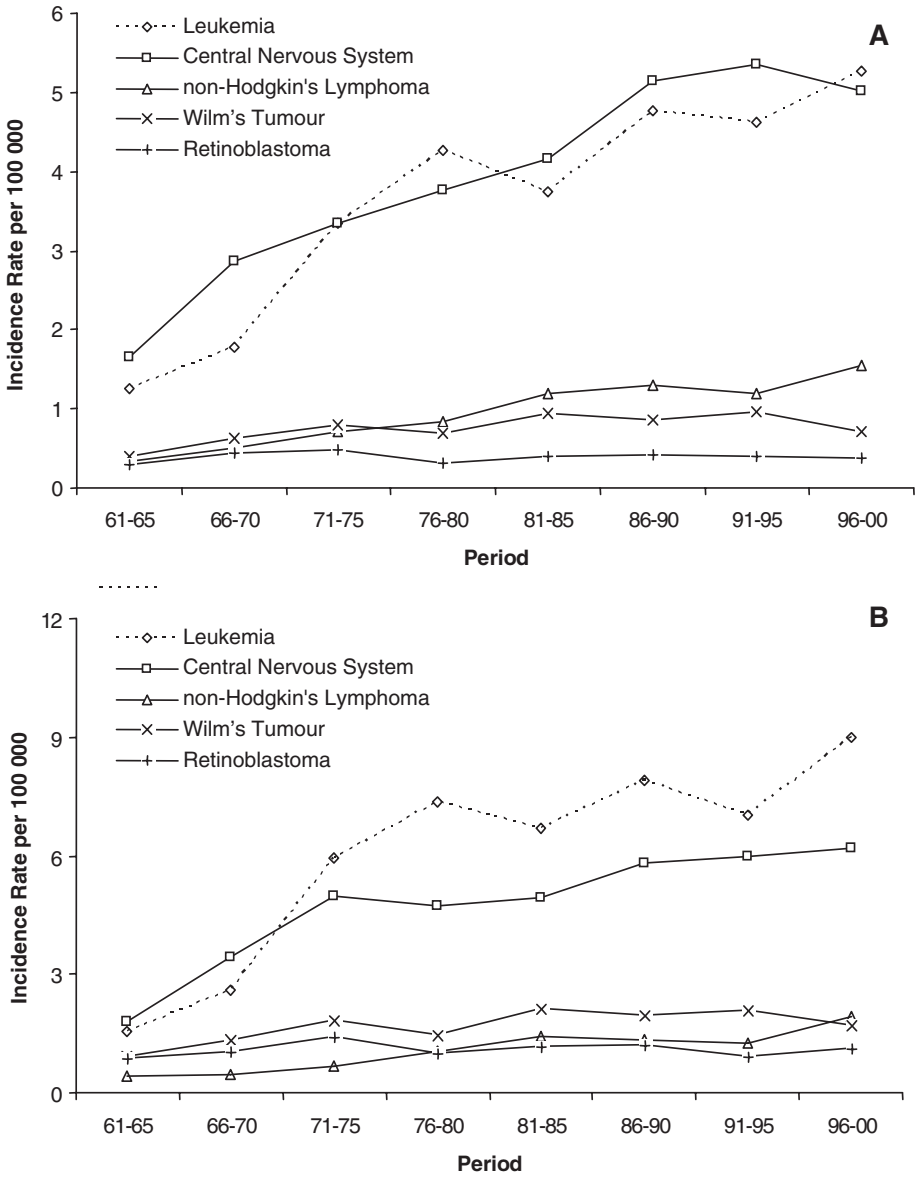

Figure 2 Incidence rates of five most common childhood cancers of children in Sweden: (**a**) children 0–14 years of age and (**b**) 0–4 years of age

children (IRR = 53.99, 95% CI = 22.16–131.54, n = 5). Family history of CNS cancer was found as an increased risk factor (IRR = 1.88; 95% CI = 1.00–3.63, n = 9).

In general, all models were well fitted; P-values of goodness-of-fit test were >0.05 for all models. The P-values of likelihood ratio test of age and period at diagnosis were significant in all regression models except for retinoblastoma. Still, for retinoblastoma, including all these parameters provided a better fit.

Discussion

In most of the developed countries, including Sweden, the incidence rate of childhood cancers has increased in the past decades, especially for CNS cancer and leukaemia.[2–3,14] Improvements in diagnostic and reporting may be one of the reasons for the increase in incidence. The previous inspection of the histology codes for brain tumours[14] revealed that most of the increase of the brain tumours was the result of low grade astrocytomas; there was no increase in the rates for high grade tumours, suggesting that the rapid increase before the year 1975 was mainly because of diagnostics/reporting. For leukaemias, there is no evidence on the change in diagnostics/reporting so as to explain the increase observed.[14]

On the other hand, the rising reproductive age of the Swedish population in the period 1961–2000 (Figure 1) may explain partially the overall increase incidence rate of childhood cancer during the same period (Figure 3). Reproductive age may affect the risk of cancer in children at least in several ways.[25] Frequencies of mutation in germ line cells of father as well as frequencies of chromosomal aberrations during the maturation of maternal germ cells increase with age and thus may increase the chance of developing cancer in offspring.

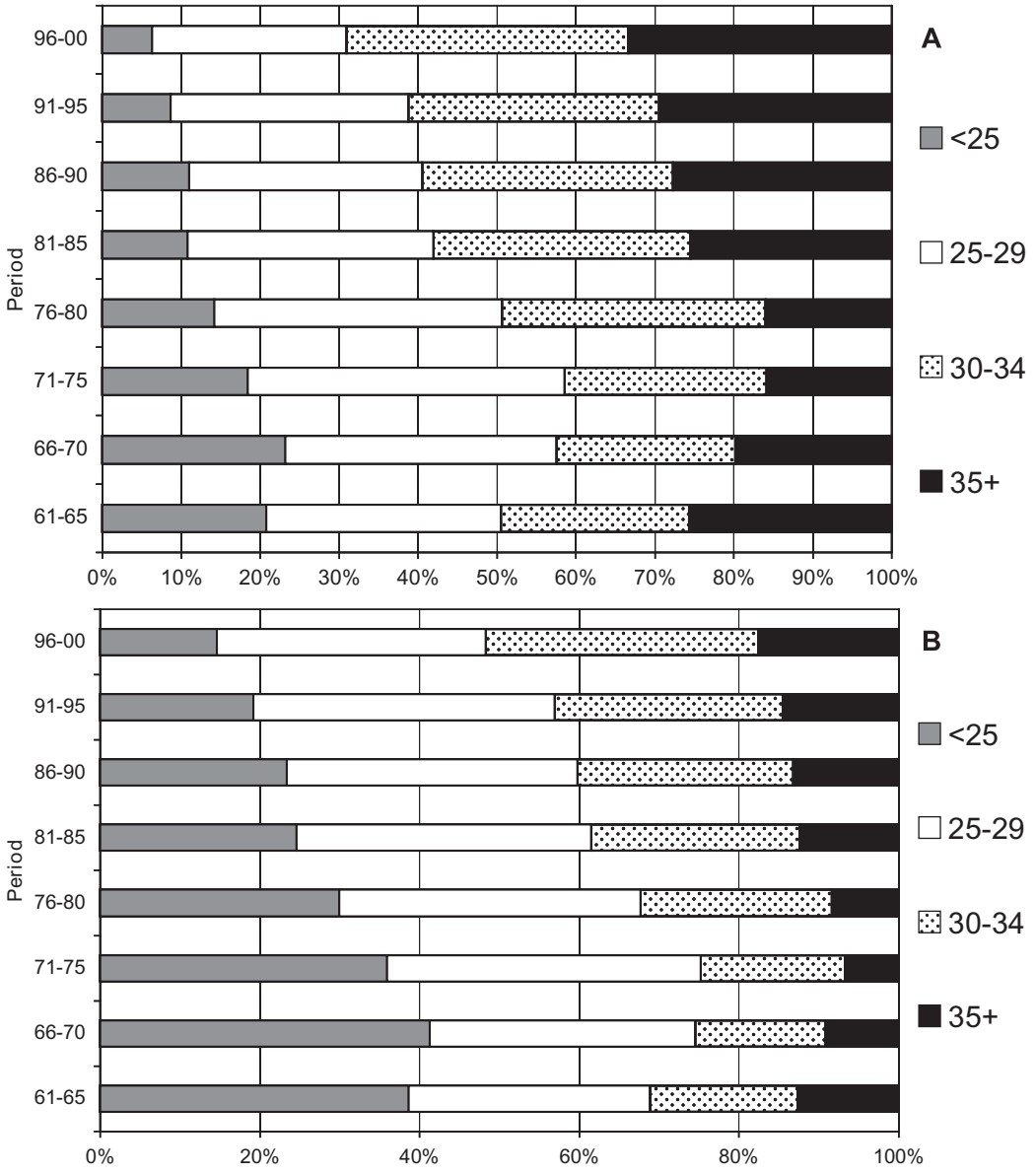

Figure 3 Distribution of parental age by 4 age group in Sweden, 1961–2000: (**a**) paternal age and (**b**) maternal age

Aging may also change physiological parameters, such as estrogens levels, which may also induce the risk of childhood cancer.[26]

We have found higher parental age to be associated with three of five most common childhood cancers in Sweden, when the children were <5 years of age. For retinoblastoma, the oldest maternal age group showed an elevated risk with IRR of 2.4 as compared with other exposure age groups. Our findings are in agreement with previous studies.[12] Interestingly, parental age is a suspected risk factor for several other autosomal dominant traits, including multiple endocrine neoplasia type 2B and neurofibromatosis.[27,28]

Our results indicated that both maternal and paternal age might have some effect on the risk of leukaemia. No association of paternal age could be found when we kept maternal age <25 years of age; this supports our conclusion that the observed risk of leukaemia was mainly contributed by maternal age. Accumulation of chromosomal aberrations during the maturation of maternal germ cells might be explanation for these findings.

There was increased risk for CNS cancer by paternal age at birth in the model adjusting for the age of mother. All age groups >30 years showed a significantly increased risk with a positive trend. This result is consistent with a previously published study for children <15 years of age.[14] By selecting the youngest maternal age group, we confirmed the paternal age effect in CNS cancer (Table 3). The results from the subdivided period 1981–2000 also confirm the effect of paternal age in CNS cancer. Based on this two different approaches, we believe that there is an increase risk of CNS cancer for children with a high-aged father with or without considering the age of the mother. Diverse histological types of CNS cancer have

Table 1 Effect of maternal age in childhood (0–4 years old) cancers, with and without adjustment of paternal age

			Maternal age only		Adjusted for paternal age	
Cancer	**Maternal age at birth**	***N***	IRR	95%CI	IRR	95%CI
Retinoblastoma	All ages	226	*P*-value = 0.049[a]		*P*-value = 0.17	
	<25[b]	52	1.00		1.00	
	25–29	88	1.40	1.00–1.98	1.41	0.95–2.10
	30–34	56	1.37	0.93–2.01	1.37	0.85–2.22
	35–39	21	1.30	0.77–2.17	1.26	0.67–2.38
	>40	9	**2.39**	**1.17–4.85**	**2.42**	**1.04–5.58**
Leukaemia	All ages	1234	*P*-value = 0.005		*P*-value = 0.11	
	<25	318	1.00		1.00	
	25–29	439	1.05	0.91–1.21	1.02	0.86–1.20
	30–34	302	1.08	0.93–1.28	1.03	0.84–1.26
	35–39	141	**1.30**	**1.07–1.59**	1.24	0.96–1.59
	>40	34	**1.44**	**1.01–2.05**	1.32	0.88–1.98
Central nervous cancer	All ages	977	*P*-value = 0.257		*P*-value = 0.00	
	<25	272	1.00		1.00	
	25–29	372	1.05	0.90–1.23	0.94	0.79–1.13
	30–34	240	1.02	0.85–1.21	0.82	0.66–1.02
	35–39	69	0.74	0.57–1.00	**0.55**	**0.40–0.76**
	>40	24	1.15	0.76–1.74	0.80	0.50–1.28
Astrocytoma	All ages	316	*P*-value = 0.816		*P*-value = 0.13	
	<25	80	1.00		1.00	
	25–29	124	1.25	0.94–1.66	1.12	0.81–1.56
	30–34	88	1.30	0.95–1.77	1.06	0.72–1.56
	35–39	18	0.69	0.41–1.15	**0.49**	**0.27–0.90**
	>40	9	1.50	0.75–2.99	0.93	0.42–2.04
Wilm's tumour	All ages	348	*P*-value = 0.615		*P*-value = 0.32	
	<25	89	1.00		1.00	
	25–29	139	1.23	0.94–1.61	1.18	0.87–1.61
	30–34	78	1.04	0.76–1.41	0.88	0.60–1.30
	35–39	32	1.07	0.71–1.61	0.79	0.48–1.30
	>40	10	1.48	0.77–2.85	1.03	0.49–2.17
Non-Hodgkin's lymphoma	All ages	218	*P*-value = 0.186		*P*-value = 0.88	
	<25	56	1.00		1.00	
	25–29	72	0.94	0.66–1.34	0.95	0.63–1.42
	30–34	54	1.03	0.70–1.50	1.01	0.63–1.63
	35–39	32	1.54	0.99–2.38	1.54	0.86–2.74
	>40	4	0.88	0.32–2.44	0.81	0.27–2.47

The data were adjusted for age and period at diagnosis.
Significant results are bolded.
[a] Where age groups are taken to be continuous in all cancers.
[b] Reference group.

different incidence and they may associate with different risk factors.[4–6,11,13–14] In our study, the association between parental age and CNS cancer respective brain cancer (data not shown) were very similar. Interestingly, our results suggest that the paternal age effect in CNS cancer was mainly contributed by the association with astrocytoma (Table 2). The mechanism of association of paternal age with the increased incidence of CNS cancer is not known but could relate to accumulation of germ cell mutations.

In addition, the association with familial history of cancer and birth order was studied, as previous studies suggested that they could be important factors.[18] In the childhood leukaemia study, Shaw *et al.*[19] reported that the subsequent child has a higher risk than the firstborn child for the development of leukaemia; it is plausible as birth order and maternal age are positively correlated. However, no association was found in the analysis of the present data by birth order, independent of maternal age. Although the number of cases were few,

Table 2 Effect of paternal age in childhood (0–4 years old) cancers, with and without adjustment maternal age

			Paternal age only		Adjusted for maternal age	
Cancer	**Paternal age at birth**	***N***	IRR	95%CI	IRR	95%CI
Retinoblastoma	All ages	226	*P*-value = 0.165[a]		*P*-value = 0.96	
	<25[b]	27	1.00		1.00	
	25–29	73	1.23	0.79–1.91	1.04	0.64–1.69
	30–34	63	1.19	0.75–1.87	0.93	0.54–1.60
	35–39	41	1.49	0.91–2.43	1.15	0.63–2.12
	>40	22	1.38	0.78–2.42	0.96	0.47–1.97
Leukaemia	All ages	1234	*P*-value = 0.015		*P*-value = 0.50	
	<25	153	1.00		1.00	
	25–29	375	1.02	0.85–1.24	1.01	0.83–1.24
	30–34	386	1.14	0.95–1.38	1.11	0.89–1.39
	35–39	192	1.10	0.89–1.36	1.02	0.78–1.32
	>40	128	**1.31**	**1.04–1.66**	1.14	0.85–1.53
Central nervous Cancer	All ages	977	*P*-value = 0.090		*P*-value <0.00	
	<25	120	1.00		1.00	
	25–29	301	1.07	0.87–1.33	1.11	0.89–1.40
	30–34	309	1.19	0.97–1.48	**1.34**	**1.04–1.72**
	35–39	150	1.11	0.87–1.41	**1.40**	**1.04–1.86**
	>40	97	1.26	0.96–1.65	**1.69**	**1.21–2.35**
Astrocytoma	All ages	316	*P*-value = 0.072		*P*-value = 0.03	
	<25	37	1.00		1.00	
	25–29	95	1.14	0.78–1.67	1.09	0.72–1.64
	30–34	102	1.35	0.92–1.98	1.30	0.83–2.04
	35–39	46	1.16	0.75–1.80	1.29	0.76–2.17
	>40	36	**1.58**	**1.00–2.51**	**1.95**	**1.10–3.45**
Wilm's tumour	All ages	348	*P*-value = 0.069		*P*-value = 0.04	
	<25	44	1.00		1.00	
	25–29	107	1.06	0.75–1.51	1.00	0.68–1.46
	30–34	95	1.03	0.72–1.47	1.02	0.66–1.56
	35–39	64	1.32	0.90–1.95	1.45	0.90–2.33
	>40	38	1.37	0.89–2.13	1.53	0.89–2.65
Non-Hodgkin's lymphoma	All ages	218	*P*-value = 0.314		*P*-value = 0.38	
	<25	29	1.00		1.00	
	25–29	59	0.83	0.53–1.29	0.84	0.52–1.36
	30–34	73	1.07	0.69–1.65	1.05	0.62–1.79
	35–39	31	0.86	0.51–1.43	0.75	0.40–1.42
	>40	26	1.29	0.75–2.19	1.09	0.55–2.16

The data were adjusted for age and period at diagnosis.

Significant results are bolded.

[a] Where age groups are taken to be continuous in all cancers.

[b] Reference group.

we demonstrated that familial history of cancer was strongly associated with retinoblastoma (IRR = 53.99) and moderately with CNS cancer (IRR = 1.88); these findings are in agreement with earlier studies.[29] Nevertheless, when family history of cancer as well as birth order was adjusted for in our models, the estimated effects of parental age in retinoblastoma and CNS tumours did not change.

The biggest advantage of the present study is that we used population-based data and therefore complete retrieval of family relationships and cancers. Thus the data are free from selection and ascertainment bias that may occur in a case–control study. Nevertheless, we are aware of several limitations in the study. One of them is the high correlation (0.74) between maternal age and paternal age that may affect our estimates. However, both models (adjusted and no adjusted) were presented in order to compare the influence of the other parental age effect. There are also a number of characteristics of mother that have been suggested to associate with childhood cancer risk and potentially confound the effect of parental age. Such factors include smoking in pregnancy, high birth weight,

Table 3 Effect of paternal age in childhood (0–4 years old) cancers, when keeping maternal age <25 years.

Cancer	Paternal age at birth	Maternal age < 25		
		N	IRR	95%CI
Leukaemia	All ages	318	*P*-value = 0.47[a]	
	<25[b]	131	1.00	
	25–29	147	1.04	0.82–1.32
	30–34	29	0.86	0.57–1.28
	35–39	8	1.00	0.49–2.05
	>40	3	0.94	0.30–2.95
Central nervous system	All ages	272	*P*-value = 0.04	
	<25	109	1.00	
	25–29	114	1.01	0.78–1.32
	30–34	31	1.14	0.76–1.70
	35–39	11	1.70	0.91–3.17
	>40	7	**2.69**	**1.25–5.79**

The data were adjusted for age and period at diagnosis.
Significant results are bolded.
[a] Where age groups are taken to be continuous in all cancers.
[b] Reference group.

and history of spontaneous abortions.[30] In addition, some authors have argued that methylation may in some cases be disturbed by in vitro fertilisation, IVF, procedures, which, in turn, could influence cancer risk. Older parents would be more likely to have undergone IVF in recent years. While there is an increasing use of IVF since 1980s it is unlikely to explain our results since births in connection to IVF contribute to <1% of all births in Sweden during 1980–2000.[31] Some authors have observed a higher risk of childhood cancer in preterm babies and in babies with malformations.[32] Thus, another explanation that may partly explain the historical time trends in childhood cancer is the decrease of infant mortality,[33] since high-risk babies may have been weeded out of the population in the past.

Conclusions

Our study is the first population-based cohort study to analyse systematically the effect of maternal and paternal age in five main cancers affecting offspring into separate diagnostic age groups <5 and 5–14 years. The divergence in results of our analysis for children <5 and 5–14 years of age suggests that reproductive-age-related cancers may have an early onset. This finding could potentially be useful in designing strategies for the early detection and treatment of parental-age-related cancers in children with this cancer predisposition.

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