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Association of childhood cancer with factors related to pregnancy and birth

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Background	It has been hypothesized that risk factors of childhood cancers may already operate during the prenatal and neonatal period. Results of previous epidemiological studies have been inconsistent.
Methods	During 1992–1997 a large case-control study on childhood cancers and a variety of potential risk factors was conducted in Germany. Cases were ascertained by the German Childhood Cancer Registry. Each case was matched to a population-based control of the same age and gender, sampled from the district where the case lived at the date of diagnosis. For the analyses, 2358 cases and 2588 controls were available.
Results	Risk of childhood acute leukaemia increased with maternal age ⩽20 years at time of delivery (odds ratio [OR] = 1.9, 95% CI : 1.1–3.2), lower (<2500 g: OR = 1.7, 95% CI : 1.1–2.8) and higher birthweight (>4000 g: OR = 1.4, 95% CI : 1.0–1.8, $P < 0.05$), and hormonal treatment because of infertility (OR = 1.6, 95% CI : 1.0–2.5, $P < 0.05$). No associations were seen for parental smoking habits, maternal alcohol consumption during pregnancy and fetal losses. Parity was associated only with subgroups of acute leukaemias. Regarding non-Hodgkin's lymphoma we observed an elevated OR for lower birthweight and heavy maternal smoking during pregnancy (>20 cigarettes/day) and a decreased OR for children with one or two siblings. Only a few significant findings were seen for the different groups of solid tumours.
Conclusions	Overall, only weak associations were identified and the evaluated risk factors operating during the neonatal and prenatal period account at most for only a small proportion of childhood cancers.

Keywords	Cancer, case-control study, child, leukaemia, lymphoma, pregnancy, risk factors
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Information regarding the aetiology of malignant diseases during childhood is still limited. With regard to the most common childhood cancer, acute lymphatic leukaemia (ALL), which accounts for almost 29% of all childhood malignancies in Germany, only genetic factors like Down's syndrome, being a homozygotic twin of a child with leukaemia, and ionizing radiation are accepted as causal.[1,2] Because a remarkable number of childhood cancers occur at very young ages, it has been hypothesized that causes may operate during the prenatal and neonatal period.[3] Many results of previous investigations examining risk factors related to pregnancy and birth have been inconsistent.[4–25] Since childhood malignancies are relatively rare diseases, sample sizes were often small and the resulting risk estimates lacked precision.

In a previous case-control study of childhood acute leukaemia in the northwestern part of Germany (Lower Saxony) conducted during 1992–1995[26–28] we have already examined the association between leukaemia and several factors operating during the prenatal and neonatal period. Based on 173 cases with acute leukaemia and 433 non-diseased children we found a weakly increased risk of childhood leukaemia with fetal losses. Neither maternal age at time of delivery nor birthweight altered the risk estimates. Neither maternal or paternal smoking habits were associated with childhood acute leukaemia. None of the results regarding prenatal or neonatal risk factors were statistically significant but, especially for extreme categories, data were sparse and only a few subjects were considered as being exposed. Moreover the study population was too small to conduct analyses for subgroups of patients, although there is evidence that the morphological and immunological subtypes of acute leukaemias should be examined separately since aetiological mechanisms may differ. For these reasons the case-control study was expanded on a nationwide basis. Here we report results of a German case-control study comprising almost 5000 subjects which allows us to calculate subgroup-specific risk estimates.

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Materials and Methods

The comprehensive nationwide part of our case-control study was conducted during 1992–1997. The following diagnostic groups were considered: acute leukaemia, non-Hodgkin's lymphoma (NHL), tumour of the central nervous system (CNS tumour), neuroblastoma, nephroblastoma, bone tumour and soft tissue sarcoma. Cases were identified from the nationwide German Childhood Cancer Registry in Mainz, which has an estimated completeness of more than 95%.[29] Cases were eligible if one of the diseases mentioned above was diagnosed in a child <15 years old between October 1992 and September 1994 and if the child lived in West Germany at the date of diagnosis. Controls were randomly selected from complete files of local offices for registration of residents. These files are an excellent sampling frame for population-based studies since they permit the sampling of individuals including children. For each case, the registration office of the district where the child lived at the date of diagnosis was asked for a list of four addresses of children of the same gender and of a similar date of birth (within one year). We randomly choose one control from this list (avoiding the case who might have been sampled as a potential control) to be selected as a control. If the selected family did not participate in the study, we got in touch with another family from the remaining names of the list. This procedure of control selection was repeated until the selected family consented to participate or until no more potential controls were left. Finally, for almost all cases there was a corresponding control matched for gender, date of birth within one year and district (smallest administrative unit in Germany).

The second part of our case-control study was embedded in an ecological study investigating childhood malignancies in the vicinity of German nuclear installations. The study population were cases of childhood acute leukaemia or NHL diagnosed between January 1980 and September 1994, aged ⩽15, born after 1 July 1975, and who at the date of diagnosis lived at most 15 km away from a nuclear installation or lived in a matched control region. Details on the choice of the control regions are described elsewhere.[30] Both parts of the study were conducted in close correspondence with respect to design, the technique of control selection and the interview techniques. We performed analyses not only separately but also calculated combined risk estimates in order to achieve greater statistical power to detect any factor associated with the diseases. Cases which fulfilled the eligibility criteria of both parts where considered in both separate analyses but only once in the combined analyses. The part of the case-control study conducted in West Germany will be abbreviated as the NW-study (nationwide part) throughout the text, the part of the case-control study in the vicinity of nuclear installations and its control regions will be abbreviated the NI-study, respectively.

Detailed information on characteristics of the prenatal and neonatal period was obtained by both questionnaire and telephone interview. The questionnaires were mailed by the physician responsible for the cancer treatment (cases) or by the study centre (controls) and were to be returned to the study centre where the information was completed and validated through a telephone interview by trained interviewers. If possible, both parents were interviewed. We checked for discrepancies between questionnaire and telephone interview to ensure a high data quality and therefore for some families parts of the interview were repeated. If the participating family had no phone, we had to rely solely on the information on the questionnaire.

The questions were based on a structured questionnaire developed by the US Children's Cancer Group (CCG).[3] It comprised details on maternal age at time of delivery, birthweight, and the number of pregnancies including fetal losses. We also asked for (1) the daily number of cigarettes smoked by each parent during the last 3 months before and during pregnancy as well as during the 3 months following birth, (2) the weekly maternal consumption of beer, wine, and strong liquor during the last 3 months before and during pregnancy, and (3) if the mother received hormones to treat her fertility problems.

We used a conditional logistic regression model (SAS 6.12, PROC PHREG[31]) to obtain the maximum likelihood estimate of the odds ratios (OR) and its 95% CI. Each case was matched to its corresponding control (1:1-matching).[32] Furthermore we adjusted for socioeconomic status (SES; average, high) which was estimated by family income and parental education. Data were analysed for all leukaemias combined and separately for the leukaemias of the NW-study and the leukaemias of the NI-study.

Since for analysing morphological or immunological subgroups data were sparse and because not all participating subjects had a matched correspondent, we applied a second model in order to increase statistical power to detect any association. Moreover, with this model results are based on larger numbers of subjects to avoid risk estimates being affected by coincidental differences in the prevalences of risk factors among small groups of control children. These analyses were done using frequency matching (m:n-matching [cases:controls]) in a conditional logistic regression model.[33] We performed *a posteriori*-stratification for gender, age (age groups of one year), year of birth, and vicinity to a nuclear installation (yes, no). Additional adjustments for degree of urbanization (rural, mixed, urban) and SES were made. With this model, analyses were conducted for acute non-lymphatic leukaemias (ANLL), for three immunological subtypes of ALL (common-ALL, pre-B-ALL, and T-ALL), for NHL and for the different diagnostic groups of solid tumours.

Results

In all, 2358 cases and 2588 controls participated in the case-control study. We received 1867 completed questionnaires from 2346 families with diseased children who fulfilled the eligibility criteria of the NW-study (response rate of 81.7%). Overall 691 cases (80.2%) out of 824 cases eligible for the NI-study sent back the questionnaire and 181 cases fulfilled the eligibility criteria for both study parts; 143 of them participated. The response rates for control families were 68.6% for the NW-study and 61.6% for the NI-study, respectively. Telephone interviews were performed with 95.0% of the participating case and 95.2% of the participating control families. Of all telephone interviews, 89.2% were done with both parents (8.8% only with the mother, 2.1% only with the father); there were no differences between the case and control groups. For cases as well as controls the response rates in urban areas were lower than in rural areas. The major reasons for non-participation were refusals (61.2%), which was more frequent among cases

Table 1 Diagnostic groups in the nationwide (NW) and vicinity of nuclear installations (NI) studies and these studies combined

	NW-study	NI-study	Combined[a]
Acute leukaemia	755	543	1184
ALL[b]	650	481	1037
common-ALL	450	307	686
pre-B-ALL	93	39	121
T-ALL	59	48	99
other subtype	48	87	131
ANLL[c]	105	62	147
Non-Hodgkin's lymphoma	172	91	234
Solid tumour	940	–	940
CNS-tumour	399	–	399
Neuroblastoma	160	–	160
Nephroblastoma	147	–	147
Bone tumour	97	–	97
Soft tissue sarcoma	137	–	137

[a] Because of the overlapping study populations the numbers are smaller than the sum of the numbers of the two individual parts of the study.

[b] Acute lymphatic leukaemia.

[c] Acute non-lymphatic leukaemia.

than among controls (70.8% versus 57.1%), lost to follow-up (13.4%; cases 4.6%, controls 17.1%), and insufficient knowledge of the German language to fill in the questionnaire (2.9%; cases 2.2%, controls 3.2%). Some 13.8% of all non-participants responded but were excluded from the study population, since after checking the information from the questionnaire we found violations of the eligibility criteria. This was the reason for 17.5% of all non-participation among cases and 12.2% of all non-participation among controls. Finally, 83 (2.8%) of all eligible case families did not receive the questionnaire, mainly for psychological reasons.

Table 1 provides details of the number of cases in each diagnostic subgroup. The group of other immunological subtypes of ALL comprises 37 children with pre-B-ALL, 7 children with B-ALL, and 87 children for which the immunological subtype was not obtained. Demographic information of cases and controls is shown in Table 2. While age, gender and district were matching criteria, there was a tendency towards a higher average family income among controls.

Table 3 shows the results for acute leukaemias and selected factors related to birth and pregnancy, derived from the 1:1-matched regression model as described in Methods.

Being younger than 20 years of age at time of delivery reveals a statistically significant association in both studies. This association is most pronounced for common-ALL (OR = 2.3, 95% CI : 1.4–3.8) based on 31 cases and 68 controls. For ANLL, pre-B-ALL and T-ALL the OR are in the range from 1.6 to 2.0, however, none of them is statistically significant. For mothers, who at time of delivery are ⩾35 years, the risk estimates are close to unity. There are no major differences between the immunological subtypes of ALL. For ANLL the OR is 1.2 (95% CI : 0.7–2.2, 14 cases, 214 controls).

Birthweight seems to have some influence on the risk of developing an acute leukaemia and affects children of both

Table 2 Distributions of age, gender, degree of urbanization and average monthly income

	ALL[a]		ANLL[b]		NHL[c]		CNS-tumour[d]		Neuro-blastoma		Nephro-blastoma		Bone tumour		Soft tissue sarcoma		Controls[e]	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Age (years)																		
0–4	634	61.1	74	50.3	59	25.2	165	41.4	145	90.6	112	76.2	8	8.2	63	46.0	1359	52.5
5–9	283	27.3	46	31.3	95	40.6	146	36.6	13	8.1	32	21.8	33	34.0	41	29.9	768	29.7
10–14	120	11.6	27	18.4	80	34.2	88	22.1	2	1.3	3	2.0	56	57.7	33	24.1	461	17.8
Gender																		
Male	615	59.3	82	55.8	174	74.4	229	57.4	89	55.6	70	47.6	52	53.6	80	58.4	1504	58.1
Female	422	40.7	65	44.2	60	25.6	170	42.6	71	44.4	77	52.4	45	46.4	57	41.6	1084	41.9
Degree of urbanization																		
Urban	377	36.4	50	34.0	89	38.0	155	38.8	73	45.6	64	43.5	40	41.2	48	35.0	1005	38.8
Mixed	368	35.5	56	38.1	82	35.0	126	31.6	52	32.5	48	32.7	21	21.6	48	35.0	872	33.7
Rural	292	28.2	41	27.9	63	26.9	118	29.6	35	21.9	35	23.8	36	37.1	41	29.9	711	27.5
Average monthly family income																		
<DM 2000	81	7.8	7	4.8	15	6.4	28	7.0	10	6.3	8	5.4	11	11.3	12	8.8	128	4.9
DM 2000–4000	573	55.3	79	53.7	116	49.6	190	47.6	84	52.5	87	59.2	45	46.4	75	54.7	1246	48.1
DM 4000–6000	234	22.6	36	24.5	47	20.1	113	28.3	36	22.5	31	21.1	27	27.8	33	24.1	709	27.4
DM 6000–8000	40	3.9	7	4.8	17	7.3	24	6.0	8	5.0	7	4.8	8	8.2	7	5.1	168	6.5
⩾DM 8000	31	3.0	1	0.7	13	5.6	15	3.8	6	3.8	6	4.1	2	2.1	4	2.9	91	3.5
Missing	78	7.5	17	11.6	26	11.1	29	6.7	16	10.0	8	5.4	4	4.1	6	4.4	246	9.5

[a] Acute lymphatic leukaemia.

[b] Acute non-lymphatic leukaemia.

[c] Non-Hodgkin's lymphoma.

[d] Tumour of the central nervous system.

[e] Combined controls.

Table 3 Odds ratios (OR) for childhood acute leukaemia derived from 1:1-matched analyses overall and in the nationwide (NW) and vicinity of nuclear installations (NI) studies

	Total[a]			NW-part			NI-part		
	Cases/controls	OR	95% CI	Cases/controls	OR	95% CI	Cases/controls	OR	95% CI
Maternal age at time of delivery (years)									
<20	45/24	1.9	(1.1–3.2)*	27/15	1.8	(0.9–3.5)	23/12	2.2	(1.0–4.8)
20–34 (reference)	877/899	1.0		576/588	1.0		388/402	1.0	
⩾35	81/80	1.1	(0.8–1.5)	56/56	1.1	(0.7–1.7)	34/31	1.1	(0.7–1.9)
Birthweight (g)									
<2500	49/30	1.7	(1.1–2.8)*	27/20	1.5	(0.8–2.7)	24/12	2.2	(1.1–4.5)*
2500–4000 (reference)	816/863	1.0		529/568	1.0		363/383	1.0	
>4000	130/102	1.4	(1.0–1.8)*	98/66	1.6	(1.2–2.3)*	55/47	1.2	(0.8–1.8)
Parity									
1 (reference)	206/180	1.0		157/128	1.0		67/66	1.0	
2 or 3	713/735	0.8	(0.7–1.1)	447/474	0.8	(0.6–1.0)	339/339	1.0	(0.7–1.5)
>3	78/82	0.8	(0.6–1.2)	51/53	0.8	(0.5–1.3)	36/37	0.9	(0.5–1.7)
Fetal losses									
None (reference)	767/775	1.0		506/506	1.0		339/339	1.0	
At least one	240/232	1.1	(0.9–1.3)	156/156	1.0	(0.8–1.4)	108/108	1.0	(0.7–1.4)
Hormonal treatment (infertility)									
No (reference)	843/861	1.0		555/567	1.0		378/392	1.0	
Yes	53/35	1.6	(1.0–2.5)*	35/23	1.7	(1.0–2.9)	26/12	2.2	(1.1–4.5)*
Maternal smoking during pregnancy (cigarettes/day)									
No (reference)	792/765	1.0		522/500	1.0		349/342	1.0	
1–10	159/174	0.8	(0.6–1.1)	111/120	0.8	(0.6–1.1)	67/71	0.9	(0.6–1.3)
11–20	25/39	0.5	(0.3–0.9)*	15/26	0.5	(0.2–1.0)*	12/19	0.6	(0.3–1.2)
>20	6/4	1.3	(0.4–4.7)	2/4	0.5	(0.1–2.7)	5/1	4.5	(0.5–39.0)
Paternal smoking before pregnancy (cigarettes/day)									
No (reference)	485/489	1.0		317/323	1.0		215/216	1.0	
1–10	112/100	1.1	(0.8–1.5)	78/63	1.2	(0.9–1.8)	45/48	0.9	(0.6–1.5)
11–20	256/259	1.0	(0.8–1.2)	171/170	1.0	(0.8–1.3)	112/115	0.9	(0.7–1.3)
>20	102/107	0.9	(0.7–1.2)	59/69	0.8	(0.5–1.2)	54/47	1.1	(0.7–1.7)

[a] Because of overlapping study populations the number of total (combined parts of the study) differs from the sum of the two separate parts.

* Statistically significant ($P < 0.05$).

lower and higher birthweight. Both OR remain increased if the analyses are restricted to cases with common-ALL: the association with birthweight <2500 g is of borderline statistical significance (OR = 1.5, 95% CI : 1.0–2.4, 33 cases, 85 controls) and the association with birthweight of >4000 g remains statistically significant (OR = 1.4, 95% CI : 1.1–1.8, 95 cases, 282 controls). Regarding pre-B-ALL we found slightly decreased OR of 0.7 (95% CI : 0.2–2.4, 3 cases, 85 controls) for lower birthweight and of 0.7 (95% CI : 0.4–1.4, 10 cases, 282 controls) for higher birthweight. Concerning ANLL, both OR are elevated, however, these associations are not statistically significant.

With regard to parity, there are considerable differences in the risk estimates for the different immunological subtypes of ALL. The inverse association with the number of births observed for all leukaemias combined holds good only for common-ALL with statistically significantly decreased OR for children with one or two siblings (OR = 0.7, 95% CI : 0.6–0.9, 475 cases, 1862 controls) and for children with at least three siblings (OR = 0.6, 95% CI : 0.4–0.8, 42 cases, 206 controls). While for T-ALL and also ANLL the OR are only slightly elevated, they are increased 1.7-fold (2–3 children: 95% CI : 0.9–2.9, 94 cases, 1862 controls) or twofold (>3 children: 95% CI : 0.9–4.6, 11 cases, 206 controls) respectively for pre-B-ALL. Taking birth order into account, there was no statistically significant elevation in risk for first-born children: the OR for children with acute leukaemia was 1.1 (95% CI: 0.9–1.3).

Children whose mothers had at least one fetal loss before the index child was born have no higher risk of developing leukaemia in our studies. For all immunological subtypes of ALL the OR range between 1.0 and 1.1. Regarding ANLL, we even found a statistically significantly decreased OR of 0.6 (95% CI : 0.4–1.0) based on 24 cases and 611 controls.

Use of hormones to treat the mother's fertility problems seems to be weakly associated with all types of childhood acute leukaemia. The OR are 1.2 for all three immunological subtypes of ALL. The highest OR is found for ANLL (OR = 1.5, 95% CI : 0.7–3.3, 9 cases, 120 controls).

The OR for maternal smoking habits during pregnancy show some inconsistencies between the two parts of our study. While for moderate smokers the risk estimates are close to unity in

Table 4 Odds ratios (OR) for non-Hodgkin's lymphomas, tumours of the central nervous system (CNS) and neuroblastomas derived from m:n-matched analyses

	Non-Hodgkin's lymphoma				CNS-tumour			Neuroblastoma		
	Controls	Cases	OR	95% CI	Cases	OR	95% CI	Cases	OR	95% CI
Maternal age at time of delivery (years)										
<20	68	12	1.8	(0.9–3.6)	12	1.1	(0.6–2.0)	2	0.7	(0.2–3.1)
20–34 (reference)	2300	206	1.0		360	1.0		146	1.0	
⩾35	214	15	0.9	(0.5–1.6)	24	0.8	(0.5–1.2)	11	0.8	(0.4–1.5)
Birthweight (g)										
<2500	85	14	2.3	(1.2–4.3)*	19	1.6	(0.9–2.7)	13	2.4	(1.2–4.8)*
2500–4000 (reference)	2210	193	1.0		321	1.0		125	1.0	
>4000	282	23	0.9	(0.5–1.4)	55	1.3	(0.9–1.8)	22	1.3	(0.8–2.1)
Parity										
1 (reference)	509	48	1.0		91	1.0		60	1.0	
2 or 3	1862	160	0.6	(0.4–0.9)*	282	0.8	(0.6–1.1)	87	0.8	(0.5–1.1)
>3	206	26	0.7	(0.4–1.2)	23	0.6	(0.4–1.0)*	12	1.3	(0.6–2.6)
Fetal losses										
None (reference)	1972	175	1.0		297	1.0		115	1.0	
At least one	611	59	1.1	(0.8–1.5)	101	1.1	(0.8–1.4)	44	1.3	(0.9–2.0)
Hormonal treatment (infertility)										
No (reference)	2323	202	1.0		358	1.0		137	1.0	
Yes	120	8	0.9	(0.4–1.9)	18	1.0	(0.6–1.8)	8	1.1	(0.5–2.4)
Maternal smoking during pregnancy (cigarettes/day)										
No (reference)	2062	173	1.0		320	1.0		114	1.0	
1–10	426	46	1.3	(0.9–1.9)	55	0.8	(0.6–1.1)	39	1.5	(1.0–2.2)
11–20	72	6	1.0	(0.4–2.5)	17	1.6	(0.9–2.8)	3	0.6	(0.2–2.0)
>20	11	3	5.2	(1.2–22.4)*	2	0.8	(0.2–3.9)	3	2.5	(0.6–10.4)
Paternal smoking before pregnancy (cigarettes/day)										
No (reference)	1336	107	1.0		195	1.0		84	1.0	
1–10	293	35	1.6	(1.0–2.5)*	37	0.8	(0.5–1.2)	11	0.6	(0.3–1.1)
11–20	647	56	1.1	(0.7–1.6)	112	1.1	(0.8–1.4)	41	1.1	(0.7–1.6)
>20	264	23	1.1	(0.7–1.8)	41	1.0	(0.7–1.4)	19	1.2	(0.7–2.1)

* Statistically significant ($P < 0.05$).

both parts and there are decreased OR for mothers smoking 11–20 cigarettes per day during pregnancy for the NW- as well as the NI-study, for heavy smokers the OR is 0.5 for the NW-study but there is a 4.5-fold increase for the NI-study (Table 3). For common-ALL we detected a weakly increasing risk with increasing number of cigarettes (1–10 cig/day: OR 1.1 [95% CI : 0.9–1.4], 11–20 cig/day: OR 1.2 [95% CI : 0.8–2.0], 20+ cig/day: OR 2.1 [95% CI : 0.7–6.3]). Since for the other types of leukaemia there were less than five cases in the two highest exposure categories, the OR are very unprecise as reflected by wide confidence intervals. Paternal smoking the last 3 months before conception is not associated with childhood acute leukaemia. The OR are close to unity for the entire study population as well as the two parts of our study separately. Heavy paternal smoking leads to an OR of 1.1 (95% CI : 0.8–1.5) for common-ALL, to an OR of 0.9 (95% CI : 0.5–1.7) for pre-B-ALL, to an OR of 1.7 (95% CI : 0.9–3.2) for T-ALL, and to an OR of 0.5 (95% CI : 0.2–1.1) for ANLL.

Table 4 shows the results for children with NHL (NW-study and NI-study combined). This is associated with a birthweight <2500 g, with heavy maternal smoking during pregnancy, with light paternal smoking before pregnancy, and is inversely associated with two or three live births of the index child's mother. None of these associations remain statistically significant if the calculations are based on the 1:1-matched regression model. This might be due to the smaller numbers of subjects, but while for a birthweight <2500 g at least the tendency towards an elevation in risk reoccurs (OR = 2.6, 95% CI : 0.9–7.4, 13 cases, 5 controls), the other associations with NHL from the m:n-matched analyses vanish.

The OR for CNS tumour, neuroblastoma, nephroblastoma, bone tumour and soft tissue sarcoma are shown in Tables 4 and 5. Distinguishing between the different types of solid tumours, we found only few associations of statistical significance. Children with neuroblastoma more often had a birthweight <2500 g compared with non-diseased children. The age of the mother at time of delivery was associated with soft tissue sarcoma: while for children of very young mothers we found a statistically significantly elevated risk, it is decreased for children of mothers ⩾35 years at time of delivery. Children with one or two siblings

Table 5 Odds ratios (OR) for nephroblastomas, bone tumours and soft tissue sarcomas derived from m:n-matched analyses

	Nephroblastoma				Bone tumour			Soft tissue sarcoma		
	Controls	Cases	OR	95% CI	Cases	OR	95% CI	Cases	OR	95% CI
Maternal age at time of delivery (years)										
<20	68	4	1.6	(0.5–4.7)	2	0.4	(0.1–1.6)	10	2.2	(1.0–4.7)*
20–34 (reference)	2300	128	1.0		90	1.0		123	1.0	
⩾35	214	13	1.0	(0.5–1.8)	5	0.7	(0.3–1.8)	4	0.4	(0.1–1.0)*
Birthweight (g)										
<2500	85	4	0.9	(0.3–2.6)	5	1.7	(0.6–4.5)	9	1.8	(0.8–3.7)
2500–4000 (reference)	2210	122	1.0		75	1.0		117	1.0	
>4000	282	20	1.3	(0.8–2.1)	15	1.5	(0.8–2.9)	11	0.7	(0.4–1.4)
Parity										
1 (reference)	509	55	1.0		19	1.0		36	1.0	
2 or 3	1862	76	0.5	(0.3–0.7)*	67	0.7	(0.4–1.2)	88	0.7	(0.5–1.1)
>3	206	15	1.1	(0.6–2.0)	10	0.7	(0.3–1.7)	13	0.9	(0.5–1.9)
Fetal losses										
None (reference)	1972	112	1.0		74	1.0		102	1.0	
At least one	611	35	1.0	(0.7–1.5)	23	0.8	(0.5–1.4)	34	1.1	(0.7–1.7)
Hormonal treatment (infertility)										
No (reference)	2323	130	1.0		91	1.0		124	1.0	
Yes	120	8	1.3	(0.6–2.7)	2	0.6	(0.1–2.4)	8	1.1	(0.5–2.4)
Maternal smoking during pregnancy (cigarettes/day)										
No (reference)	2062	117	1.0		82	1.0		113	1.0	
1–10	426	22	0.9	(0.5–1.4)	10	0.7	(0.3–1.4)	20	0.9	(0.5–1.4)
11–20	72	6	1.2	(0.5–3.0)	2	0.9	(0.2–3.9)	3	0.8	(0.2–2.6)
>20	11	0	–	–	1	2.5	(0.3–22.4)	1	1.6	(0.2–13.3)
Paternal smoking before pregnancy (cigarettes/day)										
No (reference)	1336	81	1.0		55	1.0		67	1.0	
1–10	293	14	0.8	(0.4–1.4)	6	0.5	(0.2–1.2)	13	0.8	(0.4–1.6)
11–20	647	35	0.8	(0.5–1.3)	23	0.8	(0.4–1.3)	41	1.2	(0.8–1.8)
>20	264	13	0.9	(0.5–1.6)	11	0.9	(0.4–1.8)	12	0.9	(0.4–1.6)

* Statistically significant ($P < 0.05$).

have a tendency towards a reduction in risk for all types of solid tumours, however, only for children with nephroblastoma is the OR statistically significantly decreased. Having at least three siblings is inversely associated with CNS tumours.

Information about weekly alcohol consumption was derived via questionnaire. In all, 75.0% of all mothers declared that they drank no alcohol during pregnancy. The percentage who were totally abstinent during pregnancy is almost equal between mothers of leukaemia cases and mothers of control children (75.6% c.f. 75.8%). The only difference is that, of those women drinking alcohol during pregnancy, mothers of children with leukaemia tended to prefer beer while mothers of non-diseased children were more likely to enjoy a glass of wine. As shown in Table 6, the risk estimates were close to unity. The OR for the immunological and morphological subtypes of acute leukaemia range between 0.9 and 1.1 for the medium category and are very unprecise for the highest exposure category. Combining all types of solid tumours reveals a decreased OR of 0.8 (95% CI : 0.6–0.9) for moderate alcohol consumers. As shown in Table 6, this effect is most pronounced for bone tumour with a statistically significant OR of 0.3 in the exposure category of 1–7 glasses weekly. However, the OR for the other types of solid tumours are also below unity.

Down's syndrome is known a causal risk factor for childhood acute leukaemias.[1,34] In our studies, we observed an extremely high risk estimate of 55.0 (95% CI : 7.4–410.9) based on 26 cases and one control (m:n-matched analysis, regarding 1:1-matched analyses there were 23 cases but no control). These 26 cases break down into 11 children with common-ALL, 3 children with pre-B-ALL, 1 child with T-ALL, 2 children with ALL of an unknown immunological subtype, and 9 children with ANLL. We assessed the effect of this strong risk factor on our results. We detected that seven children with both acute leukaemia and Down's syndrome had a mother who was ⩾35 years at time of delivery and two had a mother who was ⩽20 years, four of those children had a birthweight ⩽2500 g and only one child had a birthweight >4000 g. Therefore the OR for lower as well as higher birthweight without inclusion of cases with Down's syndrome are somewhat lower than those presented in Table 3, but they remain statistically significantly increased (data not shown). The risk for a younger maternal age at time of delivery changes only slightly, the OR for older mothers drops right to

Table 6 Odds ratios (OR) for childhood cancers with regard to maternal alcohol consumption during pregnancy in the study overall (total) and in the nationwide (NW) and vicinity of nuclear installations (NI) studies

	Leukaemia total[a]			**Leukaemia NW-study**			**Leukaemia NI-study**		
	Cases/controls	OR[b]	95% CI	Cases/controls	OR[b]	95% CI	Cases/controls	OR[b]	95% CI
Maternal weekly alcohol consumption during pregnancy (glasses per week)									
No (reference)	714/685	1.0		489/474	1.0		301/282	1.0	
1–7	239/261	0.9	(0.7–1.1)	148/160	0.9	(0.7–1.2)	115/128	0.9	(0.6–1.2)
>7	11/18	0.6	(0.3–1.3)	10/13	0.8	(0.3–1.8)	2/8	0.2	(0.1–1.2)
	Non-Hodgkin's lymphoma			**CNS[c]-tumour**			**Neuroblastoma**		
	Cases/controls	OR[d]	95% CI	Cases/controls	OR[d]	95% CI	Cases/controls	OR[d]	95% CI
Maternal weekly alcohol consumption during pregnancy (glasses per week)									
No (reference)	177/1875	1.0		306/1875	1.0		124/1875	1.0	
1–7	48/649	0.8	(0.6–1.2)	85/649	0.9	(0.7–1.1)	32/649	0.9	(0.6–1.3)
>7	0/33	–	–	2/33	0.4	(0.1–1.6)	2/33	1.9	(0.4–9.9)
	Nephroblastoma			**Bone tumour**			**Soft tissue sarcoma**		
	Cases/controls	OR[d]	95% CI	Cases/controls	OR[d]	95% CI	Cases/controls	OR[d]	95% CI
Maternal weekly alcohol consumption during pregnancy (glasses per week)									
No (reference)	119/1875	1.0		85/1875	1.0		109/1875	1.0	
1–7	26/649	0.7	(0.5–1.1)	11/649	0.3	(0.2–0.7)*	24/649	0.7	(0.5–1.1)
>7	0/33	–	–	1/33	0.4	(0.1–3.4)	3/33	2.2	(0.6–8.0)

[a] Because of overlapping study populations the number of total (combined parts of the study) differs from the sum of the two separate parts.

[b] From 1:1-matched conditional logistic regression analyses.

[c] Tumour of the central nervous system.

[d] From conditional logistic regression analyses stratified for gender, year of birth, study setting and age, adjusted for SES and degree of urbanization (m:n-matched analyses).

* Statistically significant ($P < 0.05$).

unity (OR = 1.0, 95% CI : 0.7–1.4, leukaemias combined, 1:1-matched regression model).

Discussion

One strength of our study is that cases were identified from an almost complete cancer registry and controls were drawn at random from complete files of population-based registries. In Germany, registration is mandatory for all residents, which makes these registries an excellent sampling frame for epidemiological studies. Response rates of more than 80% for cases and 60–70% for controls were reasonably good, however, selection bias cannot completely be ruled out. The distributions of age and gender of the cases of our study population reflect the distributions ascertained by the German Childhood Cancer Registry for the different types of tumours on the basis of all registered children, so we have reason to believe that non-participation of cases did not bias our results. Since controls were matched for gender, date of birth and district there were no major differences between the study groups concerning gender, age and degree of urbanization. Because families with non-diseased children of higher average monthly family income were more likely to participate than others, we revealed differences between cases and controls regarding SES. Therefore, in all analyses we additionally adjusted for SES.

In summary, it appears that we found no convincing factor for a strong association with childhood cancer. Although maternal age at time of delivery, low as well as high birthweight, hormonal treatment and parity were statistically significantly linked to some types of cancer, none of these factors is likely to represent a causal relationship, but rather a proxy for processes during pregnancy and birth that predispose to cancer.

The influence of maternal age at time of delivery on the subsequent risk of childhood acute leukaemia has been studied previously. Our finding of an increased risk for children of very young mothers is in accordance with a Swedish[5,6] and two US studies.[13,16] Some earlier studies also discussed an elevated risk of acute leukaemia with a higher maternal age at time of delivery.[9,11] Like others,[5,6,8,12,17] we found no confirmation of this observation. Our risk estimates for elder mothers were close to unity after exclusion of children with Down's syndrome.

In contrast to one earlier study,[22] we observed associations of birthweight <2500 g with acute leukaemia, NHL and neuroblastomas respectively. Although lower birthweight occurred more often than expected if the mother was ⩽20 years at time of delivery, if the mother received hormones because of fertility problems or if the child had Down's syndrome, these correlations could not explain our findings. While our observations for heavier babies are in accordance with some previous studies,[6–8,10,17,24] other investigators found positive associations at most restricted to subgroups of patients.[3,9,11,12] Daling *et al.*[7] hypothesize that higher birthweight might be a proxy for *in utero* X-ray exposures or maternal diabetes, but there was no evidence for this theory in our studies. Probably increased growth hormone secretion is a potential link between high birthweight and the development of a childhood malignancy.[35]

In our study, the assocation with higher birthweight was not as strong as for lower birthweight and it was statistically significant only for acute leukaemias.

In our previous study in Lower Saxony,[26] we observed a 3.5-fold risk of acute leukaemia for children whose mothers received hormones because of fertility problems. This finding was confirmed partly by the new study but should be addressed in future research. Even if this association of hormonal treatment with the incidence of childhood acute leukaemia is true, the aetiological mechanism may be more likely related to the infertility instead of the effect of the hormonal treatment.[21]

Multiparity reduced the risk of developing an acute leukaemia in our study. It is notable that this observation is restricted to children with common-ALL, which is consistent with Greaves' theory of leukaemogenesis.[2,36,37] In this two-step model for common-ALL, a spontaneous mutation of lymphoid cells takes place *in utero*, later promoted by delayed exposure to a common infection. According to this model, the lack of early exposure to this infectious agent leads to an unbalanced, probably hyperreactive response of the child's immune system to this ubiquitous virus when the child is older. We presume that a lack of early exposure is more likely for children without siblings, what might be an explanation for the negative association of common-ALL with parity. However, the leukaemia risk for first-born children, which is proposed to be increased according Greaves' hypothesis,[2] was only weakly elevated and also some types of solid tumours were inversely associated with parity in our studies. Probably some families which have a child with a malignant disease tend to decide to have no further children.

Recent reviews of the literature found no epidemiological study that revealed a statistically significantly increased risk of acute leukaemia with maternal smoking during pregnancy.[19,38] On the contrary, some investigators report a tendency towards risk reduction with a higher amount of smoked cigarettes per day.[5,10,18] We obtained a decreased OR for mothers smoking 11–20 cigarettes per day during pregnancy. As expected, maternal smoking habits for cases as well as controls are distinctly related to average monthly family income, maternal education and birthweight, which makes differential misclassification improbable. For NHL, the risk estimates were increased. Summarizing, there is no plausible biological mechanism for this observation, and of course this is of no consequence for recommendations concerning smoking habits during pregnancy.

Combining two different study populations is worth reflecting its potential for biases. The designs and the procedures of control selection of the two parts of our case-control study were equal, with the NI-study restricted to specific geographical areas. We used the same questionnaire in both parts and the telephone interviews were done by the same trained interviewers. Since the major difference of the two parts was the period of diagnosis, we had a close look on the time-dependency of the different characteristics. However, risk estimates were also calculated separately for the NW-study and the NI-study, respectively. None of the analysed characteristics related to birth or pregnancy showed any noteworthy differences attributable to the study setting. Moreover, for most evaluated risk factors like parity, maternal age at the time of delivery or birthweight, recall bias is not to be expected.

However, recall bias is of course a problem when analyses rely on information obtained by telephone interview and questionnaire. Cases and controls received the questionnaire from two different sources and the interviewers were not blinded to case-control-status, since we used phrases like 'patient' and 'child' or 'date of diagnosis' and 'reference date' during the interview. To ensure a high data quality, interviewers were trained regularly by a psychologist and the course of the interview was given in detail. The items on the questionnaire were cross-checked concerning coding and all data were recorded twice. We checked for discrepancies between interview and questionnaire. Nevertheless, recall bias might have influenced the results especially regarding smoking habits, alcohol consumption and hormonal treatment because of infertility.

The large number of comparisons could result in some statistically significant findings which might have occurred by chance and we did the analyses without adjustment for multiple testing. Instead, the choice of characteristics to be reported and the categorization into exposed and unexposed were defined in advance. Moreover, we discussed our findings taking into account the strength of the association, its consistency with previous international studies on this topic, its internal consistency derived from analyses of different subgroups and its aetiological background. Some positive as well as negative results are presented to contribute to the ongoing discussion about potential risk factors of childhood cancer, but they were characterized as obtained by exploratory analyses and they may be considered again in future studies.

While we think there is evidence that both lower and higher birthweight, younger maternal age at time of delivery, hormonal treatment because of infertility and parity have some effect on developing a malignant disease during childhood, some associations might have occurred by chance and need examination in future studies. Overall, we identified a few weak associations and the impact of prenatal and neonatal factors evaluated in our study on childhood cancers is only small. Concluding, only a small proportion of childhood cancers would be attributable to factors operating during pregnancy and birth. With the intention to explore further risk factors, our study is being extended to exposures to ionizing radiation, other environmental factors and to measurements of residential magnetic fields.

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