Eur J Pediatr (2007) 166:433–441
DOI 10.1007/s00431-006-0401-z

ORIGINAL PAPER

Medication use during pregnancy and the risk of childhood cancer in the offspring

Joachim Schüz · Thomas Weihkopf · Peter Kaatsch

Received: 8 December 2006 / Accepted: 14 December 2006 / Published online: 8 March 2007

Abstract The young age at onset of many cancers in childhood has led to investigations on maternal exposures during pregnancy. Data from a population-based case-control study in Germany (1992–1997) that included 1,867 cases and 2,057 controls was used to investigate this question. Maternal use of vitamin, folate or iron supplementation was associated with a reduced risk of non-Hodgkin lymphoma and tumors and, less clearly, with leukemia, but not with CNS tumors. An increased risk of neuroblastoma was associated most markedly with diuretics and other antihypertensives, but also with vitamin, folate or iron supplementation. No associations were seen with pain relievers, antinauseants or cold medications, nor with delivery by Caesarian section. The strengths of this study are its population base, the large number of cases and the inclusion of different case groups to identify disease specificity of associations. The limitation of this study is an exposure assessment relying on maternal self-reports. In conclusion, these data indicate a potential influence of some maternal medication during pregnancy on the risk of childhood cancer in the offspring; however, no clear picture is seen.

Sponsored by the Federal Ministry for the Environment, Nuclear Safety, and Nature Protection.

J. Schüz · T. Weihkopf · P. Kaatsch (✉)
Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), Johannes Gutenberg-University of Mainz,
55101 Mainz, Germany
e-mail: kaatsch@imbei.uni-mainz.de

J. Schüz
Institute of Cancer Epidemiology, Danish Cancer Society,
Strandboulevarden 49,
DK-2100 Copenhagen, Denmark

Keywords Child · Leukemia · Neoplasms · Pregnancy · Medication

Abbreviations

ALL	acute lymphoblastic leukemia
AML	acute myeloblastic leukemia
CNS	central nervous system
NHL	non-Hodgkin lymphoma
OR	odds ratio
CI	confidence interval
SES	socioeconomic status

Introduction

There is growing evidence that various types of childhood cancers are initiated already in utero [1, 17, 21]. It is biologically plausible that mutations in utero contribute particularly to the development of cancers in infancy, due to the young age of onset for the disease [34]. More recently, with the use of direct molecular tests, it has been shown that many cases of the most common type of childhood cancer, acute lymphoblastic leukemia (ALL), are also initiated in utero [10, 12, 13, 20, 49]. This emphasizes the importance of maternal exposures during pregnancy and their possible role in the etiology of childhood cancer. Maternal medication use during pregnancy is linked to such exposures because drugs may cross the placenta and, potentially, damage the fetus [46]. Congenital malformations are one adverse pregnancy outcome that was demonstrated to be associated with maternal medication use [15]. There are a number of epidemiological studies in which an association between maternal medication use during pregnancy and the risk of childhood cancer has been

investigated; however, no clear picture has emerged so far [21]. Among those associations that show some degree of consistency are the relation between maternal use of diuretics and an increased risk of neuroblastoma [18, 39], and a risk reduction for leukemia and CNS tumors with maternal use of folate [6, 28, 29, 44, 48].

During the years 1992 to 1997, a large-scale case-control study on causes of childhood cancer was conducted in Germany, including cases with acute leukemia, non-Hodgkin lymphoma (NHL), CNS tumor, neuroblastoma, Wilms' tumor, bone tumor and soft tissue sarcoma [36]. Questions on maternal drug use were part of the original questionnaire; however, due to the huge amount of information from a total of 1,867 cases and 2,057 controls, this information was not coded and evaluated before now. This is a report of the analyses addressing maternal medication use during pregnancy and the risk of various childhood cancers in the offspring.

Materials and methods

Cases were ascertained from the nationwide German Childhood Cancer Registry (GCCR) at the University of Mainz, which is estimated to be more than 95% complete [11]. Patients aged 14 years or less were eligible if their disease was diagnosed between October 1992 and September 1994, and if the child lived in West Germany at the date of diagnosis. For each case, one control matched by gender, date of birth within at most 1 year and community was selected from the complete files of the local resident registration offices. More details are described elsewhere [36].

Information on potential risk factors was collected by both a self-administered questionnaire and a subsequent telephone interview with both parents. The questions were based on a structured questionnaire developed by the US Children's Cancer Group [31]. Questionnaires were mailed by the physician responsible for the cancer treatment (cases) or by the study center at the GCCR (controls) and were returned to the study center. The questions on maternal medication use were on the postal questionnaire. A list of medication groups was offered to the mother with three check-boxes per group, representing "yes", "no" or "unknown". The listed medication groups included vitamin, folate or iron supplements; antinauseants or antiemetics; diuretics or other antihypertensives; tranquillizers or sleeping pills; pain relievers; cold medications; psychotropics; antiepileptics; and diet pills. In addition to that, each medication group was followed by an open text field to specify the brand names of the respective drugs. All brand names were coded according the "Rote Liste," a German dictionary of medications, to check the classifications from the questionnaire and to obtain data on specific substances. No information was available on which trimesters the medication was taken. We also asked the mother about episodes of high blood pressure or edema during pregnancy and whether the index child's delivery was by Caesarean section. Questions concerning the socioeconomic status of a family were based on parental education, on parental occupational training and on the average monthly family net income, and were all part of the telephone interview.

Statistical methods

Odds ratios (OR) and 95 percent confidence intervals (CI) were computed by conditional logistic regression analysis for matched pairs [43]. To achieve a greater statistical power to detect any association, all analyses were repeated using a post-hoc frequency-matched regression model [4, 24], involving all available cases and controls, irrespective of whether they had a matched partner or not. This model always included the total set of controls. The frequency-matched logistic regression model was stratified by gender, age (groups of 1 year) and year of birth, and additionally adjusted for the degree of urbanization (urban, rural, mixed urban-rural) to compensate for breaking the individual matching. Both conditional logistic regression analyses and frequency-matched conditional logistic analyses were adjusted for socioeconomic status (high; average). In this paper, the results from the frequency-matched analyses are presented by default. Risk estimates from the 1:1-matched model are presented only if there were major differences compared to the frequency-matched approach. We did not apply statistical procedures to adjust for multiple testing, but discuss our findings in respect to their consistency with other studies on this topic, as the adjustment would have substantially decreased the statistical power of our study to detect any association.

Results

The overall response rates were 82.6% among cases and 70.9% among controls (Table 1). The participation rates (the number of families who returned the questionnaire divided by the number of families who were contacted) among control families were lower than among case families (70.9% vs. 84.8%); however, there were only minor differences across the diagnostic groups, with participation rates ranging from 82.3% (bone tumors) to 85.5% (CNS tumors). The overwhelming reason for non-participation was parental refusal. Among families of eligible cases, only 2.6% were not contacted, mainly because of physician preference.

Table 1 Response rates in a German case-control study on maternal medication use during pregnancy and the risk of childhood cancer in the offspring

	Eligible		Contacted		Returned questionnaire		Included in analyses[a]	
	n	%	n	%	n	%	n	%
Cases	2,346	100.0	2,286	97.4	1,938	82.6	1,867	79.6
Controls			2,998	100.0	2,126	70.9	2,057	68.6

[a] Some participants had to be excluded because of violations of the eligibility criteria that were discovered using the questionnaire data

There was a general tendency that control families were more likely to have a higher socioeconomic status (SES) than case families (Table 2). All demographic characteristics were considered as potential confounders and adjusted for in all subsequent analyses.

Table 3 displays the most frequent medication groups used by the mother during pregnancy and their associations with the risk of childhood cancer in the offspring. Vitamin, folate and/or iron supplements were associated with reduced risks of ALL, NHL and Wilms' tumor and an increased risk of neuroblastoma. In the individually matched analysis, however, the association with ALL moved towards null (OR 0.96, 95 percent CI: 0.75, 1.22).

Maternal use of diuretics and other antihypertensives during pregnancy was associated with increased risks of ALL and of neuroblastoma. Again, the association with ALL was less apparent from the individually matched approach (OR 1.14, 95 percent CI: 0.50, 2.60). Regarding the risk of CNS tumors, the odds ratios varied with the type of brain tumor: The slight increase in the overall risk of CNS tumors was completely attributable to primitive neuroectodermal tumors (PNET) (OR 4.14, 95 percent CI: 1.30, 13.2), while no mothers of patients with ependymoma or astrocytoma had taken antihypertensives. It has to be noted that the risk increases for neuroblastoma observed with antihypertensives were seen for both low-stage as well as high-stage neuroblastomas.

No associations with any kind of childhood cancer were seen for maternal use of pain relievers, antinauseants or antiemetics, and cold medications.

More mothers of patients than controls reported episodes of high blood pressure or edema during pregnancy. However, the majority of mothers received no treatment for these syndromes. Table 4 presents the childhood cancer risks associated with maternal high blood pressure or edema during pregnancy, divided into groups of mothers who received no treatment and mothers who have reported an intake of antihypertensives such as diuretics. The latter group was associated only with an increased neuroblastoma risk, which was more pronounced for low-stage neuroblas-

Table 2 Demographic characteristics of cases and controls from a German case-control study on maternal medication use during pregnancy and the risk of cancer in the offspring

	Controls	ALL[a]	AML[a]	NHL[a]	CNS tumor	Neuroblastoma	Wilms' tumor	Bone tumor	Soft tissue sarcoma
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Gender									
Boys	1,182 (57.5)	389 (59.8)	59 (56.2)	129 (75.0)	229 (57.4)	86 (54.8)	70 (47.6)	52 (53.6)	80 (58.4)
Girls	875 (42.5)	261 (40.2)	46 (43.8)	43 (25.0)	170 (42.6)	71 (45.2)	77 (52.4)	45 (46.4)	57 (41.6)
Age									
0–4 years	1,047 (50.9)	380 (58.5)	52 (49.5)	43 (25.0)	165 (41.4)	145 (92.4)	112 (76.2)	8 (8.2)	63 (46.0)
5–9 years	613 (29.8)	181 (27.8)	33 (31.4)	67 (39.0)	146 (36.6)	12 (7.6)	32 (21.8)	33 (34.0)	41 (29.9)
10–14 years	397 (19.3)	89 (13.7)	20 (19.0)	62 (36.0)	88 (22.1)	0	3 (2.0)	56 (57.7)	33 (24.1)
Degree of urbanization									
Urban	862 (41.9)	278 (42.8)	42 (40.0)	67 (39.0)	155 (38.8)	71 (45.2)	64 (43.5)	40 (41.2)	48 (35.0)
Mixed	647 (31.5)	201 (30.9)	34 (32.4)	62 (36.0)	126 (31.6)	51 (32.5)	48 (32.7)	21 (21.6)	48 (35.0)
Rural	548 (26.6)	171 (26.3)	29 (27.6)	43 (25.0)	118 (29.6)	35 (22.3)	35 (23.8)	36 (37.1)	41 (29.9)
SES[a]									
Average	1,453 (70.6)	491 (75.5)	82 (78.1)	126 (73.3)	295 (73.9)	121 (77.1)	108 (73.5)	67 (69.1)	106 (77.4)
High	604 (29.4)	159 (24.5)	23 (21.9)	46 (26.7)	104 (26.1)	36 (22.9)	39 (26.5)	30 (30.1)	31 (22.6)
Total	2,057	650	105	172	399	157	147	97	137

[a] Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; NHL, non-Hodgkin lymphoma; SES, socioeconomic status

Table 3 Association between maternal medication use during pregnancy and the risk of childhood cancer, according to main groups of medications and diagnostic groups of various malignancies

Maternal medication use during pregnancy ?	No		Yes		OR[a]	95% CI[a]
	n	%	n	%		
Vitamin, folate and/or iron supplements						
Acute lymphoblastic leukemia (ALL)	391	61.8	242	38.2	0.84	0.69–1.01
Acute myeloblastic leukemia (AML)	57	56.4	44	43.6	1.13	0.74–1.72
Non-Hodgkin lymphoma (NHL)	114	68.7	52	31.3	0.68	0.48–0.97
CNS tumor	220	56.4	170	43.6	1.07	0.85–1.34
Neuroblastoma	72	45.6	86	54.4	1.50	1.06–2.13
Wilms' tumor	95	65.5	50	34.5	0.66	0.45–0.95
Bone tumor	58	61.7	36	38.3	0.95	0.60–1.50
Soft tissue sarcoma	89	65.9	46	34.1	0.74	0.50–1.08
Controls	1,153	57.3	860	42.7		
Diuretics/antihypertensives						
Acute lymphoblastic leukemia (ALL)	625	97.8	14	2.2	1.99	1.01–3.93
Acute myeloblastic leukemia (AML)	102	100.0	0	0.0	–	
Non-Hodgkin lymphoma (NHL)	163	98.8	2	1.2	0.55	0.12–2.46
CNS tumor	384	98.0	8	2.0	1.65	0.73–3.74
Neuroblastoma	153	96.8	5	3.2	3.16	1.03–9.70
Wilms' tumor	141	97.2	4	2.8	2.18	0.68–7.02
Bone tumor	92	97.9	2	2.1	1.08	0.23–5.19
Soft tissue sarcoma	132	97.8	3	2.2	1.78	0.51–6.20
Controls	1,999	98.7	26	1.3		
Pain relievers						
Acute lymphoblastic leukemia (ALL)	605	95.1	31	4.9	0.87	0.57–1.32
Acute myeloblastic leukemia (AML)	95	94.1	6	5.9	1.04	0.43–2.54
Non-Hodgkin lymphoma (NHL)	157	95.2	8	4.8	1.06	0.49–2.29
CNS tumor	370	95.1	19	4.9	1.00	0.60–1.67
Neuroblastoma	144	91.7	13	8.3	1.06	0.56–2.01
Wilms' tumor	134	92.4	11	7.6	1.11	0.57–2.15
Bone tumor	93	98.9	1	1.1	0.33	0.04–2.51
Soft tissue sarcoma	131	98.5	2	1.5	0.24	0.06–1.01
Controls	1,905	94.5	111	5.5		
Antinauseants or antiemetics						
Acute lymphoblastic leukemia (ALL)	607	95.3	30	4.7	1.17	0.76–1.83
Acute myeloblastic leukemia (AML)	96	94.1	6	5.9	1.37	0.57–3.29
Non-Hodgkin lymphoma (NHL)	160	96.4	6	3.6	1.23	0.51–3.00
CNS tumor	374	95.4	18	4.6	1.15	0.68–1.96
Neuroblastoma	150	94.9	8	5.1	1.07	0.48–2.37
Wilms' tumor	136	93.8	9	6.2	1.22	0.59–2.51
Bone tumor	91	96.8	3	3.2	0.95	0.27–3.28
Soft tissue sarcoma	128	94.8	7	5.2	1.18	0.52–2.67
Controls	1,941	95.9	83	4.1		
Cold medications						
Acute lymphoblastic leukemia (ALL)	566	88.9	71	11.1	1.10	0.82–1.48
Acute myeloblastic leukemia (AML)	88	86.3	14	13.7	1.37	0.74–2.53
Non-Hodgkin lymphoma (NHL)	152	93.3	11	6.7	0.94	0.49–1.81
CNS tumor	355	91.7	32	8.3	0.81	0.55–1.21
Neuroblastoma	134	84.8	24	15.2	0.94	0.58–1.55
Wilms' tumor	129	89.0	16	11.0	0.80	0.46–1.39
Bone tumor	90	96.8	3	3.2	0.37	0.11–1.23
Soft tissue sarcoma	119	90.2	13	9.8	0.85	0.46–1.58
Controls	1,783	89.4	211	10.6		

[a] Odds ratio (OR) and respective 95 percent confidence interval (CI) of maternal use of certain drugs during pregnancy compared to the baseline of not using this particular drug, derived from logistic regression analysis adjusted for sex, age, year of birth, degree of urbanization and socioeconomic status (SES)

Table 4 Association between high blood pressure or edema during pregnancy and the risk of childhood cancer, according to the use of medication for these syndromes and diagnostic groups of various malignancies

High blood pressure or edema?	No		Yes, no drugs		OR[a]	95% CI[a]	Yes, with drugs		OR[a]	95% CI[a]
	n	%	n	%			n	%		
Acute lymphoblastic leukemia (ALL)	490	76.6	124	19.4	1.18	0.93–1.50	26	4.1	1.14	0.71–1.82
Acute myeloblastic leukemia (AML)	77	75.5	23	22.5	1.21	0.74–2.00	2	2.0	0.71	0.17–3.01
Non-Hodgkin lymphoma (NHL)	123	74.1	36	21.7	1.43	0.95–21.6	7	4.2	1.13	0.49–2.60
CNS tumor	307	79.3	63	16.3	0.92	0.68–1.24	17	4.4	1.23	0.71–2.12
Neuroblastoma	110	70.5	37	23.7	1.33	0.88–2.02	9	5.8	2.00	0.92–4.38
Wilms' tumor	113	77.4	28	19.2	1.11	0.72–1.73	5	3.4	0.80	0.31–2.09
Bone tumor	79	82.3	15	15.6	0.85	0.47–1.53	2	2.1	0.49	0.11–2.12
Soft tissue sarcoma	97	71.9	32	23.7	1.35	0.88–2.07	6	4.4	1.41	0.59–3.37
Controls	1,607	79.1	351	17.3			74	3.6		

[a] Odds ratio (OR) and respective 95 percent confidence interval (CI) of high blood pressure or edema during pregnancy (with or without medication) compared to the baseline of not having high blood pressure or edema, derived from logistic regression analysis adjusted for sex, age, year of birth, degree of urbanization and socioeconomic status (SES)

toma (OR 3.44, 95 percent CI: 1.04, 11.44) compared to high-stage (OR 1.54, 95 percent CI: 0.52, 4.51).

Only very few mothers received antiepileptics, psychotropics or diet pills (not presented in the tables). The prevalence among control mothers was 0.1 percent, 0.3 percent and 0.8 percent, respectively. Thus, the risk estimates based on small numbers of subjects were very imprecise and revealed no associations with any risk of childhood cancer. None of the 392 mothers of a child with a CNS tumor reported the use of antiepileptics during pregnancy.

Only 1.3 percent of control mothers reported the use of tranquillizers or sleeping pills. Mothers of patients reported the use of tranquillizers or sleeping pills more often (almost 3 percent), but the higher prevalence compared to controls was entirely attributable to the use of homeopathic sleeping pills (of which some have no pharmacological effect, according to conventional medicine). This kind of medication was virtually never reported by control mothers, so we suggest that the difference between case and control mothers was likely to be attributable to a different understanding of the respective question, due to the way it was phrased in the German original.

The low prevalences of most medications precludes age-specific analyses for most diagnoses. For ALL and maternal exposure to vitamin, folate and/or iron supplements, we found a stronger protective effect in older children (age 5 years or more) than in younger children, with an odds ratio of 0.67 (95 percent CI: 0.50, 0.90) compared to 0.98 (95 percent CI: 0.76, 1.25). This, however, was not a general tendency across all diagnoses for this exposure, as for all solid tumors combined the odds ratio for older children was 0.95 and hereby similar to that for younger children (1.01).

Finally, there was no association between the risk of childhood cancer and delivery of the index child by Caesarean section (Table 5).

Discussion

One strength of the German study is its population base. Cases were ascertained from a complete nationwide cancer registry, covering a population of some 13 million children in the age range 0 to 14 years [11]. Controls were randomly selected from the study base from which the cases arose. As population registration is compulsory in Germany, these registries offer an optimal sampling frame for population-based controls.

The major limitation of this study was that maternal medication use was solely based on self-reported information, raising concern about recall bias [38]. Although all interviews were performed within 3 years after diagnosis, it was still challenging for the mother to recall periods of medication use and, in particular, brand names of medications used during pregnancy. Especially for mothers of older children this was more than a decade ago (with a maximum of 17 years). As about half of the control mothers ticked the main medication group, but provided no more details on brands, it was not possible to go beyond the main medication group in the analysis. This is a particular limitation for vitamins, folate and iron supplementation as well as the group of antihypertensives, for which other studies (that will be discussed later) provided more specific associations, which hampers a direct comparison of results. In addition to that, we had no further information on the amount of use or the timing of exposure. If effects are only related to an intake of medication during the first trimester of pregnancy or only above a certain threshold, associations may have been diluted in our study. However, the inclusion of several case groups allowed the investigation of disease specificity of the observed associations. Similar effects for heterogeneous case groups may be an indicator for some

Table 5 Association between delivery by Caesarean section and the risk of childhood cancer, according to diagnostic groups of various malignancies

Delivery by Caesarean section?	No		Yes		OR[a]	95% CI[a]
	n	%	n	%		
Acute lymphoblastic leukemia (ALL)	559	86.7	86	13.3	0.90	0.69–1.17
Acute myeloblastic leukemia (AML)	91	89.2	11	10.8	0.81	0.42–1.56
Non-Hodgkin lymphoma (NHL)	154	90.1	17	9.9	0.67	0.39–1.13
CNS tumor	335	84.8	60	15.2	1.18	0.87–1.61
Neuroblastoma	132	83.0	27	17.0	1.36	0.86–2.16
Wilms' tumor	121	82.9	25	17.1	1.31	0.82–2.07
Bone tumor	90	93.8	6	6.3	0.50	0.21–1.18
Soft tissue sarcoma	120	87.6	17	12.4	0.85	0.50–1.45
Controls	1,768	86.2	284	13.8		

[a] Odds ratio (OR) and respective 95 percent confidence interval (CI) of birth by Caesarean section compared to natural birth, derived from logistic regression analysis adjusted for sex, age, year of birth, degree of urbanization and socioeconomic status (SES)

general recall bias, while disease-specific results may argue against it.

An ambiguous finding of this study is the reduced ALL risk in children whose mothers reported a vitamin, folate or iron supplementation during pregnancy. On the one hand, our findings confirm two recent studies. One was an Australian study that found a strong risk reduction [44] (but based on a small number of subjects), while the other was a large US study (n=1,800 children) that found a modest, but significant 20% reduction in risk [48]. On the other hand, the protective association disappeared in the current study when leukemia cases were compared with their original matched controls only. No protection at all, however, was also seen in a recent Canadian study [40]. Shu et al. found no association comparing two case groups of childhood ALL with different *ras* mutations [41]. Beneficial effects with regard to the prevention of cancer are under discussion for all three substances. A well-known benefit of folate supplementation is in the prevention of congenital malformations, particularly neural tube defects [2]. The role of folate in cancer risk is supposed to be due to impaired DNA synthesis and repair as a result of folate deficiency [16]. Through their role as antioxidants, vitamins have been found to reduce the risk of various cancers in adults [47]. A recent study in California showed a strong protective association against ALL with a maternal diet rich in vitamins during the index pregnancy, but it was the first study to report this and relied on self-reports on maternal diet [14]. Iron supplementation during pregnancy is used to prevent anemia, and studies in the UK and in Greece have showed a higher leukemia risk in children whose mothers were anemic during pregnancy [27, 32]. In a second larger UK study, this risk, however, was only confirmed for AML, but not ALL [33]. A reduced risk in our study was also seen for NHL and for Wilms' tumor, but not CNS tumors. For CNS tumors this is not consistent with previous studies as several studies have shown reduced risks with maternal vitamin use during pregnancy [35]. The strength of the association, however, was always largest in US studies, and most pronounced in mothers who also had a high intake of cured meats, so it may well be that differences in the diet between the US and Germany explains the different findings. In contrast to the various protective effects, vitamin, folate or iron supplementation leads to a higher risk of neuroblastoma. This is the opposite finding compared to two large US studies in which strong protective associations of maternal vitamin use have been observed (30–70% risk reduction) [22, 26]. Flavonoids (formerly known as vitamin P) are known as topoisomerase II inhibitors, and it has been hypothesized that the maternal intake of flavonoids during pregnancy is associated with an increased risk of leukemia in the offspring [21]. However, for flavonoids, no specific galenic is available in Germany, and, hence, we were not able to address this question.

A common concern in all of these case-control studies is a higher participation rate among more affluent families [19]. In the current study, the prevalence of vitamin, folate or iron supplementation in mothers with the highest educational level was some 15 percent higher than among mothers of the lowest educational level, suggesting a possible overestimation of the protective effect of this supplementation due to selection bias (Fig. 1). Another concern is that the prevalence of use in the current study is lower than the average prevalence of 90% (range 21–100%) reported by Bonati et al. [3], who presented an overview of epidemiological studies in 1990.

Maternal use of antihypertensives during pregnancy was associated with a three-fold increased risk of neuroblastoma in the current study. This observation was strengthened by another finding, namely that among the various case groups only mothers of children with neuroblastoma reported a treatment of pregnancy-related high blood pressure or

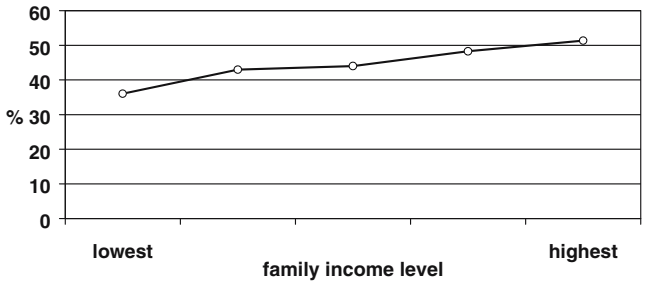

Fig. 1 Prevalence of maternal use of vitamins, folate acid and/or iron during pregnancy among control families, according to five levels of family income, Germany, 1992–1997

edema more frequently than controls. Two earlier small studies found strong associations between diuretics and neuroblastoma risk [18, 39]; however, this was not confirmed by both another small study from Germany [23] and a large study from the US [8]. In the latter study, among 504 matched case-control pairs, only three case mothers and none of the control mothers had reported the use of diuretics during pregnancy. Thus, it is rather surprising that in all the smaller studies (with about 100 cases) the numbers of exposed were higher. A possible mechanism for the association between diuretics and antihypertensives might be the toxic presence of n-nitroso precursors. N-nitroso is a strong transplancental nervous system carcinogen [25, 39] and is known to be an ingredient in some diuretics, e.g., furosemide and hydrochlorothiazid and also antihypertensives such as propanolol [7]. It might also be that, in case of a cancer of the fetus, catecholamine production might be responsible for maternal hypertension followed by the accordant medication [39]. However, hydrochlorothiazide is contradicted during pregnancy, and furosemide has been given mainly in case of emergency. The first-choice antihypertensive drug is α-methyldopa, and cardioselective betablockers are only the second choice.

The prevalence of hypertension during pregnancy in both German and US studies has been reported to be between 5 and 7% [30], and the prevalence of preeclampsia between 6 and 8%, respectively [9, 42]. Although the role of diuretics in the treatment of hypertension is inferior during pregnancy, there is a broad spectrum of established drugs like α-methydopa, beta-blockers, calcium-channel blockers and others [51]. Taking all this into account, the intake of antihypertensive drugs might have been underestimated in our study, while the intake of diuretics was overestimated. However, we were not able to subdivide the two medication groups in the analysis.

In all, there is some evidence that most associations between any maternal medication and a risk of childhood cancer in the offspring are attributable to neuroblastoma [21]. It is noticeable within this context that the neuroblastoma cases represent the youngest case group, which may strengthen the biological plausibility and may also be related to a more precise recall as the time period between pregnancy and the interview was the shortest [37]. It is reassuring that the comparison of neuroblastoma cases only with its original individually matched controls resulted in the same estimated odds ratios as those derived from the main analytical model.

The results for diuretics and antihypertensives and childhood ALL were somewhat ambiguous. Firstly, the type of the analysis had an impact on the results. Secondly, no association was seen between ALL risk and maternal high blood pressure or edema during pregnancy, indicating that most of the case mothers gave no reason for the use of diuretics. No evidence of an association between diuretics and ALL risk appeared in previous studies [21].

For pain relievers, antinauseants and cold medications, all odds ratios were close to unity. While these data suggest that there are at least no strong associations, it was not possible to confirm findings from studies with more specific data as in the neuroblastoma study showing an association between codeine and tumor risk [8]. The prevalence of pain reliever use during pregnancy in the current study was lower than the average presented in a review [3].

No associations were observed between delivery by Caesarean section and the risk of various childhood cancers. As a Caesarean section is related to the use of narcotics during labor, it may represent another aspect of medication use during pregnancy. One study on childhood brain tumors found an elevated odds ratio of 1.8 for astrocytoma [5], but this was not confirmed in the current study. However, the odds ratio for neuroblastoma was slightly elevated (odds ratio of 1.36), corresponding to a small risk excess observed in the largest neuroblastoma study to date (odds ratio 1.4, 95 percent CI: 1.0, 1.9) [7].

It has to be taken into account that the different tumor groups are heterogenous in pathogenesis and biology. However, additional subdivision of the groups would result in very small numbers.

In conclusion, this study only weakly supports the hypothesis that maternal use of vitamin, folate or iron supplementation during pregnancy is associated with a reduced risk of childhood ALL in the offspring. A stronger risk reduction, albeit not reported in previous studies [21], was seen for NHL and Wilms' tumor. A risk increase of neuroblastoma was associated with several maternal medications during pregnancy. The validity of the exposure assessment, however, remains somewhat uncertain. A large-scale ongoing study in the UK with access to medical records will hopefully provide more insight, including into the agreement between self-reported data and the practitioners' notes, but also no objective data will be available

on the use of over-the-counter medications [45]. The establishment of medication prescription registries in some of the Nordic countries (Denmark and Finland) will be a very valuable basis for future research in this area [50].

Acknowledgements We would especially like to thank Dr. Ina Reiß for her skillful work on the data set and for the preparation of preliminary analyses. We would like to thank Monika Decher-Neff and Ilona Kerenyi for their assistance in coding the medications. We would also like to thank Drs. Rolf Meinert, Uwe Kaletsch and Jörg Michaelis for their work during the conducting of the original study.

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