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Supplemental folic acid in pregnancy and childhood cancer risk

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Background: We investigated the association between supplemental folic acid in pregnancy and childhood cancer in a nation-wide study of 687 406 live births in Norway, 1999–2010, and 799 children diagnosed later with cancer.

Methods: Adjusted hazard ratios (HRs) compared cancer risk in children by approximated periconceptional folic acid levels (folic acid tablets and multivitamins (0.6 mg), only folic acid (0.4 mg), only multivitamins (0.2 mg)) and cancer risk in unexposed.

Results: Any folic acid levels were not associated with leukemia (e.g., high-level folic acid HR 1.25; 95% CI 0.89–1.76, P_{Trend} 0.20), lymphoma (HR 0.96; 95% CI 0.42–2.21, P_{Trend} 0.51), central nervous system tumours (HR 0.68; 95% CI 0.42–1.10, P_{Trend} 0.32), neuroblastoma (HR 1.05; 95% CI 0.53–2.06, P_{Trend} 0.85), Wilms' tumour (HR 1.16; 95% CI 0.52–2.58, P_{Trend} 0.76), or soft-tissue tumours (HR 0.77; 95% CI 0.34–1.75, P_{Trend} 0.90).

Conclusions: Folic acid supplementation was not associated with risk of major childhood cancers.

Health authorities in many countries recommend women planning pregnancy to take folic acid before and during pregnancy to reduce offspring risk of neural tube defects (SACN, 2006). A large number of countries also fortify flour with folic acid (CDC, 2008). Mandatory food fortification with folic acid is debated in some countries because of the suggested cancer risk in adults (Kim, 2004; Mason *et al*, 2007; Smith *et al*, 2008). However, in case–control studies on children, cancer risks (leukemia, brain tumours) were reduced if the mother had been exposed to perigestational maternal folic acid supplementation (Thompson *et al*, 2001; Milne *et al*, 2010; Milne *et al*, 2012; Metayer *et al*, 2014). And, in ecological studies from Canada and the United States of America, the childhood cancer incidence (Wilms' tumour, primitive neuroectodermal tumours, neuroblastoma) has been reduced after mandatory folic acid flour fortification (French *et al*, 2003; Grupp *et al*, 2011; Linabery *et al*, 2012).

The aim of our study was to investigate the association between maternal intake of folic acid supplementation in pregnancy and offspring risk of childhood cancer in a nation-wide cohort study in Norway.

MATERIALS AND METHODS

Data sources. The unique personal identification number assigned to all Norwegian residents enabled linkage of information between the Medical Birth Registry of Norway (MBRN) (Irgens, 2000), the Cancer Registry of Norway (CRN) (Larsen *et al*, 2009), and the Norwegian National Education Database that holds information on all individuals' education (Kinge *et al*, 2015).

Folic acid and multivitamin supplementation exposure. Folic acid and multivitamin supplementation use has been registered in

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the MBRN since December 1998. The registration form uses check boxes with the items 'folic acid before pregnancy', 'folic acid during pregnancy', 'multivitamins before pregnancy', and 'multivitamins during pregnancy'. During the study period, the folic acid content was 0.4 mg in folic acid supplements and approximately 0.2 mg in multivitamin supplements. Children were defined as exposed to folic acid if their mothers used folic acid supplements and/or multivitamins before and/or during pregnancy. Maternal folic acid intake was categorised by increasing folic acid content; no supplement use (0 mg), only multivitamins (approximately 0.2 mg), only folic acid supplements (0.4 mg), or intake of both folic acid supplements and multivitamins (approximately 0.6 mg).

Childhood cancer. Childhood cancer cases were identified through linkage with CRN. For each child, the first cancer diagnosis was used. The childhood cancers were categorised according to the International Classification of Childhood Cancer, version 3, which is based on ICD-O-3 (Steliarova-Foucher *et al*, 2005).

Study cohort. The study cohort consisted of all live births in Norway, 1 January 1999 through 31 December 2010 (excluding children with mothers with a prebirth cancer diagnosis (3371)), with follow-up until a cancer diagnosis, emigration, death, or 31 December 2010.

Statistical analysis. Risk of childhood cancers in children exposed to maternal folic acid and/or multivitamin supplements was compared with cancer risk in unexposed children and estimated with hazard ratios (HRs) using Cox proportional hazards regression models with time since birth as the time variable, adjusting for *a priori* selected covariates associated with maternal folic acid use and childhood cancer risk; that is, birth order (1, 2, ⩾3), maternal smoking (never, sometimes, ⩽10 cigarettes daily, >10 cigarettes daily, daily smoking of unknown amount), maternal and paternal age (<25, 25–34, ⩾35 years), and maternal and paternal education (compulsory, intermediate, tertiary). *P*-values for linear trend were calculated for folic acid exposure levels (0 mg, 0.2 mg, 0.4 mg, 0.6 mg). Statistical analyses were performed in STATA version 14 (STATA, 2015).

Ethics. The Regional Committee for Medical and Health Research Ethics of Western Norway approved the study.

RESULTS

Among 687 406 children included in the study, 799 developed cancer. The mean follow-up time was 6 years (range 0.04–12 years), constituting 4 052 679 person-years (Table 1). Among all births, 4% were multiple births, and 2% were born after assisted reproductive technology. Mean maternal age at childbirth was 29 years (range 13–55 years). The proportion of children exposed to perigestational supplementation increased in the study period, 1999–2010; intake of folic acid changed from 18% to 69% and multivitamins from 19% to 42%.

About 67% of all cancers were diagnosed within the first 3 years of life (Table 2). Leukemia and central nervous system (CNS) tumours accounted for 57% of the cases. We performed analyses for the six most frequent childhood cancer types (leukemia, lymphoma, CNS tumours, neuroblastoma, Wilms' tumour, soft tissue tumours) (Table 3). There was no change in childhood leukemia risk by maternal use of multivitamins only (HR 1.23; 95% CI 0.75–2.01), folic acid use only (HR 1.13; 95% CI 0.79–1.63), or combined folic acid and multivitamin use (HR 1.25; 95% CI 0.89–1.76), as compared with no supplement use (P_{Trend} 0.20). Similarly, there were no associations between CNS tumours and different levels of maternal folic acid intake; multivitamins only (HR 1.08; 95% CI 0.60–1.94), folic acid use only (HR 1.18; 95% CI 0.78–1.78), or combined folic acid and multivitamin use (HR 0.68; 95% CI 0.42–1.10), as compared with no supplement use (P_{Trend} 0.32). The HRs of the other frequent childhood cancer types (lymphoma, neuroblastoma, Wilms' tumour, soft tissue tumours) did not change for different levels of folic acid exposure. Adding birth year to adjustment models showed no substantial

Table 1. Characteristics of the study population of 687 406 live births, Norway, 1999–2010

Characteristics	Cohort (*n*)	Person-years	%	Cancer cases (*n*)
Children	687 406	4 052 679	100	799
Sex				
Boys	352 604	2 077 322	51	423
Girls	334 802	1 975 357	49	376
Gestational age (weeks)				
<37	46 682	271 770	7	60
37–41	587 197	3 447 416	85	670
⩾42	48 830	307 613	8	62
Missing	4697	25 881	1	7
Birth weight (g)				
<2500	33 804	191 809	5	39
2500–3999	516 075	3 008 163	74	587
⩾4000	136 760	847 264	21	173
Missing	767	5443	0	0
Birth order				
1	284 468	1 651 442	41	339
2	244 834	1 446 964	36	281
⩾3	158 104	954 274	24	179
Maternal age at child birth, years				
<25	117 065	697 604	17	133
25–34	452 481	2 709 049	67	539
⩾35	117 860	646 026	16	127
Paternal age at child birth, years				
<25	52 776	312 202	8	65
25–34	396 496	2 406 027	59	468
⩾35	231 836	1 307 428	32	257
Missing	6298	27 023	1	9
Maternal education[a]				
Compulsory	128 452	782 418	19	148
Intermediate	232 745	1 475 123	36	288
Tertiary	299 871	1 662 622	41	340
Missing	26 338	132 516	3	23
Paternal education[a]				
Compulsory	129 537	779 208	19	142
Intermediate	301 918	1 842 424	45	373
Tertiary	227 910	1 297 762	32	251
Missing	28 041	133 286	3	33
Maternal smoking				
Did not smoke	459 617	2 678 139	66	529
Smoked sometimes	17 222	106 380	3	15
Smoked ⩽10 cigarettes daily	69 270	455 935	11	103
Smoked >10 cigarettes daily	25 210	144 005	4	30
Smoked daily, unknown amount	5331	33 502	1	4
Missing	110 756	634 718	16	118
Maternal supplementation[b]				
No use	325 706	2 307 683	57	424
Multivitamins only	46 598	309 597	8	61
Folic acid only	145 856	675 461	17	154
Folic acid and multivitamin use	169 246	759 938	19	160

[a]Compulsory education length was 9 years until 1996 and 10 years from 1997 onwards.
[b]Maternal supplement intake before and/or during pregnancy, categorised by folic acid content: No use; multivitamins (approximately 0.2 mg); folic acid supplements (0.4 mg); and folic acid and multivitamins (approximately 0.6 mg).

Table 2. Children with first-time childhood cancer ($n = 799$) by age at diagnosis, year of diagnosis, and major cancer types (ICCC-3), identified among 687 406 livebirths, Norway, 1999–2010

	Cancer cases	%
Age at cancer diagnosis (years)		
<2	326	41
2–3	211	26
4–5	150	19
⩾6	112	14
Year of cancer diagnosis		
1999–2001	59	7
2002–2004	172	22
2005–2007	239	30
2008–2010	329	41
Cancer types (ICCC-3)		
I Leukemias, myeloproliferative diseases, and myelodysplastic diseases	268	34
Lymphoid leukemia	208	
Acute myeloid leukemias	45	
II Lymphomas and reticuloendothelial neoplasms	42	5
III CNS and miscellaneous intracranial and intraspinal neoplasms	185	23
Ependymoma	26	
Astrocytoma	79	
Intracranial and intraspinal embryonal tumours	50	
IV Neuroblastoma and other peripheral nervous cell tumours	72	9
Neuroblastoma and ganglioneuroblastoma	71	
VI Renal tumours	53	7
Wilms' tumour	52	
IX Soft tissue and other extraosseous sarcomas	64	8
Rhabdomyosarcoma	24	
Other specified soft tissue sarcomas	28	
Other cancers	115	14
Total	799	100

Abbreviations: CNS = central nervous system; ICCC-3 = International Classification of Childhood Cancer, third edition (Steliarova-Foucher *et al*, 2005).

changes in the risk estimates for neither cancer types. And excluding 867 children with Down syndrome from the analyses did not change the HR estimates for specific cancers.

DISCUSSION

In a nation-wide cohort study of all live births, estimated maternal intakes of multivitamins, folic acid, or combined intake of these supplements were not associated with childhood cancer.

Our results of no association between periconceptional folic acid supplementation and major childhood cancers are in discordance with case–control studies showing inverse associations between self-reported folic acid use and acute lymphoblastic leukemia (ALL) (Thompson *et al*, 2001; Milne *et al*, 2010; Metayer *et al*, 2014) and CNS tumours (Milne *et al*, 2012).

A recent large international collaborating study, including >7000 children with acute leukemia and 11 000 controls, found reduced risks of ALL and acute myeloid leukemia (AML) after maternal intake of folic acid supplements. And these reduced risks of ALL and AML did not vary by timing of the supplementation exposure (preconception, pregnancy, or pregnancy trimester) (Metayer *et al*, 2014). However, an Australian study found weak evidence of a reduced risk of ALL from folate supplementation before pregnancy, but no reduced risk from use during pregnancy (Milne *et al*, 2010). Also, another Australian study reported on an inverse association of childhood brain tumours and folic acid supplementation before and possibly also during pregnancy (Milne *et al*, 2012). In our study, a further stratification of the exposure data into preconceptional use and use during pregnancy was not feasable due to the limited statistical power of the analyses.

The strengths of our study include using comprehensive data from population-based registries covering the entire Norwegian population. To our knowledge, Norway is the only country where individual-level information on periconceptional folic acid and multivitamin intake has been collected for the entire birth population since 1999. All incident cancer cases have been reported to the Cancer Registry of Norway since 1952 (Larsen *et al*, 2009). And information on supplement use was collected before cancer diagnosis precluding recall bias.

Table 3. Hazard ratios (HRs) with 95% confidence intervals (95% CI) of childhood cancer by perigestational supplementation of folic acid and/or multivitamins, among 687 406 children, Norway, 1999–2010

Cancer types	Supplements[a]	Cancer cases	HR[b]	95% CI	P_{Trend}
All cancers	No supplements	424	1.00	Reference	
	Multivitamins only	61	1.05	0.78–1.42	
	Folic acid only	154	1.13	0.92–1.38	
	Folic acid and multivitamins	160	1.02	0.83–1.25	0.60
I Leukemias, myeloproliferative diseases, and myelodysplastic diseases					
	No supplements	135	1.00	Reference	
	Multivitamins only	21	1.23	0.75–2.01	
	Folic acid only	50	1.13	0.79–1.63	
	Folic acid and multivitamins	62	1.25	0.89–1.76	0.20
(a) Lymphoid leukemia					
	No supplements	100	1.00	Reference	
	Multivitamins only	16	1.30	0.75–2.27	
	Folic acid only	42	1.30	0.87–1.95	
	Folic acid and multivitamins	50	1.31	0.89–1.94	0.12
(b) Acute myeloid leukemia					
	No supplements	28	1.00	Reference	
	Multivitamins only	3	0.97	0.29–3.27	
	Folic acid only	5	0.59	0.22–1.60	
	Folic acid and multivitamins	9	0.96	0.43–2.17	0.67

Table 3. (Continued)

Cancer types	Supplements[a]	Cancer cases	HR[b]	95% CI	P_{Trend}
II Lymphomas and reticuloendothelial neoplasms					
	No supplements	25	1.00	Reference	
	Multivitamins only	3	0.55	0.13–2.33	
	Folic acid only	5	0.40	0.12–1.34	
	Folic acid and multivitamins	9	0.96	0.42–2.21	0.51
III CNS and miscellaneous intracranial and intraspinal neoplasms					
	No supplements	107	1.00	Reference	
	Multivitamins only	14	1.08	0.60–1.94	
	Folic acid only	37	1.18	0.78–1.78	
	Folic acid and multivitamins	27	0.68	0.42–1.10	0.32
(b) Astrocytoma					
	No supplements	44	1.00	Reference	
	Multivitamins only	8	1.57	0.72–3.40	
	Folic acid only	15	1.31	0.70–2.45	
	Folic acid and multivitamins	12	0.86	0.43–1.73	0.97
(c) Intracranial and intraspinal embryonal tumours					
	No supplements	28	1.00	Reference	
	Multivitamins only	2	0.61	0.14–2.59	
	Folic acid only	12	1.28	0.60–2.76	
	Folic acid and multivitamins	8	0.69	0.27–1.74	0.69
IV Neuroblastoma and other peripheral nervous cell tumours					
(a) Neuroblastoma and ganglioneuroblastoma					
	No supplements	37	1.00	Reference	
	Multivitamins only	5	0.99	0.35–2.82	
	Folic acid only	15	1.08	0.54–2.15	
	Folic acid and multivitamins	14	1.05	0.53–2.06	0.85
VI Renal tumours					
(a) Wilms' tumour					
	No supplements	28	1.00	Reference	
	Multivitamins only	5	1.60	0.60–4.25	
	Folic acid only	9	1.01	0.42–2.40	
	Folic acid and multivitamins	10	1.16	0.52–2.58	0.76
IX Soft tissue and other extraosseous sarcomas					
	No supplements	32	1.00	Reference	
	Multivitamins only	5	1.12	0.39–3.22	
	Folic acid only	18	1.72	0.90–3.29	
	Folic acid and multivitamins	9	0.77	0.34–1.75	0.90

Abbreviation: CNS = central nervous system.

[a]Maternal supplement intake before and/or during pregnancy, categorised by folic acid content: No use; multivitamins (approximately 0.2 mg); folic acid supplements (0.4 mg); and folic acid and multivitamins (approximately 0.6 mg).

[b]Hazard ratios (HR) with 95% confidence intervals (95% CI) adjusted for birth order (1, 2, ⩾3), smoking (never, sometimes, ⩽10 cigarettes daily, >10 cigarettes daily, daily smoking of unknown amount), maternal and paternal age (<25, 25–34, ⩾35 years), and maternal and paternal education (compulsory, intermediate, tertiary) comparing cancer risk in children exposed to periconceptional folic acid (multivitamins, folic acid, folic acid and multivitamins) and cancer risk in children without perigestational folic acid exposure (reference).

The study had some limitations. Even though our cohort was large, the numbers of several childhood cancer types were relatively low, which may limit the statistical power of our findings. The follow-up time of study participants were on average 6 years, and our results could only be generalised to younger children. Maternal folic acid intake could have been misclassified; in the beginning of the study period, folic acid users were under-reported to the MBRN (Nilsen *et al*, 2009). A possible misclassification of folic acid dose (independent of cancer risk) would bias risk estimates towards the null value and, in theory, could have concealed an association between folic acid intake and childhood cancer risk. Information on maternal smoking was missing for 16% of the births; however, HR estimates adjusting for maternal smoking were similar to HRs without smoking adjustments. Although we did not have information on dietary folate, residual confounding by dietary folate is less likely. In pregnant women, maternal plasma levels of serum folate is strongly related to intake of folic acid supplements (Bjorke-Monsen *et al*, 2013). And in other studies of maternal intake of folic acid supplements and offspring outcomes (oral clefts, autism), adjustment for dietary folate did not change overall risk estimates (Wilcox *et al*, 2007; Suren *et al*, 2013). We could not adjust for mother's weight and height, physical activity, diet, use of alcohol, or use of contraceptive pills, as these covariates were not available in the MBRN.

In conclusion, we found no association between maternal supplemental folic acid intake before and/or during pregnancy and risk of leukemia, lymphomas, CNS tumours, neuroblastoma, Wilms' tumour, or soft tissue tumours among younger children.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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