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 nationwide 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, PTrend 0.20), lymphoma (HR 0.96; 95% CI 0.42–2.21, PTrend 0.51), central nervous system tumours (HR 0.68; 95% CI 0.42–1.10, PTrend 0.32), neuroblastoma (HR 1.05; 95% CI 0.53–2.06, PTrend 0.85), Wilms’ tumour (HR 1.16; 95% CI 0.52–2.58, PTrend 0.76), or soft-tissue tumours (HR 0.77; 95% CI 0.34–1.75, PTrend 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...
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 25–41 years). The proportion of children exposed to reproductive technology. Mean maternal age at childbirth was 29 years (range 25–41 years). The proportion of children exposed to assisted reproductive technology. Mean maternal age at childbirth was 29 years (range 25–41 years).

### 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

|          | Person-years | %  | Cancer cases (n) |
|----------|--------------|----|-----------------|
| Boys     | 352,604      | 2,077,322 | 51 | 423             |
| Girls    | 334,802      | 1,975,357 | 49 | 376             |

#### Gestational age (weeks)

|          | Person-years | %  | Cancer cases (n) |
|----------|--------------|----|-----------------|
| <37      | 46,682       | 271,770 | 7  | 60              |
| 37–41    | 587,197      | 3,447,416 | 85 | 670             |
| ≥42      | 48,830       | 307,613  | 8  | 62              |
| Missing  | 4,697        | 25,681   | 1  | 7               |

#### Birth weight (g)

|          | Person-years | %  | Cancer cases (n) |
|----------|--------------|----|-----------------|
| <2500    | 33,804       | 191,809 | 5  | 39              |
| 2500–3999| 516,075      | 3,008,163 | 74 | 587             |
| ≥4000    | 136,760      | 847,264  | 21 | 173             |
| Missing  | 476          | 5,443    | 0  | 0               |

#### Birth order

|          | Person-years | %  | Cancer cases (n) |
|----------|--------------|----|-----------------|
| 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

|          | Person-years | %  | Cancer cases (n) |
|----------|--------------|----|-----------------|
| <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

|          | Person-years | %  | Cancer cases (n) |
|----------|--------------|----|-----------------|
| <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  | 6,298        | 27,023   | 1  | 9               |

#### Maternal education

|          | Person-years | %  | Cancer cases (n) |
|----------|--------------|----|-----------------|
| 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

|          | Person-years | %  | Cancer cases (n) |
|----------|--------------|----|-----------------|
| 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

|          | Person-years | %  | Cancer cases (n) |
|----------|--------------|----|-----------------|
| Did not smoke | 459,617      | 2,678,139 | 66 | 529             |
| Smoked    | 17,222       | 106,380  | 3  | 15              |
| Sometimes | 69,270       | 455,935  | 11 | 103             |
| Smoked ≤10 cigarettes daily | 25,210 | 144,005 | 4 | 30 |
| Smoked >20 cigarettes daily | 5,331 | 33,502 | 1 | 4 |
| Smoked daily, unknown amount | 110,756 | 634,718 | 16 | 118 |

#### Maternal supplementation

|          | Person-years | %  | Cancer cases (n) |
|----------|--------------|----|-----------------|
| No use   | 325,706      | 2,307,683 | 57 | 424             |
| Folic acid only | 46,958 | 309,597 | 8 | 61 |
| Folic acid and multivitamin use | 145,856 | 675,461 | 17 | 154 |
| Folic acid and multivitamin use | 169,246 | 759,938 | 19 | 160 |

*Compulsory education length was 9 years until 1996 and 10 years from 1997 onwards.

*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 multivitamin use (approximately 0.6 mg).
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 leukaemia and 11,000 controls, found reduced risks of ALL and acute myeloid leukaemia (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 feasible 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 2. Children with first-time childhood cancer (n = 799) by age at diagnosis, year of diagnosis, and major cancer types (ICCC-3), identified among 687,466 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 | |
| Lymphoid leukemia | 208 | 45 |
| Acute myeloid leukaemias | 268 | 34 |
| 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 extrasosseous 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).

### Table 3. Hazard ratios (HRs) with 95% confidence intervals (95% CI) of childhood cancer by perigestational supplementation of folic acid and/or multivitamins, among 687,466 children, Norway, 1999–2010

| Cancer types | Supplements | Cancer cases | HRb | 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 |
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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Table 3. (Continued)

| Cancer types | Supplementsa | Cancer cases | HRb | 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 |
| (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 | 1.51 | 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.

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

bHazard 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 authors declare no conflict of interest.

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