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Supplemental folic acid in pregnancy and maternal cancer risk

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ABSTRACT

Background: There is evidence that increased intake of folate protects against the development of several types of cancer. Some studies have, however, raised concern about the safety of folate in relation to cancer risk. Here we examined the risk of maternal cancer after intake of supplemental folic acid in pregnancy.
Methods: This is a population-based cohort study comprising 429,004 women with data from the Medical Birth Registry of Norway, the Cancer Registry of Norway, and other national registries from 1999 to 2010. Altogether 3781 cancer cases were identified during follow-up (average 7 years). Cox proportional hazards regression models were used to estimate hazard ratios of maternal cancer according to folic acid use prior to and during one or two or more pregnancies as compared to no supplement use.
Results: Folic acid supplementation use had no overall effect on cancer risk in women using folic acid supplementation in one (HR 1.08; 95% CI 1.00–1.18) or two or more pregnancies (HR 1.06; 95% CI 0.91–1.22) ($p_{trend} = 0.12$). Analyses of 13 cancer types revealed no associations between folic acid and cancer.
Conclusion: Folic acid supplementation before and during pregnancy had no overall effect on maternal cancer risk.
Impact: Folic acid substitution before and/or during pregnancy does not increase the short-term overall maternal cancer risk.

1. Introduction

Pre-gestational intake of folic acid prevents neural tube defects (NTDs) [1–3], and in many countries health authorities recommend women planning pregnancy to take folic acid supplementation before and during pregnancy [2]. Mandatory food fortification with folic acid has been implemented in many countries but remains controversial in others, with issues concerning cancer risk [4–7]. At present, there is no mandatory folic acid food fortification in Norway. The Norwegian National Nutrition Council recommends that all women who are planning pregnancy or are likely to become pregnant use 400 μg folic acid daily from one month before pregnancy throughout the first three months of pregnancy [8].

Folates are a group of B-vitamins important in DNA synthesis, replication, and genomic stability [9,10]. Folic acid is the synthetic form of folate with a substantially higher bioavailability relative to food folate [11]. Data from human studies suggests that consumption of high doses of folic acid, or with the highest blood folate concentrations, have a significantly reduced risk of developing colon polyps or cancer [12]. However, an entirely protective role for folate against carcinogenesis has been questioned. Based on human and animal evidence Kim proposed that folic acid supplementation may enhance colorectal carcinogenesis in neoplastic foci whereas folate deficiency may have an inhibitory effect [13]. Further, supraphysiologic doses of folic acid may enhance the development of cancer in normal colorectal mucosa, modest doses of folic acid may suppress, whereas folate deficiency may predispose the normal mucosa to neoplastic transformation [13]. So far, findings from epidemiologic studies have not been consistent on the subject of folate and cancer risk. A 2013 meta-analysis of 13 randomized trials including

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50,000 individuals comparing folic acid use versus placebo to prevent complications in cardiovascular disease, showed no statistically significant association with total cancer or sub-types of cancer [14].

No studies on periconceptional folic acid supplementation and maternal cancer risk have previously been conducted except for a randomized, double-blind study published in 2004 that later was criticized for the statistical approach and study design [15,16].

In the Medical Birth Registry of Norway, folic acid supplementation use has been registered since 1998. The aim of this study was to examine the subsequent risk of maternal cancer after intake of supplemental folic acid in pregnancy.

2. Material and methods

2.1. Data sources

Using the unique personal identification number given to citizens living in Norway, data was retrieved from the Norwegian Central Population Registry (NCPR) with linked data from the Medical Birth Registry of Norway (MBRN) [17], the Cancer Registry of Norway (CRN) [18], the Norwegian Labour and Welfare Administration (NAV) and the Norwegian National Education Database (NUDB). MBRN is a population-based registry containing information on all births in Norway since 1967 [17]. It is based on compulsory notification of all deliveries from gestational week 16 (since 2002 from week 12). CRN was established in 1951 and contains information on all new cancer cases and certain precancerous lesions in Norway. NAV was established in 2006 after govermental reorganization of the Directorate of Labour in Norway (founded in 1945), and holds information on employment, health status and social benefits of all individuals with residence in Norway since 1992. Since 1970, NUDB has registered information on all individuals' education since completed primary school and as far as doctoral studies in one database.

2.2. Exposure

The MBRN's notification form from December 1998 onwards has recorded information on folic acid and multivitamin supplementation by using checkboxes with the items "folic acid before pregnancy", "folic acid during pregnancy", "multivitamins before pregnancy", and "multivitamins during pregnancy". In Norway, folic acid supplements intended for use in pregnancy contained 0.4 mg folic acid, while most multivitamin supplements contained 0.0–0.2 mg of folic acid. The mothers were defined as folic acid users if folic acid were used before and/or during pregnancy. Furthermore, the mothers were defined as multivitamin users if folic acid were used before and/or during pregnancy. Based on the above information, we created two exposure variables of folic acid use, and one exposure variable of multivitamin use; the use in successive pregnancies (no use, use in one pregnancy, and use in two or more pregnancies), and the total amount of folic acid from multivitamin supplements (approximately 0.2 mg) and folic acid supplements (0.4 mg).

2.3. Outcome

Incident cancer cases (International Classification of Diseases version 10 (ICD-10)) were identified through linkage with CRN. For each mother, only the first cancer diagnosis was used. The 13 most frequent cancer sub-groups in our cohort were chosen. Sub-groups of cancers included colorectal cancer (C18–21), lung cancer (C33–34), melanoma of the skin (C43), non-melanoma skin cancer (C44), breast cancer (C50), and cancer of the uterine cervix (C53), ovary (C56), central nervous system (C70–72, D42–43), thyroid (C73), and other endocrine glands (C37, C74–75), Hodgkin's lymphoma (C81), non-Hodgkin's lymphoma (C82–85, C96), and leukemia (C91–95, D45–47). Cancer sites with less than 50 cases were combined in the group "Other cancers" (C00–17, C22–26, C30–32, C38–41, C45, C47–49, C51–52, C54, C57–58, C64–69, C76, C80, C88, C90).

2.4. Confounders

Data on maternal year of birth, maternal age at first childbirth in the study period (1999–2010), maternal age at first childbirth (prior to start of follow-up period), parity, marital status, and smoking habits was collected from the MBRN. Information on maternal smoking was recorded at start and end of pregnancy (no smoking, sometimes, daily, number of cigarettes, declined to inform about smoking habits). The smoking data was then combined into a single variable that contained the maximum cigarette consumption for each woman. Information on length of education and occupation at time of childbirth was collected from NUDB and NAV, respectively.

2.5. Study cohort

All women living in Norway and giving birth in the period January 1, 1999 to December 31, 2010 (429,004 women and 679,484 pregnancies) constituted our study cohort. Induced abortions (2491) were excluded since information on vitamin use has not been registered. Pregnancies to women who emigrated before birth (13,733) or women who were diagnosed with cancer before delivery (3334) were also excluded. The women were followed from the date of their first birth during 1999-2010 until a cancer diagnosis, death, emigration, or end of follow-up at December 31, 2010.

2.6. Statistical analysis

Hazard ratios (HRs) of cancer with 95% confidence intervals (95% CIs), among women using folic acid in successive pregnancies compared to women using no folic acid, were estimated using time-dependent Cox proportional hazard regression models [19]. Time since the first childbirth during 1999–2010 was used as time variable. Tests for linear trend over the categories of folic acid supplementation were conducted.

Similar time-dependent Cox proportional hazard regression analyses were also conducted for multivitamin use in successive pregnancies compared to women using no multivitamins.

The Cox models were adjusted for maternal age at first childbirth (age at cohort entry) during 1999–2010 (<20, 20–24, 25–29, 30–34, 35–39, ≥40 years), maternal year of birth (1949–59, 1960–69, 1970–79, 1980–89, 1990–96), and parity (1, 2, 3, ≥4), marital status (unmarried, married/registered partner/cohabitant, divorced/widowed), education (compulsory (1st–7th class level), intermediate (8th–12th class level), tertiary (14th–20th class level)), occupation (10 main groups), and smoking status at the time of birth (never, sometimes, ≤10 cigarettes daily, >10 cigarettes daily, daily smoking–unknown amount). For total cancer and breast cancer, we also adjusted for maternal age at very first childbirth (<20, 20–24, 25–29, 30–34, 35–39, ≥40 years).

For the years 2003–2010 occupational codes were available. Occupational codes registered in 2003 were applied for births during 1999–2002.

Since 16% of the study population had missing smoking information, we performed multiple imputation on missing smoking status at the time of birth according to White and Royston [20], and Sterne and colleagues [21]. Time-dependent Cox