Cancer Epidemiology 39 (2015) 805–811

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.canceepidemiology.net

Supplemental folic acid in pregnancy and maternal cancer risk

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ARTICLE INFO

Article history:
Received 16 April 2015
Received in revised form 10 September 2015
Accepted 7 October 2015
Available online 18 October 2015

Keywords:
Folic acid supplementation
Pregnancy
Maternal cancer
Cohort study

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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http://dx.doi.org/10.1016/j.canep.2015.10.009

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

Table 1
Characteristics of the study population at start of follow-up, Norway, 1999–2010.

Maternal characteristics	Cohort	Person-years	%	Cancer cases (*n*)	%
Mothers	429,004	2,933,587	100	3781	100
Maternal year of birth					
1949–59	3158	31,900	1	119	3
1960–69	102,284	920,987	31	1813	48
1970–79	227,841	1,621,811	55	1640	43
1980–89	92,535	355,060	12	208	6
1990–96	3186	3829	0	1	0
Maternal age at first childbirth in 1999–2010					
<20 years	15,119	92,407	3	45	1
20–24 years	79,225	504,471	17	344	9
25–29 years	146,380	1,013,239	35	984	26
30–34 years	124,835	890,856	30	1361	36
35–39 years	52,931	365,858	12	823	22
≥40	10,514	66,755	2	224	6
Maternal age at first childbirth[a]					
<20 years	33,626	249,038	8	256	7
20–24 years	122,114	885,507	30	916	24
25–29 years	150,240	1,054,830	36	1317	35
30–34 years	78,821	497,201	17	822	22
35–39 years	21,343	120,523	4	275	7
≥40 years	3,105	15,631	1	59	2
Missing data	19,755	110,857	4	136	4
Folic acid use in pregnancy[b]					
No use[c]	252,620	2,002,547	68	2579	68
Before pregnancy	5082	31,153	1	32	1
During pregnancy	112,874	622,961	21	801	21
Before and during pregnancy	58,428	276,926	9	369	10
Multivitamin use in pregnancy[b,d]					
No use[c]	298,543	2,187,443	75	2,826	75
Before pregnancy	5,890	33,067	1	53	1
During pregnancy	79,995	467,255	16	564	15
Before and during pregnancy	44,576	245,821	8	338	9
Education[b]					
Compulsory (1st–7th class level)	86,530	604,712	21	692	18
Intermediate (8th–12th class level)	149,530	1,093,481	37	1418	38
Tertiary (13th–20th class level)	174,222	1,133,166	39	1571	42
Missing data	18,722	102,227	3	100	3
Occupation[b,e]					
Armed forces and unspecified	144,109	1,154,409	39	1516	40
Legislators, senior officials and managers	11,397	75,386	3	124	3
Professionals	21,543	118,501	4	192	5
Technicians and associate professionals	61,202	353,946	12	464	12
Clerks	27,314	192,749	7	268	7
Service workers and shop and market sales workers	97,772	605,065	21	639	17
Agricultural, forestry and fishery workers	1443	9766	0	8	0
Craft and related trades workers	4175	26,800	1	46	1
Plant and machine operators and assemblers	8732	59,862	2	63	2
Elementary occupations	19,164	127,270	4	114	3
Missing data	32,153	209,833	7	347	9
Parity[b]					
1	278,438	1,631,675	56	1751	46
2	86,528	750,522	26	1110	29
3	45,168	391,057	13	644	17
≥4	18,870	160,333	5	276	7
Marital status[b]					
Unmarried	33,345	200,844	7	214	6
Married/partnership	385,481	2,644,365	90	3449	91
Divorced	2322	16,564	1	24	1
Missing data	7856	71,814	2	94	2
Smoking[b]					
Never	275,462	1,885,522	64	2416	64
Sometimes	12,245	85,200	3	115	3
≤10 cigarettes daily	49,956	367,012	13	520	14
>10 cigarettes daily	18,304	117,721	4	151	4
Daily, unknown amount	4061	27,608	1	23	1
Missing data	68,976	450,524	15	556	15

[a] Including births before 1999.
[b] At start of follow-up.
[c] No information on use.
[d] Multivitamins used in Norway contain on average 0.2 mg folic acid.
[e] Occupational codes registered in 2003 were applied for births during 1999–2002.

Table 2
Cancer cases registered during follow-up (1999–2010) according to age at diagnosis and calendar year among 429,004 women in Norway.

	Cancer cases (n)	%
Age at primary cancer diagnosis (years)		
<20	6	0
20–24	77	2
25–29	418	11
30–34	884	23
35–39	1157	31
≥40	1239	33
Year of primary cancer diagnosis		
1999–2001	199	5
2002–2004	630	17
2005–2007	1194	32
2008–2010	1758	46
Total	3781	100

proportional hazard regression analyses were then conducted on the imputed data set.

The statistical analyses were carried out with the statistical packages SPSS version 22 and STATA version 13 [22,23].

3. Results

The women were followed for an average of 7 years (range 0.04–12 years), constituting 2,933,587 person-years. The mean age at start of follow-up was 29 years (range 13–54 years). Characteristics of the study population at start of follow-up are presented in Table 1.

During follow-up, 3781 cancer cases were diagnosed. The mean age at diagnosis was 37 years (range 18–56 years). Mean time between the first birth in the study period and cancer diagnosis was five years (range 0.1–12 years). Breast cancer was the most frequent cancer type in the cohort (1166 cases). A total of 343 cancer cases were grouped into the "Other" category when the cancer site frequency was less than 50 cases. Table 2 shows maternal age and year of primary cancer diagnosis.

Fig. 1 shows the use of supplements (folic acid, multivitamins) and smoking related to pregnancy from 1999 to the end of the study period in 2010. In 1999, only 18% of the women used folic acid in pregnancy compared to 71% in 2010. Multivitamin use increased from 19% in 1999 to 42% in 2010. Daily and intermittent smoking registered among women in our cohort decreased from 26% in 1999 to 20% in 2010.

The adjusted HRs of cancer (total and sub-types) with 95 % CIs by folic acid use (before and/or during pregnancy) in one and two or more pregnancies compared to no folic acid use during the study period are presented in Table 3. No increased risk was seen for total cancer among women using folic acid 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), and other sub-types of cancer, except for an increased risk for lung and trachea cancer (p_{trend} = 0.06) and thyroid cancer (p_{trend} = 0.05) of borderline significance.

Further adjustments for multivitamin use (in the analyses of folic acid use) showed no substantial changes in the risk estimates, neither for total cancer nor specific sub-types (data not shown). Analyses of total dose of folic acid (continuous variable) ingested from multivitamin supplements (0.2 mg folic acid) and folic acid supplements (0.4 mg folic acid) revealed no substantial changes in the risk estimates, neither for total cancer nor specific sub-types (data not shown).

Multivitamin use (before and/or during pregnancy) in one, or two or more pregnancies compared to no multivitamin use were not associated with increased risk of total cancers. However, increased risk was seen for melanoma of the skin among women using multivitamins in one (HR 1.19; 95% CI: 0.96–1.48), and two or more pregnancies (HR 1.58; 95% CI: 1.05–2.38) (p_{trend} = 0.02). Additionally, increased risk of non-Hodgkin's lymphoma was seen among multivitamin users in one (HR 1.54; 95% CI: 0.94–2.53) and two or more pregnancies (HR 2.82; 95% CI: 1.15–6.95) (p_{trend} = 0.01).

Imputed analyses (on missing smoking data) showed no substantial changes in the risk estimates, neither for total cancer nor specific sub-types (data not shown).

4. Discussion

The aim of this study was to evaluate the association between the recommended folic acid supplementation use and cancer risk. Our population-based cohort study comprising 429,004 women with data from the national registries in Norway, showed no significant relationship between periconceptional folic acid use and cancer risk.

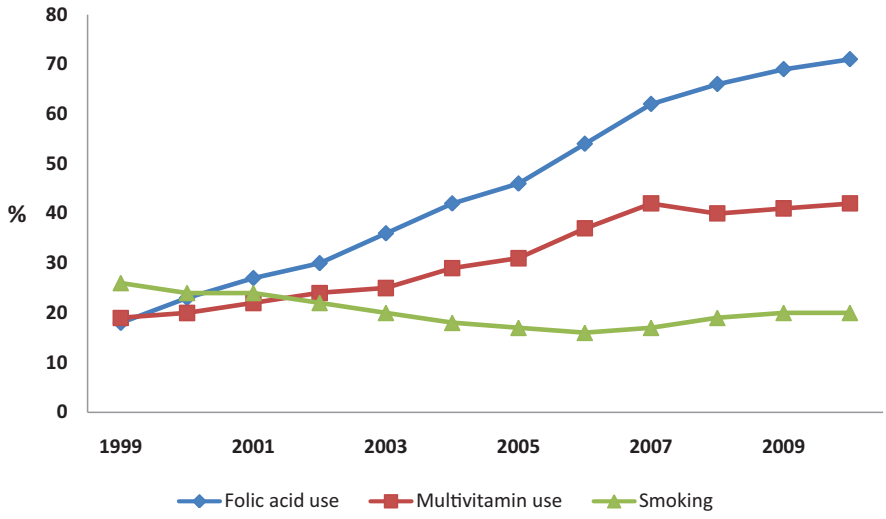

Fig. 1. Percentage folic acid (before and/or during pregnancy), multivitamin (before and/or during pregnancy) and cigarette use (intermittent or daily before/during pregnancy) among 679,484 pregnancies in Norway, 1999–2010.

Table 3
Hazard ratios (HR) of cancer with 95% confidence intervals (95% CI) by folic acid supplementation in one, or two or more pregnancies among 429,004 women in Norway, 1999–2010.

Cancer types	ICD-10 codes	Number of pregnancies with folic acid use	Cancer cases (*N*)	Model 1			Model 2		
				HR	CI95%	p_{trend}	HR	CI95%	p_{trend}
Total cancer		0	2269	1.00	Reference		1.00	Reference	
		1	1214	1.09	1.01–1.17		1.08	1.00–1.18	
		≥2	298	1.04	0.92–1.17	0.08	1.06	0.91–1.22	0.12
Colorectal	C18–21	0	98	1.00	Reference		1.00	Reference	
		1	52	1.11	0.79–1.56		0.91	0.60–1.38	
		≥2	19	1.75	1.06–2.90	0.06	1.96	1.10–3.50	0.16
Lung and trachea	C33–34	0	31	1.00	Reference		1.00	Reference	
		1	17	1.20	0.66–2.17		1.69	0.82–3.48	
		≥2	6	1.80	0.74–4.39	0.21	2.41	0.83–7.01	0.06
Melanoma of the skin	C43	0	275	1.00	Reference		1.00	Reference	
		1	164	1.18	0.97–1.43		1.08	0.87–1.35	
		≥2	55	1.52	1.13–2.04	0.00	1.35	0.96–1.89	0.11
Skin, non-melanoma	C44	0	34	1.00	Reference		1.00	Reference	
		1	16	0.98	0.54–1.78		0.79	0.39–1.63	
		≥2	1	0.26	0.04–1.92	0.31	0.29	0.04–2.17	0.20
Breast	C50	0	728	1.00	Reference		1.00	Reference	
		1	356	1.07	0.94–1.21		1.10	0.94–1.28	
		≥2	82	0.95	0.75–1.20	0.80	0.96	0.73–1.27	0.62
Cervix uteri	C53	0	269	1.00	Reference		1.00	Reference	
		1	151	1.09	0.89–1.33		1.06	0.83–1.34	
		≥2	37	0.93	0.66–1.32	0.85	0.93	0.63–1.39	0.99
Ovary	C56	0	48	1.00	Reference		1.00	Reference	
		1	23	0.95	0.58–1.56		1.04	0.58–1.86	
		≥2	3	0.57	0.17–1.84	0.43	0.90	0.26–3.10	0.99
Central nervous system	C70-72, D42-43	0	208	1.00	Reference		1.00	Reference	
		1	121	1.15	0.92–1.44		1.13	0.86–1.47	
		≥2	28	1.04	0.70–1.56	0.40	0.97	0.61–1.53	0.72
Thyroid	C73	0	138	1.00	Reference		1.00	Reference	
		1	84	1.17	0.89–1.54		1.36	0.99–1.86	
		≥2	30	1.57	1.05–2.35	0.03	1.41	0.88–2.26	0.05
Other endocrine glands	C37, C74–75	0	59	1.00	Reference		1.00	Reference	
		1	28	0.92	0.59–1.45		0.80	0.46–1.38	
		≥2	4	0.48	0.17–1.34	0.22	0.54	0.19–1.58	0.20
Hodgkin's lymphoma	C81	0	44	1.00	Reference		1.00	Reference	
		1	34	1.46	0.93–2.28		1.34	0.81–2.23	
		≥2	6	1.00	0.42–2.38	0.34	0.78	0.29–2.10	0.79
Non-Hodgkin's lymphoma	C82–85, C96	0	54	1.00	Reference		1.00	Reference	
		1	34	1.18	0.77–1.82		1.24	0.75–2.05	
		≥2	5	0.90	0.36–2.29	0.72	1.00	0.37–2.67	0.61
Leukaemia	C91–95, D45–47	0	60	1.00	Reference		1.00	Reference	
		1	31	1.05	0.68–1.62		1.19	0.71–2.00	
		≥2	5	0.74	0.29–1.86	0.76	0.65	0.19–2.18	0.96
Other cancers	C00–17, C22–26, C30–32, C38–41, C45, C47–49, C51–52, C54, C57–58, C64–69 C76, C80, C88, C90	0	223	1.00	Reference		1.00	Reference	
		1	103	0.92	0.73–1.17		1.07	0.81–1.41	
		≥2	17	0.65	0.39–1.07	0.11	0.92	0.53–1.58	0.93

Model 1: Adjusted for maternal age (<20, 20–24, 25–29, 30–34, 35–39, ≥40 years) at first childbirth in the study period 1999–2010.
Model 2: Further adjusted for maternal year of birth (1949–59, 1960–69, 1970–79, 1980–89, 1990–96), 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 (armed forces/unspecified, legislators, senior officials/managers, professionals, technicians/associate professionals, clerks, service workers/shop workers/market sales workers, agricultural/forestry/fishery workers, craft/ related trades workers, plant/machine operators, assemblers/elementary occupations), and smoking (never, intermittent, ≤10 cigarettes daily, >10 cigarettes daily, daily smoking–unknown number of cigarettes). For total cancer and breast cancer the model was also adjusted for maternal age at first childbirth (<20, 20–24, 25–29, 30–34, 35–39, ≥40 years) prior to start of follow-up.

4.1. Comparisons with the literature

Our results are in accordance with several prospective cohort studies and meta-analyses showing no overall or site-specific association between folic acid use and cancer risk [14,24–26]. However, there are inconsistencies in the literature regarding folate status and the risk of cancer. Some prospective cohort studies have found an inverse association between dietary folate intake or blood folate concentrations and risk of cancer of the colon, breast, ovary, and pancreas [27–32]. Contrary to these observational studies, two randomized controlled trials found no protective association between folic acid use (in combination with other B-vitamins) and cancer risk (overall and site-specific) [24,25].

Several potential mechanisms have been proposed by which folate or the bioactive form of folic acid may increase the risk of cancer. Folate is important for the synthesis of DNA, methylation, and repair [9,10]. An imbalance in these three functions might play a role in carcinogenesis. Unmetabolized folic acid may compromise the immunological defense against cancer and augment the growth of established cancer cells [33]. Other reports suggest that folic acid supplementation may promote cancer cells in already established neoplastic foci through de novo methylation of tumor suppressor genes with consequent gene inactivation, leading to tumor progression [5,34].

Interestingly, a potential dual modulatory role of folate on colorectal cancer has been proposed by Kim [13]. Folic acid may enhance the growth of cancer cells in established neoplastic foci whereas folate deficiency may inhibit progression of established colorectal neoplasms. On the other hand, in normal colorectal mucosa, folate deficiency may stimulate the initial stages of carcinogenesis in the colon and rectum, moderate doses of folic acid use may suppress, whereas high doses of folic acid may enhance the development of cancer [13].

The complex relationship between folate intake and colorectal cancer risk may be further modulated by genetic variants of folate metabolism enzymes. The enzyme methylenetetrahydrofolate reductase (MTHFR) is involved in the folate metabolism necessary for both DNA methylation and DNA synthesis. A common polymorphism in the *MTHFR* gene (MTHFR 677C→T polymorphism) is connected to reduced MTHFR enzyme activity and function that is important for the nucleotide and methylation pathways [35]. However, the MTHFR 677C→T polymorphism appears to decrease the risk of several adult cancer types (colorectal, liver, uterine cervical and acute lymphocytic leukemia) [35]. The MTHFR 677 TT genotype seems, however, to increase the risk of esophageal, gastric and pancreatic cancer [36].

We also evaluated the association between multivitamin use and risk of cancer. Our finding of no association between multivitamin use and total cancer risk is supported by other studies, reporting little or no influence from multivitamin use on total risk of cancer, including colorectal cancer [37,38]. Though, in sub-group analyses we found an increased risk of malignant melanoma and non-Hodgkin's lymphoma. These findings are in discrepancy with a large prospective cohort study on antioxidant supplementation that did not show increased melanoma risk [39]. However, a study by Zhang et al. in 2001 showed that multivitamin use was associated with a higher risk of non-Hodgkin's lymphoma among women, but not among men, and the authors concluded that their observed findings were the results of chance [40].

4.2. Strengths and limitations

To our knowledge, this is the largest study on cancer risk and folic acid use among pregnant women to date. The strengths of our study are the large cohort consisting mainly of healthy women in fertile age and the use of population-based registries covering the entire Norwegian population, assuring generalizability of our results. The loss to follow-up was minimal.

A limitation of this study is no records on dose, frequency, or precise duration of folic acid or multivitamin use throughout pregnancy. However, supplemental folic acid and multivitamin use as recorded in the MBRN, has also been used in other epidemiological studies [41,42]. In this study, we could not control for other health behaviours than smoking. Consequently, there could be confounding from other risk factors.

Altogether 16% of the pregnancies included in the study lacked smoking data, but imputation of missing values for smoking did not change our estimates. Most childbearing women know the adverse health effects of smoking to the foetus, which could reduce the reliance of self-reported smoking habits. On the other hand, smoking habits were documented before a possible cancer diagnosis.

Breast cancer was the most frequent cancer type in our cohort. Since young women at first full-term pregnancy have a decreased risk of developing hormone receptor positive breast cancer later in life [43], we also adjusted risks of breast cancer and total cancer for maternal age at her very first birth (including first birth before cohort entry in 1999). Adjustments for other potentially confounding factors (age at first childbirth in the study period, maternal year of birth, marital status, occupation, and smoking) showed minor changes in estimates, which reduced the likelihood of residual confounding. But, we could not adjust for other potential confounders, such as body mass index (BMI), physical activity, diet, alcohol intake, use of NSAIDs, exogenous hormones, and familial cancer syndromes, because these covariates were not available. Alcohol use, known to antagonise folate absorption and metabolism, is unlikely an important confounder, as the consumption of alcohol during pregnancy is generally low in Norway [44].

5. Conclusion

Overall, we found no association between folic acid supplementation and cancer risk. Our study cannot, however, assess the long-term impact of folic acid supplementation on cancer risk. The complex biological relation between folate and cancer needs cautious interpretation, and additional epidemiological research is warranted.

Ethical approval

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

Funding

This work was supported by the Norwegian Cancer Society and the Western Norway Regional Health Authority, project number 911629, to Dr. Nina Øyen.

Conflict of interest

The authors have no conflicts of interest to disclose.

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