

Prenatal Multivitamin Supplementation and Rates of Pediatric Cancers: A Meta-Analysis

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Prenatal supplementation of folic acid has been shown to decrease the risk of several congenital malformations. Several studies have recently suggested a potential protective effect of folic acid on certain pediatric cancers. The protective role of prenatal multivitamins has not been elucidated. We conducted a systematic review and meta-analysis to assess the potential protective effect of prenatal multivitamins on several pediatric cancers. Medline, PubMed, EMBASE, Toxline, Healthstar, and Cochrane databases were searched for studies published in all languages from 1960 to July 2005 on multivitamin supplementation and pediatric cancers. References from all articles collected were reviewed for additional articles. Two blinded independent reviewers assessed the articles for inclusion and exclusion. Rates of cancers in women supplemented with multivitamins were compared with unsupplemented women using a random effects model. Sixty-one articles were identified in the initial search, of which, seven articles met the inclusion criteria. There was an apparent protective effect for leukemia (odds ratio (OR) = 0.61, 95% confidence interval (CI) = 0.50–0.74), pediatric brain tumors (OR = 0.73, 95% CI = 0.60–0.88) and neuroblastoma (OR = 0.53, 95% CI = 0.42–0.68). In conclusion, maternal ingestion of prenatal multivitamins is associated with a decreased risk for pediatric brain tumors, neuroblastoma, and leukemia. Presently, it is not known which constituent(s) among the multivitamins confer this protective effect.

It is estimated that 9,510 children in the United States under the age of 15 were diagnosed with cancer in 2005.¹ The most prevalent forms of childhood cancer are leukemia, malignant brain and spinal cord tumors, and neuroblastoma.^{2,3} Leukemia is estimated to account for 25–35% of pediatric cancers.⁴ The two major morphological types of blood-borne cancers are acute lymphocytic leukemia (ALL) and acute myeloid leukemia (AML). The American Cancer Society estimates that 2,670 and 1,196 children were diagnosed with ALL and AML in 2005, respectively.^{5,6} Malignant brain and spinal cord tumors occur in 2,200 (17%) of pediatric cancers.⁷ These cancers include astrocytoma, primitive neuroectodermal tumors, and medulloblastoma.² Neuroblastoma is diagnosed in approximately 650 American children annually.⁷ An estimated 463 children die from ALL in the United States each year⁵ and only about half of children with brain tumors will survive more than five years.³

A large number of investigations into the epidemiology of these pediatric cancers have been undertaken in an attempt to identify risk factors and protective agents. Investigators have

looked for relationships between genes and environmental exposures such as radiation,^{8,9} N-nitroso compounds,¹⁰ pesticides,¹¹ tobacco,^{12,13} electromagnetic frequencies,¹⁴ infectious agents,^{8,15,16} parental occupation,¹⁷ drugs,^{18,19} alcohol,²⁰ infant feeding,²¹ multivitamins,^{22,23} and cancer.

It is now generally accepted that women of childbearing potential should supplement with folic acid before pregnancy and in early pregnancy to decrease the proven risk of neural tube defects. This suggested relationship was proven by the British and Hungarian randomized studies of supplementation with folic acid before pregnancy and in early pregnant women.^{24,25} Folic acid fortification of flour has subsequently resulted in decreasing rates of neural tube defects.^{26,27} In addition, it has most recently been suggested that folic-acid containing multivitamins may also be beneficial in preventing congenital anomalies other than neural tube defects.^{28,29} Botto *et al.*²⁸ noted that there was an apparent decreased risk for orofacial clefts, limb deficiencies, and cardiovascular abnormalities with multivitamin supplementation. In addition, Bailey *et al.*²⁹ reported a decrease of cardiovascular

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abnormalities and orofacial clefts. A recent study conducted by our group followed the prevalence of neuroblastoma rates after folic acid fortification of flour in Ontario, Canada, showing an apparent protective effect.²⁷ To date, several studies have investigated the potential effect of multivitamin use before and in early pregnancy on rates of common pediatric tumors. The objective of this study was to conduct a systematic review and meta-analysis of prenatal multivitamin use before and in early pregnancy and the risk of pediatric cancers.

RESULTS

Sixty-one articles were compiled from initial searches and reference review. Using our exclusion criterion, seven articles were eligible for inclusion: two articles addressing brain tumors, two addressing neuroblastoma, and two articles addressing leukemia, and one article addressing both brain tumors and leukemia^{10,19,30–37} (Table 1). All studies were of case-control design. Thirty-eight articles were excluded because they did not contain information on maternal

multivitamin use during pregnancy.^{22,38–75} Three studies were excluded because they dealt with vitamin ingestion by children.^{76–78} Two studies were excluded because they combined multivitamin and iron supplementation into one category.^{18,79} One article reported on folic acid fortification in food.²⁷ Two articles were excluded because they focused only on folate.^{80,81} Three studies were rejected because they did not provide complete raw data to allow analysis.^{36,37,82} Two papers were rejected because they were duplicates of articles published in different journals:^{83,84} one contained data that were previously published,¹⁰ and one was rejected because it was a news report.⁸⁵

Use of prenatal multivitamins by the pregnant mothers was associated with a protective effect for childhood leukemia (odds ratio (OR) = 0.64, 95% confidence interval (CI) = 0.53–0.78). As pediatric leukemia has different origins, ALL and AML were analyzed separately. The ingestion of prenatal multivitamins was associated with a protective effect for ALL (OR = 0.61, 95% CI = 0.50–0.74) (Figure 1). There was no significant heterogeneity among

Table 1 Characteristics of articles included in meta-analysis

Author	Year published	Country	Dates of study	Age of children (years)	Language	Matching controls	Primary outcome	Matching variables
Sarasua <i>et al.</i>	1994	United States (Denver)	January 1, 1976–December 31, 1983	0–14	English	Random-digit dialing	Brain tumors, ALL	±3 years of age; telephone exchange area
Bunin <i>et al.</i>	1994	United States, Canada	1986–1989	<6	Not specified	Random-digit dialing ^a	Astrocytic glioma	Matching area code and next five digits of phone number; date of birth ±1 year and race; black and non-black
Michaelek <i>et al.</i>	1996	United States (New York)	January 1, 1976–December 1, 1987	<15	English	Birth certificate registry	Neuroblastoma	Birth year; race
Preston-Martin <i>et al.</i>	1998	United States, France, Italy, Israel, Canada, Australia	1976–1994	Varied by location	Not specified	Varied by location	Brain tumors	Varied by location
Olshan <i>et al.</i>	2002	United States, Canada	May 1, 1992–April 30, 1994	<19	English, Spanish	Random-digit dialing	Neuroblastoma	Date of birth ±6 months for cases <3 years or date of birth ±1 year for cases >3 years
Wen <i>et al.</i>	2002	United States, Canada, Australia	January 1, 1989–June 15, 1993	<15	English	Random-digit dialing ^a	ALL	±2 years of age; race; telephone area code and exchange
Ross <i>et al.</i>	2005	United States	January 1997–October 2002	<20	English	Physician's patient roster	ALL, AML	

ALL, acute lymphocyte leukemia. ^aRandom-digit dialing criteria relaxed in order to find a match.

the ALL studies ($\chi^2 = 1.27$, $I^2 = 0\%$). There was only one study that reported information regarding AML therefore it could not be meta-analyzed; nevertheless it suggested a protective effect as well. The use of multivitamins by pregnant mothers was associated with a protective effect for several solid tumors. Supplementation with prenatal vitamins was associated with a decreased risk for neuroblastoma (OR = 0.53, 95% CI = 0.42–0.68) (Figure 2). Prenatal supplementation was also associated with decreased risk for pediatric brain tumors (OR = 0.73, 95% CI = 0.60–0.88) (Figure 3). A funnel plot did not show significant publication bias.

DISCUSSION

There is a large body of evidence supporting the protective effect of folic acid in decreasing the effect of neural tube defects.^{24,25} In addition, folic-acid containing multivitamins have also been associated with prevention of other congenital anomalies other than neural tube defects.²⁹ The data from the present meta-analysis suggest that prenatal supplementation of multivitamins containing folic acid is associated with an overall 18% protective decreased risk for pediatric brain tumors, 47% for neuroblastoma, and 36% protective effect for leukemia. To our knowledge, this is the first systematic review and meta-analysis examining such protective effect. Based on these data, one can estimate that maternal multivitamin supplementation may prevent 900 cases of pediatric leukemia and 300–400 cases of pediatric brain tumors annually in the United States.

The most apparent limitation of all studies considered in this meta-analysis is their retrospective design and the

potential for recall or reporting bias. The bias may stem from parents of the case group wishing to attribute their child's cancer to a cause. On the other hand, recall bias may alter the exposure rate they report. Hence, reporting bias may result in over-reporting or lack of multivitamin use. In addition, some studies specifically asked about multivitamin use, whereas other studies posed an open-ended question on whether women took any medications.

Second, the composition of the multivitamins probably varied, as did the timing and duration of exposure. This may be a limitation because different components within the multivitamin may be responsible for these protective effects. However, as different brands of multivitamins contain different amounts of vitamins and minerals, it is difficult to ascertain which component is responsible for the protective effect. In addition, women who began supplementing before pregnancy and continue throughout pregnancy may have a different risk of delivering a child with pediatric cancer compared to women who began supplementing after discovering they were pregnant. Considering that, different vitamins and minerals are important in the production and replication of DNA and cells, mothers who began supplementation prior to pregnancy may theoretically have a lower risk of delivering a child with pediatric cancer.

Third, the selection of control groups varied between studies. The majority of the investigators utilized a random-digit telephone-dialing method; however, their inclusion criterion varied in certain circumstances.^{10,19,20,31,32,34} In cases where matches could not be found to meet the original criteria, investigators loosened different criteria in order to find a match.³² In addition, as random dialing is being used, some

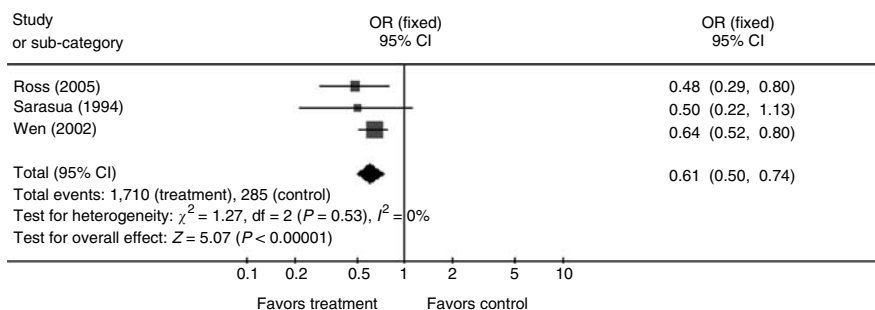


Figure 1 Maternal multivitamin consumption and risk for ALL in their children.

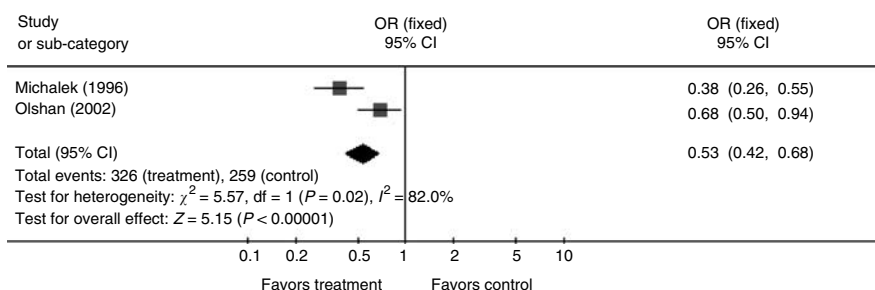


Figure 2 Maternal multivitamin consumption and risk for neuroblastoma in their children.

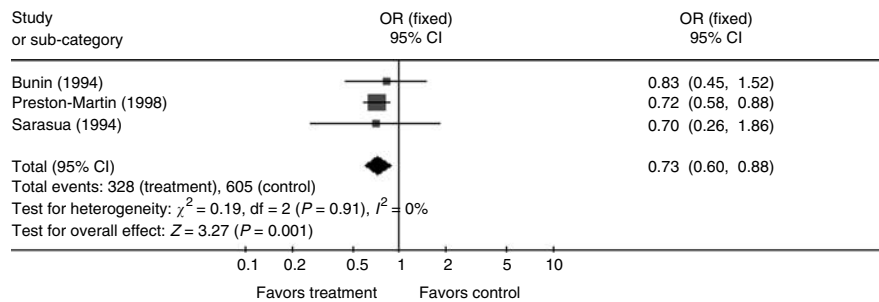


Figure 3 Maternal multivitamin consumption and risk for pediatric brain tumors in their children.

households with multiple phone lines have a greater chance of selection. In terms of identifying controls, one study matched by birth certificate registry,³³ whereas another matched by physician's patient roster.³⁵ Most studies matched based on ± 1 years of age; however, there was a study that matched on ± 2 years of age¹⁹ or ± 3 years of age.³¹ In addition, a fair number of studies did not match for ethnicity³¹ or matched on a black/non-black basis.³² Moreover, social class differences were not considered.³¹ Mothers of lower social class may not have had sufficient resources to afford a well-balanced diet. Maternal medical history and medication intake were also not reported in all articles. Confounding effects such as absorption problems and drug interactions involving multivitamins were therefore not addressed.

In addition to the articles included in this meta-analysis, one rejected article, which did not present raw data, also reported an apparent protective effect. A study conducted by Bunin *et al.*³⁶ of the Children's Cancer Group from 1986 to 1989 found that the use of multivitamins during the first 6 weeks of pregnancy decreased the risk of primitive neuroectodermal brain tumors (OR = 0.56, $P = 0.02$). In addition, a later case-control study, which also did not report raw data, used the Children's Cancer Study Group to compare children who were diagnosed with retinoblastoma between 1982 and 1985, and found a decreased occurrence of retinoblastoma with prenatal multivitamin supplementation in both sporadic and heritable tumors (OR = 0.4, $P = 0.03$, OR = 0.2, $P = 0.02$, respectively).³⁷

Although our conclusions suggest that folic-acid containing multivitamins are associated with a decrease in certain pediatric cancers, the available data do not allow determination of which of the constituent(s) may cause these protective effects. The papers included in the study were based on maternal reports of multivitamin use. As such, the components and the quantity of each vitamin contained within the multivitamins, were not available in some of the papers included.

It may be possible that the observed effect may be related to folic acid. It has been hypothesized that the potential association of folate deficiencies and pediatric cancer is due to partially altered DNA methylation and impaired DNA synthesis and repair.² This transformation may be the source

for the primitive neuroectodermal tumors.² In addition, polymorphism of the MTHFR gene may also be an important etiologic factor.⁸⁶⁻⁸⁸ Polymorphism of C677T and A1298C may reduce the risk of ALL.⁸⁹ In contrast, the same authors hypothesized that folate may also enhance the development and progression of already existing, undiagnosed premalignant or malignant lesions.^{90,91} Conversely, other researchers reported that folate supplementation may prevent breast cancer,⁹²⁻⁹⁶ colorectal adenoma, and carcinoma in adults,⁹⁷ and folate receptor overexpression has been noted in ependymomas.⁹⁸

Several other vitamins have also been investigated regarding their ability to prevent cancer. The antioxidant mechanism of vitamins C and E has been investigated in the reduction of nitrosation process in cured meats and the formation of carcinogens.¹⁰

To date, there have been no experimental data establishing a direct relationship between multivitamins and the pathogenesis of pediatric brain tumors. Because folic acid is the standard prophylactic therapy to reduce the risk of neural tube defects in pregnancy, there is no way to ethically conduct a randomized-control trial to separate these effects. The only possible method to elucidate whether the observed protective effect is due to folic acid itself or other vitamins would be to conduct a head-to-head comparison of folic acid versus folic-acid containing multivitamins. This, however, is not feasible given the large sample size that would need to be followed for a long period of time. Presently, many women actively planning pregnancy commence prenatal multivitamins before conception, and hence it is not likely that such comparison is presently feasible.

In conclusion, prenatal multivitamins containing folic acid appear to be associated with a significant protective effect on three common pediatric cancers. Given that women who are considering pregnancy are generally advised to supplement with folic acid, the results from this study suggest that supplementation with a folic acid-containing multivitamin may be a preferred method.

METHODS

A search of the existing literature regarding pre- and periconceptional ingestion of multivitamins and the rates of cancer in offspring was undertaken. The outcome of interest was pediatric cancer.

All original research articles using case-control or cohort study design were included. Included articles must have contained a control group of healthy children with accounts of maternal intake of multivitamins during pregnancy. In addition, all included articles must have contained raw data of number of cases and controls using multivitamins. We excluded articles that did not involve women taking multivitamins during pregnancy or focused on specific vitamins, mothers exposed to other known teratogens, review articles, or data reported in abstracts or meetings.

Articles were searched using the terms multivitamin, pregnancy, cancer, and neoplasms in Medline (1966–July 2005), PubMed (–July 2005), EMBASE (1980–July 2005), Toxline (1960–July 2005), Healthstar (–July 2005), and the Cochrane database in all languages. References from all collected articles were reviewed for additional original studies of interest.

All of the articles were reviewed using the above selection criterion by two reviewers who were blinded to the study outcome, names, and institutions of authors. Data from the articles were extracted by the two reviewers onto collection forms. In cases of discrepancies, discussions were undertaken and if unresolved, the article was reviewed by a third blinded reviewer who served as a tiebreaker. All data were entered into 2 × 2 tables. OR and 95% CI were calculated for each case-control study using Review Manager 4.2.7 (2004, The Cochrane Collaboration). Homogeneity among effects was tested by calculating χ^2 . A funnel plot was used to assess publication bias, following which the Begg–Mazumdar test was executed to calculate Kendall's τ ; a test that evaluates the agreement between the effect and variances.

CONFLICT OF INTEREST

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