National Toxicology Program
U.S. Department of Health and Human Services

SUPPLEMENTARY MATERIAL: STUDY SUMMARIES

CANCER POOLED AND META-ANALYSES

IDENTIFYING RESEARCH NEEDS FOR ASSESSING SAFE USE OF HIGH INTAKES OF FOLIC ACID

May 8, 2015

Office of Health Assessment and Translation
Division of the National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

TABLE OF CONTENTS

1. BAO, 2011

Full citation: Bao Y, Michaud DS, Spiegelman D, Albanes D, Anderson KE, Bernstein L, van den Brandt PA, English DR, Freudenheim JL, Fuchs CS, Giles GG, Giovannucci E, Goldbohm RA, Hakansson N, Horn-Ross PL, Jacobs EJ, Kitahara CM, Marshall JR, Miller AB, Robien K, Rohan TE, Schatzkin A, Stevens VL, Stolzenberg-Solomon RZ, Virtamo J, Wolk A, Ziegler RG, Smith-Warner SA. 2011. Folate intake and risk of pancreatic cancer: pooled analysis of prospective cohort studies. J Natl Cancer Inst 103(24): 1840-1850.
Funding: This study was supported by grants from the National Cancer Institute, National Institutes of Health, Bethesda, MD (CA55075 to W. C. Willett and CA124908 to C.S.F.). The funders did not have any involvement in the design of the study; the collection, analysis, and interpretation of the data; the writing of the article; or the decision to submit the article for publication.

1.1. Pooling Project of Prospective Studies of Diet and Cancer (Pooling Project)

Protocol: Pooling Project of Prospective Studies of Diet and Cancer (Pooling Project)	
Literature Search Strategy: Other	**Protocol type:** Pooled-analysis
	Inclusion Criteria: assessed the validity of their dietary assessment method or a closely related instrument, at least one publication on the relation between diet and cancer, dietary assessment method that was of sufficient detail to calculate intakes of most nutrients, including energy, and that assessed intake over a period of months or years, identification of at least 50 incident pancreatic cancer cases **Exclusion Criteria:**
Starting date:	**Ending date:**
Total references from search: 16	**References Included:** 14

Additional Notes:

1.2. Result(s)

1.2.A <u>pancreatic cancer, dietary folate, men and women nonusers of supplements: Q5 vs. Q1</u>
Studies (12), Total Subjects (775272)

Exposure	Assessed Outcome	adjusted relative risk	95% CI (low, high)	Test of Heterogeneity
dietary folate	pancreatic cancer	1.2	(1.01, 1.43)	p=0.42 (due to sex, p=0.36)

Notes: Ptrend = 0.08

1.2.B <u>pancreatic cancer, dietary folate, men and women: Q5 vs. Q1</u>
Studies (14), Total Subjects (862664)

Exposure	Assessed Outcome	adjusted relative risk	95% CI (low, high)	Test of Heterogeneity

Exposure	Assessed Outcome	adjusted relative risk	95% CI (low, high)	Test of Heterogeneity
dietary folate	pancreatic cancer	1.06	(0.9, 1.25)	p=0.15 (due to sex, p=0.83)

Notes: Ptrend = 0.47

1.2.C pancreatic cancer, dietary folate, men: Q5 vs. Q1

Studies (8), Total Subjects (319716)

Exposure	Assessed Outcome	adjusted relative risk	95% CI (low, high)	Test of Heterogeneity
dietary folate	pancreatic cancer	1.05	(0.77, 1.42)	p=0.04

Notes: Ptrend = 0.47

1.2.D pancreatic cancer, dietary folate, women: Q5 vs. Q1

Studies (11), Total Subjects (542948)

Exposure	Assessed Outcome	adjusted relative risk	95% CI (low, high)	Test of Heterogeneity
dietary folate	pancreatic cancer	1.08	(0.9, 1.3)	p=0.50

Notes: Ptrend = 0.84

1.2.E pancreatic cancer, total folate, men and women: Q5 vs. Q1

Studies (14), Total Subjects (627433)

Exposure	Assessed Outcome	adjusted relative risk	95% CI (low, high)	Test of Heterogeneity
total folate from both food and supplements	pancreatic cancer	0.96	(0.8, 1.16)	p=0.22 (due to sex p=0.07)

Notes: Ptrend = 0.90

1.2.F pancreatic cancer, total folate, men: Q5 vs. Q1

Studies (8), Total Subjects (219542)

Exposure	Assessed Outcome	adjusted relative risk	95% CI (low, high)	Test of Heterogeneity
total folate from both food and supplements	pancreatic cancer	1.14	(0.89, 1.45)	p=0.44

Notes: Ptrend = 0.11

1.2.G pancreatic cancer, total folate, women: Q5 vs. Q1

Studies (11), Total Subjects (407891)

Exposure	Assessed Outcome	adjusted relative risk	95% CI (low, high)	Test of Heterogeneity
total folate from both food and supplements	pancreatic cancer	0.85	(0.67, 1.07)	p=0.30

Notes: Ptrend = 0.39

1.3. Statistical Method(s)

Results: pancreatic cancer, dietary folate, men and women nonusers of supplements: Q5 vs. Q1; pancreatic cancer, dietary folate, men and women: Q5 vs. Q1; pancreatic cancer, dietary folate, men: Q5 vs. Q1; pancreatic cancer, dietary folate, women: Q5 vs. Q1; pancreatic cancer, total folate, men and women: Q5 vs. Q1; pancreatic cancer, total folate, men: Q5 vs. Q1; pancreatic cancer, total folate, women: Q5 vs. Q1

Adjustment factors: alcohol intake, body mass index (BMI), diabetes, energy intake, smoking

Statistical metric description: After applying the study-specific exclusion criteria, we further excluded participants with a previous cancer diagnosis other than non-melanoma skin cancer at baseline or who reported implausible energy intakes of more than three SDs from the study-specific natural log (log-e)–transformed mean intake of total energy. Data analyses composed of two steps. First, we calculated study-specific relative risks (RRs) and 95% confidence intervals (CIs) using the Cox proportional hazards model. We tested the assumption of proportional hazards and observed no evidence of violation. Second, we pooled study-specific relative risks to calculate a pooled relative risk using the DerSimonian and Laird random effects model. Heterogeneity across studies was tested using the Q statistic. Folate intake was analyzed in study-specific quintiles. For the Canadian National Breast Screening Study and the Netherlands Cohort Study, each of which used a case–cohort design, study-specific quintiles were based on the distributions in the subcohort; for the remaining studies, study-specific quintiles were based on the distributions in the entire cohort. In further analyses, folate intake was analyzed in study-specific quartiles to ensure that the results were not sensitive to the number of folate intake groups. In addition, folate intakes were also categorized by identical absolute cut points across studies. We used the lowest intake category as the reference category throughout the analyses, and the cut point for the referent category was chosen to ensure that the number of cancers in the referent category was large enough to generate stable relative risk estimates in each study. If no participants were diagnosed with pancreatic cancer in the highest intake category in a study, the participants in the highest category in that study were included in the second highest intake category. Linear trends were tested by the Wald test of a score variable set to the median values of the corresponding category of intake.

2. CARROLL, 2010

Full citation: Carroll C, Cooper K, Papaioannou D, Hind D, Tappenden P, Pilgrim H, Booth A. 2010. Meta-analysis: folic acid in the chemoprevention of colorectal adenomas and colorectal cancer. Aliment Pharmacol Ther 31(7): 708-718.

Funding: This study was funded [in part] by the UK National Coordinating Centre for Health Technology Assessment (NCCHTA 06/70/01). Writing support was provided by University of Sheffield.

2.1. Folic acid and prevention of colorectal cancer

Protocol: Folic acid and prevention of colorectal cancer	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
A literature search was performed to identify relevant research using database thesaurus and free text terms for folate or folic acid and colorectal cancer. A validated study design filter to identify RCTs was used. This search also included other agents of interest, such as NSAIDs and calcium, as it was part of a larger assessment of numerous potential chemopreventive agents for colorectal cancer. (Search strategies are available from authors). Eight databases were searched for published and unpublished trials: Cochrane Library, MEDLINE, PreMEDLINE, CINAHL, EMBASE, Web of Science, Biological Abstracts (BIOSIS) and Research Registers. There was no limitation by either language or date. All searches were conducted in June 2008. The reference lists of relevant studies were also searched for additional papers.	**Inclusion Criteria:** adults with Familial Adenomatous Polyposis (FAP), Hereditary Non-Polyposis Colorectal Cancer (HNPCC), a history of colorectal adenomas, or with no increased baseline risk of colorectal cancer, control is placebo or agent other than folic acid, outcome includes the recurrence of adenomas or advanced adenomas or the occurrence of colorectal cancer, randomized controlled trials of folic acid or folate **Exclusion Criteria:**
Starting date:	**Ending date:** 2008-06-30
Total references from search: 3785	**References Included:** 10

Additional Notes: The search of electronic databases produced 3785 citations, of which seven papers (four trials) satisfied the inclusion criteria. Three additional papers (two trials) were identified from the references of these studies.

2.2. Result(s)

2.2.A Adenoma recurrence, Folic acid vs. placebo (2 studies)

Studies (2), Total Subjects (749)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid supplementation	Adenoma recurrence	1.16	(0.97, 1.39)	I=0%, P=0.66

Notes:

2.2.B Adenoma recurrence, Folic acid vs. placebo (3 studies)

Studies (3), Total Subjects (840)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid supplementation	Adenoma recurrence	0.93	(0.61, 1.41)	I=77%, P=0.01

Notes:

2.2.C Colorectal cancer incidence, plus antioxidants

Studies (3), Total Subjects (11062)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid supplementation	Colorectal cancer incidence	1.13	(0.77, 1.64)	I=7%, P=0.34

Notes:

2.3. Statistical Method(s)

Results: Adenoma recurrence, Folic acid vs. placebo (2 studies); Adenoma recurrence, Folic acid vs. placebo (3 studies); Colorectal cancer incidence, plus antioxidants

Adjustment factors:

Statistical metric description: Meta-analysis of trials was performed using REVMAN 5.0. For discrete and numerical outcomes, relative risks (RR) and risk differences (RD) are reported with 95% confidence intervals. The random effects model was used to account for clinical and methodological variations between trials. Statistical heterogeneity was described using the I-squared statistic. Two types of comparison are analysed and presented: Folic acid alone vs. placebo alone; and folic acid with or without other interventions vs. placebo (with or without other interventions). Only randomized participants for whom a valid outcome had been evaluated and reported are included in the analysis.

3. CHAN, 2011

Full citation: Chan AL, Leung HW, Wang SF. 2011. Multivitamin supplement use and risk of breast cancer: a meta-analysis. Ann Pharmacother 45(4): 476-484.
Funding: None reported

3.1. Multivitamin supplement use and risk of breast cancer

Protocol: Multivitamin supplement use and risk of breast cancer	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
We searched MEDLINE (1950 through July 2010), EMBASE (1980 through July 2010), and the Cochrane Central Register of Controlled Trials (The Cochrane Library 2010, issue 1). Studies in English that described the association between supplemental multivitamin use and breast cancer risk in women were identified. The search strategy for MEDLINE and EMBASE was (breast cancer and multivitamin or vitamin) AND (clinical or cohort [title/abstract] AND trial [title/abstract] OR clinical trials [MeSH terms] OR cohort studies [MeSH terms] OR therapeutic use [MeSH terms subheading]). The authors manually screened the reference lists incorporated in a meta-analysis published by Larsson et al., a systematic review of the literature published by Velicer et al. in 2008, and the references in all identified studies.	**Inclusion Criteria:** breast cancer outcome, includes women taking multivitamins or vitamins **Exclusion Criteria:** no information on supplemental multivitamin use and diet, studies performed in patients with a history of breast cancer
Starting date: 1950-01-01	**Ending date:** 2010-07-01
Total references from search: 27	**References Included:** 8

Additional Notes:

3.2. Result(s)

3.2.A <u>case-control, breast cancer in women and multivitamin use/no use</u>
Studies (3), Total Subjects (6970)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
multivitamins	breast cancer	1.0	(0.51, 1.97)	I2 = 0%; p=0.99

Notes:

3.2.B <u>cohort, breast cancer in women and multivitamin use/no use</u>
Studies (5), Total Subjects (56294)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
multivitamins	breast cancer	0.99	(0.6, 1.6)	I2 = 0%; p=1.00

Notes:

3.3. Statistical Method(s)

Results: case-control, breast cancer in women and multivitamin use/no use; cohort, breast cancer in women and multivitamin use/no use

Adjustment factors:

Statistical metric description: A quantitative meta-analytic technique was used to pool data for the relative risk of breast cancer to explore the differences between women who took multivitamins and those who did not. The meta-analysis was performed using the random-effects model. The hypothesis of our study was that there was no significant association between multivitamin intake and an increased or decreased risk of breast cancer. The extent of heterogeneity was quantified using I. The I2 statistic describes the percentage of variation across studies that is caused by heterogeneity rather than chance. I2 can be readily calculated from basic results obtained from a typical metaanalysis as $I2 = 100\% \times (Q - df)/Q$, where Q is Cochran's heterogeneity statistic and df is the degrees of freedom. Values of I 2 less than the degrees of freedom are set equal to zero so that I2 lies between 0% and 100%. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. The overall effect was expressed as the relative risk. All analyses were performed using REVMAN statistical software (version 5.0) by the Cochrane Collaboration. We also analyzed the association between breast cancer risk and the frequency and duration of multivitamin intake.

4. CHEN, 2014

Full citation: Chen P, Li C, Li X, Li J, Chu R, Wang H. 2014. Higher dietary folate intake reduces the breast cancer risk: a systematic review and meta-analysis. Br J Cancer 110(9): 2327-2338.
Funding: This study was supported by grants from the Ministry of Science and Technology of China (2012BAK01B00), the National Nature Science Foundation (81125020, 81302507 and 81302809), the Science and Technology Commission of Shanghai Municipality (12XD1407000, 12431900500, 11391902000 and 12391901300), Director Foundation (20090101) and the Food Safety Research Center and Key Laboratory of Food Safety Research of INS, SIBS, CAS. Peizhan Chen was partially supported by the SA-SIBS scholarship program.

4.1. Folate and risk of breast cancer

Protocol: Folate and risk of breast cancer	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
We searched the MEDLINE and PubMed databases for relevant studies published updated to January, 2014. To minimise the restrictions, the terms breast cancer in combination with folate or folic acid were used in the literature search. The references of the retrieved publications were checked to identify any missing studies. Only studies reported in English were included. The study was conducted following the MOOSE statement and the PRISMA guidelines. Two authors (PC and CL) independently reviewed the retrieved abstracts or manuscripts to determine the eligibility of the studies for inclusion in our meta-analysis. Published studies were selected based on the following criteria: (1) a prospective, case–control or cross-sectional study design; (2) reported an association between folate intake or circulating folate levels in categories and breast cancer risk; (3) provided the relative risk (RR) or odds ratio (OR) estimates and their 95% confidence intervals (95% CIs) or sufficient data to calculate the estimates for the higher category exposure level compared with the lowest category level. As a result, we identified 49 eligible studies from a total of 1051 published studies. The working flowchart for selecting the eligible studies is briefly explained in Figure 1.	**Inclusion Criteria:** English, prospective, case-control, or cross-sectional study design, provided the relative risk (RR) or odds ratio (OR) estimates and their 95% confidence intervals (95% CIs) or sufficient data to calculate the estimates for the higher category exposure level compared with the lowest category level, reported an association between folate intake or circulating folate levels in categories and breast cancer risk **Exclusion Criteria:**
Starting date:	**Ending date:** 2014-01-31
Total references from search: 1051	**References Included:** 49

Additional Notes: Exact N's from each meta-analysis are not provided and the studies referenced in text are not consistent with the figures or Supplementary Tables. For example, Text states that the case-control study Negri 2000 was excluded for overlap, but it is included in the Figure 4 results while the study it overlaps with is not. There are also 5 studies listing Total Folate measures in Supplementary Table 2, but Table 2 lists 3 studies as the basis for the meta-analysis.

4.2. Result(s)

4.2.A Breast cancer, Folate Intake, Dietary, Case-Control Studies

Studies (25), Total Subjects (39806)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
Folate	Breast cancer	0.79	(0.67, 0.92)	I2 = 82.3%; p = <0.001

Notes: Inconsistencies between Table 2 and the Supplementary Materials and text make calculation of the total N questionable.

4.2.B Breast cancer, Folate Intake, Dietary, Prospective Studies

Studies (15), Total Subjects (655249)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
Folate	Breast cancer	0.95	(0.87, 1.03)	I2 = 66.2%; p = <0.001

Notes:

4.2.C Breast cancer, Folate Intake, Supplement, Prospective Studies

Studies (3), Total Subjects (86647)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
Folate	Breast cancer	1.07	(0.95, 1.21)	I2 = 21.7%; p = 0.288

Notes:

4.2.D Breast cancer, Folate Intake, Total, Case-Control Studies

Studies (3), Total Subjects (6403)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
Folate	Breast cancer	0.87	(0.61, 1.23)	I2 = 67.4%; p = 0.047

Notes: The text and table state that 3 studies were included, while the supplemental materials give details for 5 included studies. Inconsistencies between Table 2 and the Supplementary Materials and text make calculation of the total N questionable.

4.2.E Breast cancer, Folate Intake, Total, Prospective Studies

Studies (11), Total Subjects (476625)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
Folate	Breast cancer	0.97	(0.87, 1.08)	I2 = 66.5%; p = <0.001

Notes:

4.3. Statistical Method(s)

Results: Breast cancer, Folate Intake, Dietary, Case-Control Studies; Breast cancer, Folate Intake, Dietary, Prospective Studies; Breast cancer, Folate Intake, Supplement, Prospective Studies; Breast

cancer, Folate Intake, Total, Case-Control Studies; Breast cancer, Folate Intake, Total, Prospective Studies

Adjustment factors:

Statistical metric description: We used the inverse variance weighting method to calculate the summary estimate and related 95% CI. The RRs and ORs with their 95% CIs for the highest category in comparison with the lowest category for each study were extracted or calculated, and the ORs from nested case–control studies were assumed as the estimates of the RRs for prospective studies. The squared inverse variance for the logarithm RR/OR was considered as the appropriate weight for each study. We used the standard fixed-effect model as well as the DerSimonian and Laird random- effects model that considers both within- and between-study variations. When the risk estimates were provided in a stratified way (such as by menopausal status, oestrogen status, alcohol use) in the original report, we calculated the pooled estimate for each study before the final meta-analysis unless the stratification analysis was conducted. For studies having overlapping participants, the most completed one or the one with largest sample size was used to evaluate the overall association between dietary or total folate intake level and the breast cancer risk; however, the one with the most detailed information related to the stratification factors was included in the stratification studies to assess the association between folate intake level and breast cancer sufficiently. In the dose-response meta-analysis of folate intake and breast cancer risk, we first used the methods reported by Greenland and Longnecker (1992) and Orsini et al (2006) to compute the study-specific dose-response effects from the correlated log RR or log OR estimates across the categories for folate intake. For any report that did not provide the distribution of case patients and control subjects by exposure category, we estimated the slopes with the variance-weighted least squares regression model as suggested by Larsson et al (2007). Then, the individual estimates were pooled with the inverse variance weighting method to calculate the overall estimates for folate intake (per 100 mg per day increment) and breast cancer risk. To estimate the dose-response trend for log RRs or log ORs across exposure categories, we applied the generalised least squares regression model (Greenland and Longnecker, 1992) to pool the prospective studies and the case–control studies that have reported dose-specific RRs/ORs for dietary or total folate intake and breast cancer risk, respectively. We examined the potential nonlinear dose-response relationship between folate intake levels and breast cancer risk by modelling folate intake levels using restricted cubic splines with three knots at 10%, 50% and 90% percentiles of the folate intake distribution. To reduce potential statistical bias, at least four eligibility individual studies were pooled with the generalised least squares regression model in the stratification studies. The P-value for nonlinearity test was determined by testing the null hypothesis that the coefficient of the second spline is equal to 0. The Cochrane Q-test and I2 statistics were used to evaluate the statistical heterogeneity among studies under the assumption of random-effects model. A P-value of <0.05 for Q-test or I2 >25% was considered statistically significant heterogeneity among the studies. If significant heterogeneity was detected, the results for the random-effects model were used as a more appropriate model for interpretation compared with the fixed-effects model. To identify any potential publication bias, the funnel plots and Egger's linear regression test were executed, and significant publication bias was considered when the P-value was <0.05. When significant publication bias for folate intake or circulating folate level and breast cancer risk was identified, the trim and fill method was used to adjust the publication bias (Duval and Tweedie, 2000). All statistical analyses were conducted with R software (version 2.14.2) and the Meta package for R (www.r-project.org), the Stata statistical software (version 12.0, StataCorp, College Station, TX, USA) and the Review Manager (version 5.2.4, The Nordic Cochrane Centre, Copenhagen, Denmark).

5. CHO, 2006

Full citation: Cho E, Hunter DJ, Spiegelman D, Albanes D, Beeson WL, van den Brandt PA, Colditz GA, Feskanich D, Folsom AR, Fraser GE, Freudenheim JL, Giovannucci E, Goldbohm RA, Graham S, Miller AB, Rohan TE, Sellers TA, Virtamo J, Willett WC, Smith-Warner SA. 2006. Intakes of vitamins A, C and E and folate and multivitamins and lung cancer: a pooled analysis of 8 prospective studies. Int J Cancer 118(4): 970-978.
Funding: None reported

5.1. Pooling Project of Prospective Studies of Diet and Cancer

Protocol: Pooling Project of Prospective Studies of Diet and Cancer

Protocol: Pooling Project of Prospective Studies of Diet and Cancer	
Literature Search Strategy: Systematic	**Protocol type:** Pooled-analysis
To maximize the quality and comparability of the studies in the Pooling Project, we formulated several inclusion criteria a priori. First, we include prospective studies which 1) had at least one publication on the relation between diet and cancer; 2) used a dietary assessment method that was of sufficient detail to calculate intakes of most nutrients, including energy, and that assessed intake over a period of months or years; and 3) assessed the validity of their dietary assessment method or a closely related instrument. Second, for each cancer site evaluated, we specify a minimum number of cases required for a study to be included in the analysis. Additional inclusion criteria also may be made for each cancer site. Third, for each analysis, we include only those studies that assessed the specified exposure and in which participants consumed the dietary item of interest. For analyses that are going on simultaneously in the Pooling Project and the European Prospective Investigation into Cancer and Nutrition, we intend to coordinate analyses so that, to the extent possible, we can use similar analytic approaches and provide comparable results. Sixteen studies (32–46) are currently included in the Pooling Project (table 1). As we become aware of new studies meeting the inclusion criteria, the investigators from those studies are invited to join the Project. The Canadian National Breast Screening Study and the Netherlands Cohort Study are each analyzed as case-cohort studies, because the investigators in these two studies each selected a random sample of the cohort to provide the person-time data for the cohort and have processed questionnaires for only this random sample and the cases. We divide the person-time and numbers of cases compiled during follow-up of the Nurses' Health Study into two segments to take advantage of the expanded food frequency questionnaire administered in 1986 as compared with 1980. In this paper, we refer to the follow-up period from 1980 to 1986 as ''Nurses' Health Study A''; the follow-up period beginning in 1986 is referred to as ''Nurses' Health Study B.'' Following standard survival data analysis theory, blocks of person-time in different time periods are asymptotically uncorrelated, regardless of the extent to which they are derived from the same people (48, 49). Thus, pooling of the estimates from these two time periods produces estimates and standard errors which are as valid as those from a single time period.	**Inclusion Criteria:** **Exclusion Criteria:** history of cancer other than nonmelanoma skin cancer at baseline, log(e)-transformed energy intakes beyond 3 standard deviations from the study-specific log(e)-transformed mean energy intake of the baseline population, missing information on smoking habits
Starting date:	**Ending date:**
Total references from search: 16	**References Included:** 8

Additional Notes:

5.2. Result(s)

5.2.A lung cancer, folate from food, adenocarcinomas, Q4

Studies (4), Total Subjects (215466)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folate from food	lung cancer adenocarcinomas	0.93	(0.71, 1.2)	p = 0.02

Notes: p-trend = 0.47

5.2.B lung cancer, folate from food, current smokers, Q4

Studies (4), Total Subjects (45382)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folate from food	lung cancer	0.86	(0.75, 1.0)	p = 0.56

Notes: p-trend = 0.06

5.2.C lung cancer, folate from food, men and women, multivariate, Q5

Studies (4), Total Subjects (215466)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folate from food	lung cancer	0.88	(0.74, 1.04)	p = 0.09

Notes: p-trend = 0.08

5.2.D lung cancer, folate from food, men, multivariate, Q5

Studies (2), Total Subjects (72286)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folate from food	lung cancer	0.8	(0.58, 1.08)	p = 0.03

Notes: p-trend = 0.18

5.2.E lung cancer, folate from food, never smokers, Q4

Studies (4), Total Subjects (100700)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folate from food	lung cancer	0.69	(0.38, 1.26)	p = 0.03

Notes: p-trend = 0.23

5.2.F lung cancer, folate from food, past smokers, Q4

Studies (4), Total Subjects (69384)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folate from food	lung cancer	0.96	(0.78, 1.17)	p = 0.89

Notes: p-trend = 0.69

5.2.G lung cancer, folate from food, small cell carcinomas, Q4

Studies (4), Total Subjects (215466)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folate from food	lung cancer small cell carcinomas	1.02	(0.8, 1.31)	p = 0.22

Notes: p-trend = 0.79

5.2.H lung cancer, folate from food, squamous cell carcinomas, Q4

Studies (4), Total Subjects (215466)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folate from food	lung cancer squamous cell carcinomas	0.92	(0.7, 1.2)	p = 0.04

Notes: p-trend = 0.43

5.2.I lung cancer, folate from food, women, multivariate, Q5

Studies (3), Total Subjects (143180)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folate from food	lung cancer	0.95	(0.79, 1.13)	p = 0.56

Notes: p-trend = 0.31

5.2.J lung cancer, total folate, >600 mcg/d, men and women, multivariate

Studies (4), Total Subjects (215466)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
total folate	lung cancer	1.12	(0.85, 1.46)	p = 0.09

Notes: p-trend = 0.45

5.2.K lung cancer, total folate, adenocarcinomas, Q4

Studies (4), Total Subjects (215466)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
total folate	lung cancer adenocarcinomas	1.28	(0.97, 1.68)	p = 0.17

Notes: p-trend = 0.04

5.2.L lung cancer, total folate, current smokers, Q4

Studies (4), Total Subjects (45382)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
total folate	lung cancer	1.03	(0.83, 1.27)	p = 0.20

Notes: p-trend = 0.77

5.2.Mlung cancer, total folate, men and women, multivariate, Q5

Studies (4), Total Subjects (215466)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
total folate	lung cancer	1.02	(0.83, 1.26)	p = 0.07

Notes: p-trend = 0.51

5.2.N lung cancer, total folate, men, multivariate, Q5

Studies (2), Total Subjects (72286)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
total folate	lung cancer	0.86	(0.54, 1.38)	p = 0.06

Notes: p-trend = 0.78

5.2.O lung cancer, total folate, never smokers, Q4

Studies (4), Total Subjects (100700)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
total folate	lung cancer	1.21	(0.59, 2.45)	p = 0.04

Notes: p-trend = 0.41

5.2.P lung cancer, total folate, past smokers, Q4

Studies (4), Total Subjects (69384)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
total folate	lung cancer	1.0	(0.8, 1.25)	p = 0.66

Notes: p-trend = 0.38

5.2.Q lung cancer, total folate, small cell carcinomas, Q4

Studies (4), Total Subjects (215466)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
total folate	lung cancer small cell carcinomas	1.2	(0.83, 1.75)	p = 0.32

Notes: p-trend = 0.31

5.2.R lung cancer, total folate, squamous cell carcinomas, Q4

Studies (4), Total Subjects (215466)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
total folate	lung cancer squamous cell carcinomas	0.9	(0.59, 1.36)	p = 0.11

Notes: p-trend = 0.68

5.2.S lung cancer, total folate, women, multivariate, Q5

Studies (3), Total Subjects (143180)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
total folate	lung cancer	1.12	(0.93, 1.34)	p = 0.36

Notes: p-trend = 0.09

5.3. Statistical Method(s)

Results: lung cancer, folate from food, adenocarcinomas, Q4; lung cancer, folate from food, men and women, multivariate, Q5; lung cancer, folate from food, men, multivariate, Q5; lung cancer, folate from food, small cell carcinomas, Q4; lung cancer, folate from food, squamous cell carcinomas, Q4; lung cancer, folate from food, women, multivariate, Q5; lung cancer, total folate, >600 mcg/d, men and women, multivariate; lung cancer, total folate, adenocarcinomas, Q4; lung cancer, total folate, men and women, multivariate, Q5; lung cancer, total folate, men, multivariate, Q5; lung cancer, total folate, small cell carcinomas, Q4; lung cancer, total folate, squamous cell carcinomas, Q4; lung cancer, total folate, women, multivariate, Q5
Adjustment factors: alcohol intake, amount smoked, body mass index (BMI), education, energy intake, smoking, smoking duration
Statistical metric description: Vitamin intake was examined as quintiles in the primary analysis and as quartiles in the stratified analyses. Study-specific quintiles and quartiles were assigned on the basis of the distributions of the subcohorts in the Canadian National Breast Screening Study and the Netherlands Cohort Study, which each used a case–cohort design, and on the distributions of the whole cohort in the remaining studies. The Netherlands Cohort Study and the AlphaTocopherol Beta-Carotene Cancer Prevention Study were not included in the quantile analyses for total vitamins A, C and E and folate intakes, because fewer than 10% of the participants in these studies reported of using multivitamins, a main source of supplemental intake; thus, their total intakes in the higher quantiles were not comparable to those in other studies in which more than 30% of the participants used multivitamins. We also examined total vitamin intakes as categorical variables with uniform absolute intake cutpoints across the studies; both the Netherlands Cohort Study and the AlphaTocopherol Beta-Carotene Cancer Prevention Study were included in these categorical analyses so that the contribution from supplemental intake to total intake in these studies could be taken into account. To calculate the p-value for the test for trend, participants were assigned the median value of their category of intake, and this variable was used as a continuous variable in the study-specific regression models. Each study was analyzed using the Cox proportional hazards model. Incidence rate ratios were estimated using SAS PROC PHREG41 for all studies except the Canadian National Breast Screening Study and the Netherlands Cohort Study. These 2 studies were analyzed using Epicure software. For the analyses of each study, we stratified participants by age at baseline and the year in which the baseline questionnaire was returned. Person-years of follow-up were calculated from the date the baseline questionnaire was returned until the date of lung cancer diagnosis, death or end of follow-up, whichever came first. Multivariate models were adjusted for education (less than high school graduate, high school graduate and more than high school graduate), body-mass index (<23, 23–<25, 25–<30 and >30 kg/m2), alcohol consumption (0, >0–<5, 5–<15, 15–<30 and >30 gal/day), smoking status (current, past and never smokers), smoking duration for current smokers (continuous), smoking duration for past smokers (continuous), amount smoked for current smokers (continuous) and energy intake (continuous). The proportion of missing values for each covariate was <7% in each study; in the multivariate analyses, an indicator variable for missing responses was created for covariates, if applicable. Two-sided 95% confidence intervals (CIs) and p-values were calculated. To obtain a single pooled estimate, a random-effects model was used to combine the loge relative risks (RRs) from the multiple studies; the study-specific RRs were weighted by the inverse of the sum of their variance and the estimated between-studies variance component. Tests of heterogeneity were conducted using the Q statistic. We tested for variation in RRs by sex, smoking status and alcohol consumption, using a meta-regression model. We

also tested whether associations differed between adenocarcinomas, small cell carcinomas and squamous cell carcinomas, using a 2 degree of freedom squared Wald test statistic. Collectively, these 3 histological types represented at least 60% of the cases in each study.

Results: lung cancer, folate from food, current smokers, Q4; lung cancer, total folate, current smokers, Q4
Adjustment factors: alcohol intake, amount smoked, body mass index (BMI), education, energy intake, smoking duration
Statistical metric description: Vitamin intake was examined as quintiles in the primary analysis and as quartiles in the stratified analyses. Study-specific quintiles and quartiles were assigned on the basis of the distributions of the subcohorts in the Canadian National Breast Screening Study and the Netherlands Cohort Study, which each used a case–cohort design, and on the distributions of the whole cohort in the remaining studies. The Netherlands Cohort Study and the AlphaTocopherol Beta-Carotene Cancer Prevention Study were not included in the quantile analyses for total vitamins A, C and E and folate intakes, because fewer than 10% of the participants in these studies reported of using multivitamins, a main source of supplemental intake; thus, their total intakes in the higher quantiles were not comparable to those in other studies in which more than 30% of the participants used multivitamins. We also examined total vitamin intakes as categorical variables with uniform absolute intake cutpoints across the studies; both the Netherlands Cohort Study and the AlphaTocopherol Beta-Carotene Cancer Prevention Study were included in these categorical analyses so that the contribution from supplemental intake to total intake in these studies could be taken into account. To calculate the p-value for the test for trend, participants were assigned the median value of their category of intake, and this variable was used as a continuous variable in the study-specific regression models. Each study was analyzed using the Cox proportional hazards model. Incidence rate ratios were estimated using SAS PROC PHREG41 for all studies except the Canadian National Breast Screening Study and the Netherlands Cohort Study. These 2 studies were analyzed using Epicure software. For the analyses of each study, we stratified participants by age at baseline and the year in which the baseline questionnaire was returned. Person-years of follow-up were calculated from the date the baseline questionnaire was returned until the date of lung cancer diagnosis, death or end of follow-up, whichever came first. Multivariate models were adjusted for education (less than high school graduate, high school graduate and more than high school graduate), body-mass index (<23, 23–<25, 25–<30 and >30 kg/m2), alcohol consumption (0, >0–<5, 5–<15, 15–<30 and >30 gal/day), smoking status (current, past and never smokers), smoking duration for current smokers (continuous), smoking duration for past smokers (continuous), amount smoked for current smokers (continuous) and energy intake (continuous). The proportion of missing values for each covariate was <7% in each study; in the multivariate analyses, an indicator variable for missing responses was created for covariates, if applicable. Two-sided 95% confidence intervals (CIs) and p-values were calculated. To obtain a single pooled estimate, a random-effects model was used to combine the loge relative risks (RRs) from the multiple studies; the study-specific RRs were weighted by the inverse of the sum of their variance and the estimated between-studies variance component. Tests of heterogeneity were conducted using the Q statistic. We tested for variation in RRs by sex, smoking status and alcohol consumption, using a meta-regression model. We also tested whether associations differed between adenocarcinomas, small cell carcinomas and squamous cell carcinomas, using a 2 degree of freedom squared Wald test statistic. Collectively, these 3 histological types represented at least 60% of the cases in each study.

Results: lung cancer, folate from food, past smokers, Q4; lung cancer, total folate, past smokers, Q4
Adjustment factors: alcohol intake, body mass index (BMI), education, energy intake, smoking duration

Statistical metric description: Vitamin intake was examined as quintiles in the primary analysis and as quartiles in the stratified analyses. Study-specific quintiles and quartiles were assigned on the basis of the distributions of the subcohorts in the Canadian National Breast Screening Study and the Netherlands Cohort Study, which each used a case–cohort design, and on the distributions of the whole cohort in the remaining studies. The Netherlands Cohort Study and the AlphaTocopherol Beta-Carotene Cancer Prevention Study were not included in the quantile analyses for total vitamins A, C and E and folate intakes, because fewer than 10% of the participants in these studies reported of using multivitamins, a main source of supplemental intake; thus, their total intakes in the higher quantiles were not comparable to those in other studies in which more than 30% of the participants used multivitamins. We also examined total vitamin intakes as categorical variables with uniform absolute intake cutpoints across the studies; both the Netherlands Cohort Study and the AlphaTocopherol Beta-Carotene Cancer Prevention Study were included in these categorical analyses so that the contribution from supplemental intake to total intake in these studies could be taken into account. To calculate the p-value for the test for trend, participants were assigned the median value of their category of intake, and this variable was used as a continuous variable in the study-specific regression models. Each study was analyzed using the Cox proportional hazards model. Incidence rate ratios were estimated using SAS PROC PHREG41 for all studies except the Canadian National Breast Screening Study and the Netherlands Cohort Study. These 2 studies were analyzed using Epicure software. For the analyses of each study, we stratified participants by age at baseline and the year in which the baseline questionnaire was returned. Person-years of follow-up were calculated from the date the baseline questionnaire was returned until the date of lung cancer diagnosis, death or end of follow-up, whichever came first. Multivariate models were adjusted for education (less than high school graduate, high school graduate and more than high school graduate), body-mass index (<23, 23–<25, 25–<30 and >30 kg/m2), alcohol consumption (0, >0–<5, 5–<15, 15–<30 and >30 gal/day), smoking status (current, past and never smokers), smoking duration for current smokers (continuous), smoking duration for past smokers (continuous), amount smoked for current smokers (continuous) and energy intake (continuous). The proportion of missing values for each covariate was <7% in each study; in the multivariate analyses, an indicator variable for missing responses was created for covariates, if applicable. Two-sided 95% confidence intervals (CIs) and p-values were calculated. To obtain a single pooled estimate, a random-effects model was used to combine the loge relative risks (RRs) from the multiple studies; the study-specific RRs were weighted by the inverse of the sum of their variance and the estimated between-studies variance component. Tests of heterogeneity were conducted using the Q statistic. We tested for variation in RRs by sex, smoking status and alcohol consumption, using a meta-regression model. We also tested whether associations differed between adenocarcinomas, small cell carcinomas and squamous cell carcinomas, using a 2 degree of freedom squared Wald test statistic. Collectively, these 3 histological types represented at least 60% of the cases in each study.

Results: lung cancer, folate from food, never smokers, Q4; lung cancer, total folate, never smokers, Q4
Adjustment factors: alcohol intake, body mass index (BMI), education, energy intake
Statistical metric description: Vitamin intake was examined as quintiles in the primary analysis and as quartiles in the stratified analyses. Study-specific quintiles and quartiles were assigned on the basis of the distributions of the subcohorts in the Canadian National Breast Screening Study and the Netherlands Cohort Study, which each used a case–cohort design, and on the distributions of the whole cohort in the remaining studies. The Netherlands Cohort Study and the AlphaTocopherol Beta-Carotene Cancer Prevention Study were not included in the quantile analyses for total vitamins A, C and E and folate intakes, because fewer than 10% of the participants in these studies reported of using multivitamins, a main source of supplemental intake; thus, their total intakes in the higher quantiles were not comparable to those in other studies in which more than 30% of the participants used multivitamins.

We also examined total vitamin intakes as categorical variables with uniform absolute intake cutpoints across the studies; both the Netherlands Cohort Study and the AlphaTocopherol Beta-Carotene Cancer Prevention Study were included in these categorical analyses so that the contribution from supplemental intake to total intake in these studies could be taken into account. To calculate the p-value for the test for trend, participants were assigned the median value of their category of intake, and this variable was used as a continuous variable in the study-specific regression models. Each study was analyzed using the Cox proportional hazards model. Incidence rate ratios were estimated using SAS PROC PHREG41 for all studies except the Canadian National Breast Screening Study and the Netherlands Cohort Study. These 2 studies were analyzed using Epicure software. For the analyses of each study, we stratified participants by age at baseline and the year in which the baseline questionnaire was returned. Person-years of follow-up were calculated from the date the baseline questionnaire was returned until the date of lung cancer diagnosis, death or end of follow-up, whichever came first. Multivariate models were adjusted for education (less than high school graduate, high school graduate and more than high school graduate), body-mass index (<23, 23–<25, 25–<30 and >30 kg/m2), alcohol consumption (0, >0–<5, 5–<15, 15–<30 and >30 gal/day), smoking status (current, past and never smokers), smoking duration for current smokers (continuous), smoking duration for past smokers (continuous), amount smoked for current smokers (continuous) and energy intake (continuous). The proportion of missing values for each covariate was <7% in each study; in the multivariate analyses, an indicator variable for missing responses was created for covariates, if applicable. Two-sided 95% confidence intervals (CIs) and p-values were calculated. To obtain a single pooled estimate, a random-effects model was used to combine the loge relative risks (RRs) from the multiple studies; the study-specific RRs were weighted by the inverse of the sum of their variance and the estimated between-studies variance component. Tests of heterogeneity were conducted using the Q statistic. We tested for variation in RRs by sex, smoking status and alcohol consumption, using a meta-regression model. We also tested whether associations differed between adenocarcinomas, small cell carcinomas and squamous cell carcinomas, using a 2 degree of freedom squared Wald test statistic. Collectively, these 3 histological types represented at least 60% of the cases in each study.

6. CHUANG, 2013

Full citation: Chuang SC, Rota M, Gunter MJ, Zeleniuch-Jacquotte A, Eussen SJ, Vollset SE, Ueland PM, Norat T, Ziegler RG, Vineis P. 2013. Quantifying the dose-response relationship between circulating folate concentrations and colorectal cancer in cohort studies: a meta-analysis based on a flexible meta-regression model. Am J Epidemiol 178(7): 1028-1037.
Funding: This paper was made possible by grant 2008/51 from the World Cancer Research Fund, grant ECNIS2-266198 to P.V. from the European Commission, and grant PH-102-PP-29 to S-C.C. from the National Health Research Institutes, Taiwan.

6.1. Circulating folate and colorectal cancer

Protocol: Circulating folate and colorectal cancer	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
We conducted a literature search of the PubMed database until February 2012. The search was restricted to English-language articles and human studies and used the following search terms: “folate” and “colorectal cancer” in the abstract and title. We also checked the reference lists of articles retrieved from the PubMed search. Studies were included in the meta-analysis if they met the following criteria: case-control studies nested within a prospective cohort study; the exposure of interest was circulating (plasma or serum) levels of folate; and the outcome of interest was colorectal, colon, or rectal cancer. When several publications were available from the same study, the most recent publication, or the one including the largest number of subjects, was included. Figure 1 illustrates the study search and selection process.	**Inclusion Criteria:** case-control study nested within a prospective cohort study, circulating (plasma or serum) levels of folate, colorectal, rectal, or colon cancer, English language article **Exclusion Criteria:**
Starting date: 1966-01-01	**Ending date:** 2012-02-29
Total references from search: 4226	**References Included:** 8

Additional Notes:

6.2. Result(s)

6.2.A Colorectal cancer, circulating folate, Microbiological assay

Studies (3), Total Subjects (5831)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
Circulating folate	Colorectal cancer	1.03	(0.83, 1.22)	I2 = 12.0%, p = 0.321

Notes:

6.2.B Colorectal cancer, circulating folate, Overall

Studies (10), Total Subjects (10516)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
Circulating folate	Colorectal cancer	0.91	(0.77, 1.05)	I2 = 21.5%, p = 0.239

Notes: Lee 2012 is one publication, but contains results on 3 separate cohorts. So total number of publications captured int he search was 8, but data is included in the meta-analysis from 10 separate cohorts.

6.2.C Colorectal cancer, circulating folate, Radioimmunoassay

Studies (7), Total Subjects (4685)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
Circulating folate	Colorectal cancer	0.8	(0.61, 0.99)	I2 = 9.4%, p = 0.357

Notes: Lee 2012 is one publication, but contains results on 3 separate cohorts, 2 using the radioimmunoassay. The total number of publications with the radioimmunoassay is 6, but the meta-analysis is of 7 separate cohorts. Otani is considered one cohort, although results are presented separately for men and women.

6.3. Statistical Method(s)

Results: Colorectal cancer, circulating folate, Microbiological assay; Colorectal cancer, circulating folate, Overall; Colorectal cancer, circulating folate, Radioimmunoassay

Adjustment factors:

Statistical metric description: We used a flexible meta-regression model, which provides the best fitting 2-term fractional-polynomial model, to test a linear or a nonlinear dose-response relationship between circulating folate concentrations and CRC risk. The statistical methods used for this analysis are described in detail elsewhere. In brief, this approach takes into account the correlation within the same study among reported dose-specific log (relative risk) estimates due to the common reference group, the heterogeneity among studies, and the nonlinear trend component of the dose-response relationship. For each study, the midpoint/median level of circulating folate for each category, except the highest, and a level 1.2 times the lower cut point of the highest category were assigned to each corresponding relative risk estimate. The best fitting model is defined as the one with the smallest Akaike's Information Criterion. Because folate levels never reach null values, we investigated the relationship between folate levels and CRC risk on the basis of the contrast of each folate level with the reference category within a study. All circulating folate values were converted to nmol/L. The heterogeneity among the studies was tested with the Q statistic by using the linear trend estimates. The statistical analyses were repeated by converting the exposure levels using the equation provided by Fazili et al. to improve the comparability of the measurements among studies. We also combined the study-specific relative risks, comparing the highest with the lowest category, with an assumption that the measurement error due to interlab variation in absolute concentrations would be less likely to influence a comparison based on study-specific quantiles. The degree of heterogeneity was estimated by using the I2 statistic, which represents the percentage of total variation contributed by between-study variance.

7. CLARKE, 2010

Full citation: Clarke R, Halsey J, Lewington S, Lonn E, Armitage J, Manson JE, Bonaa KH, Spence JD, Nygard O, Jamison R, Gaziano JM, Guarino P, Bennett D, Mir F, Peto R, Collins R. 2010. Effects of lowering homocysteine levels with B vitamins on cardiovascular disease, cancer, and cause-specific mortality: Meta-analysis of 8 randomized trials involving 37 485 individuals. Arch Intern Med 170(18): 1622-1631.

Funding: Sources of funding for the individual trials are described in their separate publications. The Clinical Trial Service Unit and Epidemiological Studies Unit, where the BVTT Secretariat is located, has a policy of not accepting fees, honoraria, or paid consultancies directly or indirectly from industry. It receives funding from the British Heart Foundation, UK Medical Research Council, and Cancer Research UK. Support for this project was also provided by a grant from the UK Food Standards Agency.

7.1. Folic acid supplementation and cancer incidence

Protocol: Folic acid supplementation and cancer incidence	
Literature Search Strategy: Other	**Protocol type:** Meta-analysis
Randomized trials were eligible if (1) they involved a double-blind randomized comparison of B-vitamin supplements containing folic acid vs placebo for the prevention of vascular disease (irrespective of whether any other treatment was administered factorially); (2) the relevant treatment arms differed only with respect to the intervention to lower homocysteine levels (ie, they were unconfounded); and (3) the trial involved at least 1000 participants for a scheduled treatment duration of at least 1 year. Unpublished trials were sought through electronic searches and discussions with other experts in the field, but none was found. Individual participant data were obtained from 37 485 participants from all 8 available trials completed by the end of 2009. Data are not yet available from 3 unpublished trials involving almost 15 000 participants with prior CVD or renal disease, and these are not expected to report their results before late 2010. Another trial that intended to involve 15 000 participants with hypertension only started enrollment in 2008.	**Inclusion Criteria:** at least 1000 participants, B-vitamin supplements containing folic acid, double blind, has a placebo control, outcome is vascular disease, randomized controlled trials, scheduled treatment duration of at least 1 year, treatment arms differ only with respect to intervention to lower homocysteine levels **Exclusion Criteria:** nonfatal melanoma skin cancers
Starting date:	**Ending date:**
Total references from search: 8	**References Included:** 8

Additional Notes:

7.2. Result(s)

7.2.A <u>cancer incidence, folic acid</u>

Studies (7), Total Subjects (35603)

Exposure	**Assessed Outcome**	relative risk	95**% CI (low, high)**	**Test of Heterogeneity**

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid	cancer incidence	1.05	(0.98, 1.13)	X (2)(5) = 5.90; P=0.3

Notes:

7.3. Statistical Method(s)

Results: cancer incidence, folic acid
Adjustment factors:
Statistical metric description: Comparisons were intention-to-treat, time-to-event analyses of first events of a particular type occurring during the scheduled treatment period among all patients allocated to folic acid vs all allocated to the control treatment. The log-rank observed minus expected (o−e) statistics and their variances (v) from each trial were summed to produce, respectively, a grand total observed minus expected statistic (G) and its variance (V). The 1-step estimate of the logarithm of the event rate ratio is then G/V with variance 1/V (and 95% CI [G/V]±[1.96/V1/2]). For n trials, the X2 statistic for heterogeneity with n− 1 degrees of freedom (X2(n−1) is S−(G2/V), where S is the sum over all the trials of (o−e)2/v. The effects on vascular outcomes were assessed in the following predefined subgroups: sex, age, approximate thirds of pretreatment blood levels of folate (<4.4,4.4-7.9, and >7.9 ng/mL [to convert to nanomoles per liter, multiply by 2.266]) or of homocysteine (<11, 11-14, and >= 15 µmol/L), mandatory folic acid fortification, years since randomization, baseline smoking (current/not), alcohol consumption (current/not), presence of diabetes mellitus, statin use, aspirin use, body mass index (calculated as weight in kilograms divided by height in meters squared) (<25.0, 25.0-29.9, and >=30.0), and approximate thirds of serum creatinine levels (<0.90, 0.90-1.06, and >=1.07 mg/dL [to convert to micromoles per liter, multiply by 88.4]). Heterogeneity of the rate ratios (RRs) among these prespecified subgroups was investigated by a global test to reduce the chance of misinterpreting false-positive results arising from multiple comparisons. The CIs used were 99% for individual trials or subgroups and 95% for the overall estimates. In addition, the RR for major vascular events in each trial was plotted against the percentage homocysteine reduction achieved in that trial. The mean percentage homocysteine reduction in the aggregate of all trials was calculated as the weighted mean of the study-specific percentage reductions, with weights equal to the variances of the log-rank statistics for major vascular events. Analyses used commercially available software (SAS, version 9.1; SAS Institute Inc, Cary, North Carolina)

8. CLARKE, 2011

Full citation: Clarke R, Halsey J, Bennett D, Lewington S. 2011. Homocysteine and vascular disease: review of published results of the homocysteine-lowering trials. J Inherit Metab Dis 34(1): 83-91.
Funding: This work was supported by the British Heart Foundation and Medical Research Council.

8.1. B vitamins and risk of cancer

Protocol: B vitamins and risk of cancer	
Literature Search Strategy: Other	**Protocol type:** Meta-analysis
Randomized trials were eligible if: (1) they involved a randomized comparison of folic-acid-based B-vitamin supplements for prevention of cardiovascular disease versus placebo (irrespective of whether any other treatment was administered factorially); (2) the relevant treatment arms differed only with respect to the homocysteine-lowering intervention (i.e., they were unconfounded); and (3) the trial involved 1,000 or more participants for a scheduled treatment duration of at least 1 year. Unpublished trials that fulfilled the inclusion criteria were sought through electronic searches and discussions, but none were found. Summary data were extracted from all trials completed before 2009. Data were not available from three trials involving 15,000 participants [8,000 from VITATOPS (Hankey et al. 2007), 4,000 from FAVORIT (Bostom et al. 2009), and 3,000 from SU.FOL.OM3 (Galan et al. 2008)]. A further controlled trial of folic acid or control involving 15,000 Chinese participants with elevated blood pressure was commenced in 2008.	**Inclusion Criteria:** at least 1000 participants, B-vitamin supplements containing folic acid, has a placebo control, randomized controlled trials, scheduled treatment duration of at least 1 year, treatment arms differ only with respect to intervention to lower homocysteine levels **Exclusion Criteria:**
Starting date:	**Ending date:**
Total references from search: 8	**References Included:** 8

Additional Notes:

8.2. Result(s)

8.2.A <u>cancer events, B vitamins</u>
Studies (5), Total Subjects (29867)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
B-vitamin supplements	cancer	1.08	(0.99, 1.17)	X(2)(4) = 2.31; p=0.7

Notes:

8.3. Statistical Method(s)

Results: cancer events, B vitamins
Adjustment factors:
Statistical metric description: Comparisons were intention-to-treat analyses of first events during the scheduled treatment period in all participants allocated to folic-acid-based B vitamins or control (irrespective of any other treatment allocated factorially). For each trial, data were abstracted on the number allocated to each treatment and the number of coronary events, stroke events, cancer events, and deaths from any cause by treatment allocation. The expected number of events assuming treatment had no effect, and the observed minus expected (o-e) statistics and their variances (v) were calculated for each trial and summed to produce, respectively, a grand total observed minus expected (G) and its variance (V) (Early Breast Cancer Trialists' Collaborative Group 1990). The one-step estimate of the event rate ratio is G/V. The χ2 test statistic (χ(n-1)^2) for heterogeneity between n trials is S-(G^2/V), where S is the sum over all the trials of (o-e)(^2)/v (Yusuf 1985). All analyses were carried out using SAS (Version 9.1).

9. COLLIN, 2010

Full citation: Collin SM, Metcalfe C, Refsum H, Lewis SJ, Zuccolo L, Smith GD, Chen L, Harris R, Davis M, Marsden G, Johnston C, Lane JA, Ebbing M, Bonaa KH, Nygard O, Ueland PM, Grau MV, Baron JA, Donovan JL, Neal DE, Hamdy FC, Smith AD, Martin RM. 2010. Circulating folate, vitamin B12, homocysteine, vitamin B12 transport proteins, and risk of prostate cancer: a case-control study, systematic review, and meta-analysis. Cancer Epidemiol Biomarkers Prev 19(6): 1632-1642.
Funding: National Cancer Research Institute (administered by the Medical Research Council) provided support for the development of the ProtecT epidemiologic database through the Prostate Mechanisms of Progression and Treatment collaborative. The ProtecT study is supported by the UK NIHR Health Technology Assessment Programme (projects 96/20/06, 96/20/99). Support for the ProtecT biorepository in Cambridge is provided by NIHR through the Biomedical Research Centre. The funders were nonprofit organizations with no participating role in the study.

9.1. Circulating folate and risk of prostate cancer: with ProtecT study

Protocol: Circulating folate and risk of prostate cancer: with ProtecT study	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
Eligible studies of the association of prostate cancer risk with serum or plasma folate, B12, or tHcy levels were identified by searching the Medline and Embase online databases using text search terms for “folate/folic,” “B12/cobalamin,” and “tHcy,” each in conjunction with the MeSH heading “Prostatic Neoplasms” and text terms “prostate cancer” and “prostatic carcinoma.” No language or publication date restrictions were imposed. All databases were last searched on September 26, 2009. References of retrieved articles were screened. Case-control and cohort studies that reported associations of blood (serum or plasma) levels of folate, B12, and tHcy with prostate cancer risk were included. We also included data from the placebo arms of randomized controlled trials of folic acid and B12 supplementation. Studies reported their results in several different ways and presented various models with different adjustments. We selected the age-adjusted estimate or a more fully adjusted estimate where available, except where the model was deemed by us to be overadjusted (e.g., adjusted for vegetable intake). Data were extracted independently by two investigators (SMC and RH).	**Inclusion Criteria:** blood folate level, case-control or cohort study **Exclusion Criteria:**
Starting date:	**Ending date:** 2009-09-26
Total references from search: 414	**References Included:** 7

Additional Notes:

9.2. Result(s)

9.2.A Fixed effects pooled estimate, including ProtecT

Studies (7), Total Subjects (144234)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
blood (serum or plasma) folate	prostate cancer	1.04	(0.98, 1.11)	I2 = 39.5%, P=0.13

Notes: more fully adjusted estimates used, where available, except where the model was deemed by us to be overadjusted (e.g., adjusted for vegetable intake)

9.2.B Fixed effects pooled estimate, prospective cohort studies

Studies (6), Total Subjects (141266)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
blood (serum or plasma) folate	prostate cancer	1.19	(1.03, 1.37)	I2 = 13.1%, P=0.33

Notes: more fully adjusted estimates used, where available, except where the model was deemed by us to be overadjusted (e.g., adjusted for vegetable intake)

9.2.C Random effects pooled estimate, including ProtecT

Studies (7), Total Subjects (144234)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
blood (serum or plasma) folate	prostate cancer	1.11	(0.96, 1.28)	

Notes: more fully adjusted estimates used, where available, except where the model was deemed by us to be overadjusted (e.g., adjusted for vegetable intake)

9.2.D Random effects pooled estimate, prospective cohort studies

Studies (6), Total Subjects (141266)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
blood (serum or plasma) folate	prostate cancer	1.18	(1.0, 1.4)	

Notes: more fully adjusted estimates used, where available, except where the model was deemed by us to be overadjusted (e.g., adjusted for vegetable intake)

9.3. Statistical Method(s)

Results: Fixed effects pooled estimate, including ProtecT; Fixed effects pooled estimate, prospective cohort studies; Random effects pooled estimate, including ProtecT; Random effects pooled estimate, prospective cohort studies

Adjustment factors: age

Statistical metric description: To compare across studies, we calculated the log OR or hazard ratio per unit increase in vitamin and metabolite concentration. For studies presenting their results within categories of exposure (e.g., quantiles), we used the mean or median exposure in each category when they were reported and calculated the log OR per unit increase in exposure using the method of Greenland and Longnecker. When the mean or median in each group was not reported and a range of

exposure in each group was given, we estimated the mean exposure in each group using the method of Chêne and Thompson. Having fitted means to each group, the data were analyzed using the Greenland and Longnecker method. We used Stata's metainf command to investigate whether the exclusion of any one study would significantly change the pooled estimate, that is, whether the pooled point estimate with one study excluded would lie outside the 95% confidence interval (95% CI) of the pooled estimate with all studies included (38).

10. COOPER, 2010

Full citation: Cooper K, Squires H, Carroll C, Papaioannou D, Booth A, Logan RF, Maguire C, Hind D, Tappenden P. 2010. Chemoprevention of colorectal cancer: systematic review and economic evaluation. Health Technol Assess 14(32): 1-206.

Funding: The research reported in this issue of the journal was commissioned by the HTA programme as project number 06/70/01. The contractual start date was in February 2008. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design.

10.1. Folic acid and colorectal adenomas

Protocol: Folic acid and colorectal adenomas	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
A systematic review identified randomised controlled trials (RCTs) assessing drug and nutritional agents for the prevention of CRC or adenomatous polyps. A separate search identified qualitative studies relating to individuals' views, attitudes and beliefs about chemoprevention. MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, CINAHL, the Cochrane Database of Systematic Reviews, Cochrane CENTRAL Register of Controlled Trials, DARE, NHS-EED (NHS Economic Evaluation Database), HTA database, Science Citation Index, BIOSIS previews and the Current Controlled Trials research register were searched in June 2008. Data were extracted by one reviewer and checked by a second.	**Inclusion Criteria:** includes subjects from general population, increased risk, and high risk, randomized controlled trials **Exclusion Criteria:** Dose-finding and administration studies without an alternative intervention or placebo control group, observational studies
Starting date: 2003-01-01	**Ending date:** 2008-06-01
Total references from search: 6	**References Included:** 3785

Additional Notes: Multiple other exposures considered in review (broad search), folic acid results begin on page 42, Figure 6 summarizes results. Folic acid results also include aspirin as a co-exposure with folic acid and in placebo.

10.2. Result(s)

10.2.A Incidence of advanced adenoma, Folic acid alone vs. placebo alone

Studies (2), Total Subjects (749)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
Folic acid	Incidence of advanced adenoma	1.34	(0.77, 2.36)	I2 = 55%; p = 0.14

Notes:

10.2.B Recurrence of any adenoma, Folic acid alone vs. placebo alone

Studies (2), Total Subjects (749)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
Folic acid	Any adenoma	1.16	(0.97, 1.39)	I2 = 0%; p = 0.66

Notes:

10.3. Statistical Method(s)

Results: Incidence of advanced adenoma, Folic acid alone vs. placebo alone; Recurrence of any adenoma, Folic acid alone vs. placebo alone
Adjustment factors:
Statistical metric description:

11. DAI, 2013

Full citation: Dai WM, Yang B, Chu XY, Wang YQ, Zhao M, Chen L, Zhang GQ. 2013. Association between folate intake, serum folate levels and the risk of lung cancer: a systematic review and meta-analysis. Chinese Medical Journal 126(10): 1957-1964.
Funding: none reported

11.1. Folate intake and lung cancer risk

Protocol: Folate intake and lung cancer risk	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
Two independent researchers performed a systematic literature search on databases of PubMed and Medline using the terms “folate intake”, “folate consumption” or “serum folate” in combination with “lung cancer”. No more restrictions were put in order to get an overall inclusion. Overlapped publications were excluded. Relevant studies prior to February 1, 2013 were identified for screening.	**Inclusion Criteria:** case-control or prospective cohort studies, concerning the association between folate or its metabolism-related gene and lung cancer, English language article, provides data on risk estimates **Exclusion Criteria:** literature conducted in the same population
Starting date:	**Ending date:** 2013-02-01
Total references from search: 100	**References Included:** 13

Additional Notes:

11.2. Result(s)

11.2.A lung cancer, folate intake, dietary

Studies (6), Total Subjects (9275)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
folate intake	lung cancer	0.73	(0.63, 0.85)	I2 = 9.6%; p = 0.35

Notes: p-value <0.001

11.2.B lung cancer, folate intake, overall

Studies (6), Total Subjects (10528)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
folate intake	lung cancer	0.74	(0.65, 0.84)	I2 = 0; p = 0.63

Notes: p-value <0.001

11.2.C lung cancer, serum folate levels, overall

Studies (5), Total Subjects (6008)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
serum folate levels	lung cancer	0.78	(0.6, 1.02)	I2 = 0; p = 0.59

Notes: p-value = 0.075

11.3. Statistical Method(s)

Results: lung cancer, folate intake, dietary; lung cancer, folate intake, overall; lung cancer, serum folate levels, overall

Adjustment factors:

Statistical metric description: We pooled estimate effects of studies by the use of standard inverse variance weighting method and each study was weighed under inverse square of the standard error (SE) or logarithm OR. For prospective cohort study included in the meta-analysis, HR/RR was considered as OR in statistical analysis since there was barely numeric difference between the two. The DerSimonian and Laird random-effects methods were applied to assess the variability between studies. It is accepted that random-effects model should be used when significant heterogeneity was detected, because it provides results with wider confidence intervals. And on the other hand, results from the fixed- and random-effects models were consistent when there is no significant heterogeneity between studies. We evaluated statistical heterogeneity by Cochrane Q test ($P<0.05$) and I2 statistics ($I2>25\%$). Funnel plot as well as Egger's linear regression test ($P<0.05$) were conducted to determine the publication bias of studies. For a more comprehensive view, we assessed the influence of individual study on the overall estimates through the sensitivity test, in which we omitted one single study each time from the meta-analysis to see the change of final results. All statistical tests were two sided. Original data on effects of highest folate intake (serum folate) versus lowest were adopted directly; and in studies proving data on lowest folate intake (serum folate) versus highest, we calculated the corresponding reciprocals before the analysis. Similarly, we examined and extracted data for calculation of the effects from studies without original information, in which conditional Logistic regression was used to calculate the ORs and 95% CIs without adjustment. Subgroup results from studies without overall estimate effects were pooled first, after which the summarized data were used in final calculation. We also performed subgroup analysis besides overall one. We stratified studies by "folate source", "study design" and "study region" in folate intake analysis, and by "study type", "study design" and "study region" in serum folate analysis. We used R software (version: R-2.15.2) (R Development Core Team, Vienna, Austria) and its Meta package throughout the statistical analysis (http://www.r-project.org).

12. FIFE, 2011

Full citation: Fife J, Raniga S, Hider PN, Frizelle FA. 2011. Folic acid supplementation and colorectal cancer risk: a meta-analysis. Colorectal Dis 13(2): 132-137.
Funding: None reported

12.1. RCTs for Folic Acid Supplementation and Colorectal Cancer Risk

Protocol: RCTs for Folic Acid Supplementation and Colorectal Cancer Risk	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
A structured search of the MEDLINE, EMBASE, Cochrane and CINAHL databases was undertaken in July 2008 (Appendix S1) (Fig. 1 QUORUM diagram). All full articles that matched the inclusion criteria were retrieved and the reference lists in those articles were hand-searched for other relevant publications.	**Inclusion Criteria:** adenoma as primary or secondary outcome, comparison of subjects who received folate vs subjects who did not in relation to their risk of adenoma or advanced adenomatous lesions, English language article, outcome is bowel cancer, Randomized clinical trials **Exclusion Criteria:**
Starting date:	**Ending date:** 2008-07-01
Total references from search: 296	**References Included:** 3

Additional Notes:

12.2. Result(s)

12.2.A **adenoma and advanced adenoma, folate supplementation, longer follow-up, >3 years**
Studies (2), Total Subjects (6736)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
folic acid supplementation	Colorectal Cancer	1.35	(1.06, 1.7)	I2 = 0%, p = 0.54

Notes: Overall effect P=0.01

12.2.B **adenoma and advanced adenoma, folate supplementation, shorter follow up, <4 years**
Studies (2), Total Subjects (3686)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
folic acid supplementation	Colorectal Cancer	1.09	(0.93, 1.28)	I2 = 0%, p = 0.70

Notes: Overall effect P=0.30

12.3. Statistical Method(s)

Results: adenoma and advanced adenoma, folate supplementation, longer follow-up, >3 years; adenoma and advanced adenoma, folate supplementation, shorter follow up, <4 years

Adjustment factors:
Statistical metric description: A weighted treatment effect (using fixed effects) was calculated across trials using the RevMan. The results were expressed as odds ratios (OR) and 95% confidence intervals (CI) for dichotomous outcomes. All analyses were by intention to treat. Tests of heterogeneity were conducted using Cochran's Q-test. Subgroup analysis was used to investigate possible differences in the occurrence of adenoma and advanced adenomatous lesions and early (up to 3 years) vs late (more than 3 years) follow up.

13. FIGUEIREDO, 2011

Full citation: Figueiredo JC, Mott LA, Giovannucci E, Wu K, Cole B, Grainge MJ, Logan RF, Baron JA. 2011. Folic acid and prevention of colorectal adenomas: a combined analysis of randomized clinical trials. Int J Cancer 129(1): 192-203.
Funding: National Cancer Institute, National Institutes of Health; Grant numbers: N01-CO-12400, R01-CA-059005, U54-CA-100971, CA 55075, CA95589, R01 CA 67883

13.1. AFPPS, NHS/HPFS, and ukCAP, 1994-2001

Protocol: AFPPS, NHS/HPFS, and ukCAP, 1994-2001	
Literature Search Strategy: Other	**Protocol type:** Pooled-analysis
From literature searches in PubMed using keywords such as ''folic acid,'' ''trial'' and ''colorectal adenoma'' and by contacting colleagues, we identified three placebo-controlled randomized trials with more than 500 randomly assigned subjects that investigated folic acid in any dose as a chemopreventive agent for large-bowel adenomas.	**Inclusion Criteria:** folic acid in any dose as chemopreventive agent for large bowel adenomas, randomized controlled trials, trial included at least 500 participants **Exclusion Criteria:** Follow-up examinations prior to 6 months
Starting date:	**Ending date:**
Total references from search:	**References Included:** 3

Additional Notes:

13.2. Result(s)

13.2.A Advanced adenoma within 42 months, Folic acid

Studies (3), Total Subjects (1922)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
Folic acid	Advanced adenoma	1.06	(0.81, 1.39)	I2 = 2.0; p= 0.36

Notes: P = 0.65

13.2.B Any adenoma within 42 months, Folic acid

Studies (3), Total Subjects (1957)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
Folic acid	Any adenoma	0.98	(0.82, 1.17)	I2 = 70.0; p= 0.19

Notes: P = 0.81

13.3. Statistical Method(s)

Results: Advanced adenoma within 42 months, Folic acid; Any adenoma within 42 months, Folic acid
Adjustment factors:

Statistical metric description: The statistical analysis of the combined datasets followed standard random-effects meta-analysis methods in a two-stage approach. In the first stage, each clinical trial was analyzed separately to obtain trial-specific unadjusted estimates of the risk ratio (RR) of one or more adenomas or advanced lesions for the subjects randomly assigned to receive folic acid versus those allocated to placebo. Subsequently, the trial-specific relative RRs were combined using standard methods for random-effects meta-analysis. All p-values were derived from two-sided tests, and we considered a p-value less than 0.05 to be statistically significant. Between-study heterogeneity was assessed using the Q statistic and the I2 statistic. An I2 value of greater than 50%, or a p-value less than 0.05 for the Q statistic, was taken to indicate heterogeneity. All analyses of folic acid treatment were conducted according to the principle of intention to treat. In this analysis of randomized studies, effect estimates were unadjusted for covariates.

14. GALEONE, 2015

Full citation: Galeone C, Edefonti V, Parpinel M, Leoncini E, Matsuo K, Talamini R, Olshan AF, Zevallos JP, Winn DM, Jayaprakash V, Moysich K, Zhang ZF, Morgenstern H, Levi F, Bosetti C, Kelsey K, McClean M, Schantz S, Yu GP, Boffetta P, Lee YC, Hashibe M, La Vecchia C, Boccia S. 2015. Folate intake and the risk of oral cavity and pharyngeal cancer: a pooled analysis within the International Head and Neck Cancer Epidemiology Consortium. Int J Cancer 136(4): 904-914.

Funding: The INHANCE core data pooling was supported by NIH grants (NCI R03CA113157 and NIDCRR03DE016611). The individual studies were supported by the following grants: Milan study (2006–2009): Italian Association for Research on Cancer (AIRC, grant no. 10068) and Italian Ministry of Education (PRIN 2009 X8YCBN). Italy Multicenter study: Italian Association for Research on Cancer (AIRC), Italian League Against Cancer and Italian Ministry of Research. Swiss study: Swiss League against Cancer and the Swiss Research against Cancer/Oncosuisse (KFS-700, OCS-1633). Boston study: National Institutes of Health (NIH) US (R01CA078609, R01CA100679). Los Angeles study: National Institute of Health (NIH) US (P50CA090388, R01DA011386, R03CA077954, T32CA009142, U01CA096134 and R21ES011667) and the Alper Research Program for Environmental Genomics of the UCLA Jonsson Comprehensive Cancer Center. MSKCC study: NIH (R01CA051845). North Carolina (1994–1997): National Institutes of Health (NIH) USA (R01CA061188), and in part by a grant from the National Institute of Environmental Health Sciences (P30ES010126). US Multicenter study: The Intramural Program of the NCI, NIH, USA. Japan (2001–2005): Scientific Research grant from the Ministry of Education, Science, Sports, Culture and Technology of Japan (17015052) and grant for the Third-Term Comprehensive 10-Year Strategy for Cancer Control from the Ministry of Health, Labor and Welfare of Japan (H20-002). The work of S.B. was supported by Italian Association for Research on Cancer (AIRC, grant no. 10491-2010/2013). The work of C.G. and E.L. was supported by Fondazione Veronesi.

14.1. Folate intake and oral cavity and pharyngeal cancer

Protocol: Folate intake and oral cavity and pharyngeal cancer	
Literature Search Strategy: Other	**Protocol type:** Pooled-analysis
All case–control studies in the INHANCE Consortium were eligible for inclusion in our analysis if information on folate intake was available from the corresponding food frequency questionnaire (FFQ) for at least 80% of the subjects.	**Inclusion Criteria:** information on folate intake available for at least 80% of the subjects **Exclusion Criteria:** laryngeal cancer cases
Starting date:	**Ending date:**
Total references from search: 10	**References Included:** 10

Additional Notes:

14.2. Result(s)

14.2.A <u>not otherwise specified oral cavity/pharyngeal cancer, total folate intake, V Quintile</u>

Studies (10), Total Subjects (5181)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
total folate intake	oral cavity/pharyngeal type not otherwise specified cancer	0.58	(0.42, 0.81)	p-value for heterogeneity between studies = 0.24 (in Fig. 1 I2=28.9%, p=0.187)

Notes: p-value for trend <0.01

14.2.B **oral cavity cancer, total folate intake, V Quintile**

Studies (10), Total Subjects (5484)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
total folate intake	oral cavity cancer	0.57	(0.43, 0.75)	p-value for heterogeneity between studies = 0.74 (in Fig. 1 I2=0.0%, p=0.641)

Notes: p-value for trend <0.01

14.2.C **ororopharynx/hypopharynx cancer, total folate intake, V Quintile**

Studies (10), Total Subjects (5836)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
total folate intake	ororopharynx/hypopharynx cancer	0.74	(0.42, 1.3)	p-value for heterogeneity between studies = 0.06 (in Fig. 1 I2=73.5%, p=0.000)

Notes: p-value for trend = 0.28

14.2.D **total oral cavity and pharyngeal cancer, total folate intake, V Quintile**

Studies (10), Total Subjects (6816)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
total folate intake	total oral cavity and pharyngeal cancer	0.65	(0.43, 0.99)	p-value for heterogeneity between studies = 0.04 (in Fig. 1 I2=72.7%, p=0.00)

Notes: p-value for trend = 0.04

14.3. Statistical Method(s)

Results: not otherwise specified oral cavity/pharyngeal cancer, total folate intake, V Quintile; oral cavity cancer, total folate intake, V Quintile; ororopharynx/hypopharynx cancer, total folate intake, V Quintile; total oral cavity and pharyngeal cancer, total folate intake, V Quintile
Adjustment factors: age, alcohol intake, cigarette smoking (pack-years), education, gender, race/ethnicity, study, total energy intake
Statistical metric description: The main analyses were based on total folate intake, defined as the most complete information on folate intake reported in each of the ten studies. A secondary analysis was based on those studies (eight studies) providing information on the natural sources of dietary folate only. For all the analyses, we calculated the study-specific quintiles for folate intake among controls. The study-specific cutoff values are listed in Table 1. The association between folate intake and OPC risk was assessed by estimating the ORs and the corresponding 95% CIs, using unconditional logistic regression model for each case–control study, adjusted for age (quinquennia, categorically), gender, education level (no formal education, less than junior high school, some high school, high-school graduate, vocational/some college and college graduate/postgraduate), race/ethnicity (non-Hispanic White, Black, Hispanic/Latino, Asian and other), cigarette smoking (never, 1–10, 11–20, 21–30, 31–40, 41–50, >50 pack-years), alcohol drinking (nondrinkers, 0 to <1, >=1 to <3, >=3 to <5, >=5 drinks/day) and total energy intake (continuous). The pooled effect estimates from all studies were estimated with fixed-effects and random-effects logistic regression models. We tested for heterogeneity between the study-specific ORs by conducting a likelihood ratio test comparing a model that included the product terms between each study (other than the reference study) and the variable of interest and a model without product terms, for the risk of oral cavity and pharyngeal cancers combined and for that of each anatomical subsite. We used the random-effects estimates when heterogeneity was detected ($p<0.10$), and the fixed-effects estimates otherwise. We quantified inconsistencies across studies and their impact on the analysis by using Cochrane's Q and the I2 statistic. We also conducted a sensitivity analysis in which each study was excluded one at a time to ensure that the magnitude of the overall estimates was not dependent on any specific study. Subgroup analyses were also conducted by stratifying the results for total folate intake according to age, gender, geographic region, education level, study design, cancer subsite, body mass index, tobacco status and alcohol drinking status. Effect measure modification was evaluated by testing for deviation from a multiplicative interaction model, using the log-likelihood ratio test to compare the fit of logistic models with and without an interaction term. Biological interaction between alcohol, tobacco smoking and total folate intake was estimated using departure from additivity of effects as the criterion of interaction as proposed by Rothman. To quantify the amount of interaction, the attributable proportion (AP) owing to interaction was calculated as described by Andersson et al. The AP owing to interaction is the proportion of individuals among those exposed to the two interacting factors that is attributable to the interaction per se and it is equal to 0 in the absence of a biological interaction. Data analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC) statistical software.

15. GOH, 2007

Full citation: Goh YI, Bollano E, Einarson TR, Koren G. 2007. Prenatal multivitamin supplementation and rates of pediatric cancers: a meta-analysis. Clin Pharmacol Ther 81(5): 685-691.
Funding: None reported

15.1. Prenatal multivitamin supplementation and rates of pediatric cancers

Protocol: Prenatal multivitamin supplementation and rates of pediatric cancers	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
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 (–July2005), 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.	**Inclusion Criteria:** case-control or cohort study, contain raw data of number of cases and controls using multivitamins, control group of healthy children with accounts of maternal intake of multivitamins during pregnancy **Exclusion Criteria:** data reported in abstracts or meetings, did not involve women taking multivitamins during pregnancy, focused on specific vitamins, mothers exposed to other known teratogens, review articles
Starting date: 1960-01-01	**Ending date:** 2005-07-01
Total references from search: 61	**References Included:** 7

Additional Notes:

15.2. Result(s)

15.2.A Acute Lymphoblastic Leukemia, maternal multivitamin consumption

Studies (3), Total Subjects (1995)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
maternal multivitamin consumption	Acute Lymphoblastic Leukemia	0.61	(0.5, 0.74)	I2 = 0%; p=0.53

Notes: overall effect: P<0.00001

15.2.B Neuroblastoma, maternal multivitamin consumption

Studies (2), Total Subjects (585)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
maternal multivitamin consumption	Neuroblastoma	0.53	(0.42, 0.68)	I2 = 82%; p=0.02

Notes: overall effect: P<0.00001

15.2.C Pediatric brain tumors, maternal multivitamin consumption

Studies (3), Total Subjects (933)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
maternal multivitamin consumption	Pediatric brain tumors	0.73	(0.6, 0.88)	I2 = 0%; p=0.91

Notes: overall effect: P=0.001

15.3. Statistical Method(s)

Results: Acute Lymphoblastic Leukemia, maternal multivitamin consumption; Neuroblastoma, maternal multivitamin consumption; Pediatric brain tumors, maternal multivitamin consumption

Adjustment factors:

Statistical metric description: 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 x 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 w2. A funnel plot was used to assess publication bias, following which the Begg–Mazumdar test was executed to calculate Kendall's t; a test that evaluates the agreement between the effect and variances.

16. HE, 2014

Full citation: He H, Shui B. 2014. Folate intake and risk of bladder cancer: a meta-analysis of epidemiological studies. Int J Food Sci Nutr 65(3): 286-292.
Funding: none reported

16.1. Folate intake and risk of bladder cancer

Protocol: Folate intake and risk of bladder cancer	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
This report followed the standards of quality for reporting meta-analyses of observational studies in epidemiology (Stroup et al.,2000). The literature search was performed using the MEDLINE and EMBASE databases up to June 2013. To identify all relevant published reports, we used medical subject headings (MeSH) and free-text search terms for ''folate'' or ''folic acid'' (MeSH Terms) combined with ''bladder cancer'' or ''urothelial cancer'' or ''urinary tract cancer'' or ''urinary bladder neoplasms'' (MeSH Terms). We limited the results to humans only. Additional publications identified by hand-searching of reference lists were also included. We contacted experts to obtain any possible additional published or unpublished data.	**Inclusion Criteria:** case-control or cohort study, English language article, include folate intake data, presented risk estimate (RE) on the association between folate intake and incidence of bladder cancer **Exclusion Criteria:**
Starting date:	**Ending date:** 2013-06-30
Total references from search: 221	**References Included:** 13

Additional Notes:

16.2. Result(s)

16.2.A bladder cancer, folate intake from diet

Studies (9), Total Subjects ()

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folate intake from diet	bladder cancer	0.82	(0.65, 0.99)	I2 = 57.9%, p = 0.015

Notes: It is unclear which studies are included in these results so an N could not be determined.

16.2.B bladder cancer, folate intake from diet and supplement

Studies (5), Total Subjects ()

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folate intake from diet and supplement	bladder cancer	0.87	(0.7, 1.03)	I2 = 10.3%, p = 0.348

Notes: It is unclear which studies are included in these results so an N could not be determined.

16.2.C bladder cancer, folate intake from supplement

Studies (3), Total Subjects ()

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folate intake from supplement	bladder cancer	0.91	(0.58, 1.25)	I2 = 62.6%, p = 0.069

Notes: It is unclear which studies are included in these results so an N could not be determined.

16.2.D bladder cancer, folate intake, case-control

Studies (6), Total Subjects (8752)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folate intake	bladder cancer	0.73	(0.57, 0.89)	I2 = 34.8%, p = 0.176

Notes:

16.2.E bladder cancer, folate intake, cohort

Studies (7), Total Subjects (489620)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folate intake	bladder cancer	0.96	(0.81, 1.1)	I2 = 0.0%, p = 0.657

Notes:

16.2.F bladder cancer, folate intake, overall

Studies (13), Total Subjects (498372)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folate intake	bladder cancer	0.84	(0.72, 0.96)	I2 = 28.9%, p = 0.154

Notes:

16.3. Statistical Method(s)

Results: bladder cancer, folate intake, case-control; bladder cancer, folate intake, cohort; bladder cancer, folate intake from diet; bladder cancer, folate intake from diet and supplement; bladder cancer, folate intake from supplement; bladder cancer, folate intake, overall

Adjustment factors:

Statistical metric description: We estimated a summary RE with 95% CI based on random-effects model, which considers both within study and between-study variation. Statistical heterogeneity among studies was evaluated by using the Q (DerSimonian & Laird, 1986) and I2 statistics (Higgins et al., 2003). We also conducted sensitivity analyses according to some characteristics of the studies – sex (male, female), geographical area (European countries, United States) and source of folate intake (foods, supplements, foods and supplements combined). We assessed publication bias using the tests of Egger et al. (1997) and Begg & Mazumdar (1994). All statistical analyses were performed with Stata software, version 11 (Stata Corp, College Station, TX). $p<0.05$ was considered statistically significant.

17. HEINE-BRÖRING, 2015

Full citation: Heine-Broring RC, Winkels RM, Renkema JM, Kragt L, van Orten-Luiten AC, Tigchelaar EF, Chan DS, Norat T, Kampman E. 2015. Dietary supplement use and colorectal cancer risk: A systematic review and meta-analyses of prospective cohort studies. Int J Cancer 136(10): 2388-2401.
Funding: Grant sponsor: Wereld Kanker Onderzoeks Fonds (WCRF NL); Grant sponsor: World Cancer Research Fund International (WCRF International)

17.1. Dietary supplement use and colorectal cancer risk

Protocol: Dietary supplement use and colorectal cancer risk	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
The present systematic literature review has been carried out according to the guidelines of the WCRF. The search strategy identified several terms on dietary supplement use and colorectal cancer risk, and yielded studies with outcomes on colorectal adenomas and colorectal carcinomas as it was part of a larger research project. As the current study focuses on colorectal carcinomas only, studies on colorectal adenomas were excluded. We retrieved relevant articles by searching in Medline, Embase and Cochrane from their inception up to January 2013, and hand-searched reference lists for additional studies (Supporting Information 1). No language restrictions were made.	**Inclusion Criteria:** cohort study, exposure is dietary supplement use, outcome is colorectal, colon, or rectal cancer incidence, Prospective **Exclusion Criteria:** cancer deaths only
Starting date:	**Ending date:** 2013-01-31
Total references from search: 7214	**References Included:** 4

Additional Notes:

17.2. Result(s)

17.2.A colorectal cancer, folic acid, highest-lowest supplement use

Studies (3), Total Subjects (291006)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid	colorectal cancer	0.88	(0.78, 0.98)	I2 = 6.2%, p = 0.34

Notes:

17.2.B colorectal cancer, intake of supplemental folic acid

Studies (3), Total Subjects (291006)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid	colorectal cancer	0.98	(0.97, 1.0)	I2 = 0.0%, p = 0.713

Notes:

17.3. Statistical Method(s)

Results: colorectal cancer, folic acid, highest-lowest supplement use; colorectal cancer, intake of supplemental folic acid

Adjustment factors:

Statistical metric description: Random effects models were used to calculate summary RRs and 95% CIs for the associations of colorectal, colon or rectal cancer with use of multivitamins, vitamin A, vitamin C, vitamin D, vitamin E, calcium, folic acid and garlic supplements. We performed a meta-analysis if at least two cohort studies were available. We used the most fully adjusted relative risk in the analysis. "Use-no use" meta-analyses were done for the association between multivitamins and supplemental vitamin A, vitamin C, vitamin D, vitamin E, calcium and garlic with colorectal cancer risk. In those meta-analyses, "no use" incorporates either "never use," "no current use" and/or "no past use." In addition, "use" was defined as "current use," "past use" and/or "any use" in those meta-analyses. Studies that focussed on current use of dietary supplements only, and reported on specified categories of dietary supplement use were included in the "highest-lowest" meta-analyses. In those analyses, we always compared the highest versus the lowest category of intake, and did not include the middle categories, and we included the association as reported in the original publication, which could be tertiles, quartiles, or quintiles. Details about the contrasts between categories in the original publications can be found in Table 1. For the association between supplemental vitamin A, vitamin C, vitamin D, vitamin E, calcium and folic acid and colorectal cancer risk, "highest-lowest" meta-analyses were conducted. In the "dose-response" meta-analyses, we tested whether there was a linear association between the dosage of a supplement and colorectal cancer risk: thus, in those analyses we could only include studies that provided information on the dosage of intake. According to the DerSimonian and Laird method, "dose-response" meta-analyses were possible for the association between vitamin C, vitamin D, vitamin E, calcium and folic acid supplements and colorectal cancer risk, and were carried out when three or more categories of the dosage of intake of the dietary supplement were available. We used the method of Greenland and Longnecker to compute the trend across categories of exposure. We estimated the distribution of cases or person-years in studies that did not report these, and reported results by quantiles. The median level of exposure in each category was used for the corresponding relative risk. If not reported, the value assigned was the midpoint of the lower and upper bound in each category. For open-ended categories, the midpoint was calculated by adding or subtracting half the width of the adjacent exposure category for the uppermost or lowermost category respectively. For studies that reported supplement use in >= 3 categories, we calculated a combined estimate of dietary supplement use by using Hamling's procedure before including the study in the overall analysis. For studies that reported results for men and women separately, and for studies that showed separate results for colon and rectal cancer, we used fixed effect meta-analyses to obtain an overall estimate for overall gender and for colorectal cancer, respectively. Statistical heterogeneity between studies was assessed by the I2 statistic. Small study bias was examined in funnel plots and by Egger's test. If feasible, stratified analyses were performed for gender, cancer site, or geographical region. Sensitivity analyses were done by excluding one study at a time, and pooling the rest to explore whether a single study could have markedly affected the results. Statistical analyses were conducted with STATA version 11.0 (StataCorp, College Station, TX). A p-value <0.05 was considered statistically significant.

18. HUTTER, 2012

Full citation: Hutter CM, Chang-Claude J, Slattery ML, Pflugeisen BM, Lin Y, Duggan D, Nan H, Lemire M, Rangrej J, Figueiredo JC, Jiao S, Harrison TA, Liu Y, Chen LS, Stelling DL, Warnick GS, Hoffmeister M, Kury S, Fuchs CS, Giovannucci E, Hazra A, Kraft P, Hunter DJ, Gallinger S, Zanke BW, Brenner H, Frank B, Ma J, Ulrich CM, White E, Newcomb PA, Kooperberg C, LaCroix AZ, Prentice RL, Jackson RD, Schoen RE, Chanock SJ, Berndt SI, Hayes RB, Caan BJ, Potter JD, Hsu L, Bezieau S, Chan AT, Hudson TJ, Peters U. 2012. Characterization of gene-environment interactions for colorectal cancer susceptibility loci. Cancer Res 72(8): 2036-2044.

Funding: ARTIC was supported by a GL2 grant from the Ontario Research Fund, the Canadian Institutes of Health Research, and the Cancer Risk valuation (CaRE) Program grant from the Canadian Cancer Society Research Institute. T.J. Hudson and B.W. Zanke are recipients of Senior Investigator Awards from the Ontario Institute for Cancer Research, through generous support from the Ontario Ministry of Research. ASTERISK was supported by a regional Hospital Clinical Research Program (PHRC) and supported by the Regional Council of Pays de la Loire, the Groupement des Entreprises Fran¸caises dans la Lutte contre le Cancer (GEFLUC), the Association Anne de Bretagne Genetique, and the Ligue Regionale Contre le Cancer (LRCC). CCFR was supported by the National Cancer Institute, NIH under RFA # CA-95-011 and through cooperative agreements with members of the Colon Cancer Family Registry and P.I.s. The Colon CFR Center, Ontario Registry for Studies of Familial CRC, contributed data to this manuscript and was supported by (U01 CA074783). DACHS was supported by grants from the German Research Council (Deutsche Forschungsgemeinschaft, BR 1704/6-1, BR 1704/6-3, BR 1704/6-4, and CH 117/1-1), and the German Federal Ministry of Education and Research (01KH0404 and 01ER0814). DALS was supported by the National Cancer Institute, NIH, U.S. Department of Health and Human Services (R01 CA48998 to M.L. Slattery). Funding for the genome-wide scan of DALS, PLCO, and WHI was provided by the National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services (R01 CA059045 to U. Peters). C.M. Hutter was supported by a training grant from the National Cancer Institute, Institutes of Health, U.S. Department of Health and Human Services (R25 CA094880). Additional funding for this work was provided by National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services (U01 CA137088 to U. Peters). HPFS was supported by the NIH (P01 CA 055075 to C.S. Fuchs, R01 137178 to A.T. Chan, and P50 CA 127003 to C.S. Fuchs), NHS by the NIH (R01 137178 to A.T. Chan., P50 CA 127003 to C.S. Fuchs., and P01 CA 087969 to E.L. Giovannucci) and PHS by the NIH (CA41281).

18.1. Colorectal cancer and gene-environment inteactions

Protocol: Colorectal cancer and gene-environment inteactions

Protocol: Colorectal cancer and gene-environment inteactions	
Literature Search Strategy: Other	**Protocol type:** Meta-analysis
The studies used are listed in Table 1 and have been described in detail previously (10). In brief, we used data from 5 nested case–control studies in prospective U.S. cohorts [Health Professionals Follow-up Study (HPFS); Nurses' Health Study (NHS); Physician's Health Study (PHS); Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO); and Woman's Health Initiative (WHI)] and 4 case–control studies from the United States, Canada, and Europe [Assessment of Risk in Colorectal Tumors in Canada (ARCTIC); French Asso- ciation STudy Evaluating RISK for sporadic CRC (ASTERISK); Darmkrebs: Chancen der Verhuetung durch Screening (DACHS); Diet, Activity and Lifestyle Survey (DALS)].	**Inclusion Criteria:** Cases confirmed by medical record, pathology report, or death certificate, Cases were invasive colorectal adenocarcinoma, Nested case-control or case-control designs **Exclusion Criteria:** Studies reported as racial / ethnic groups other than "White"
Starting date:	**Ending date:**
Total references from search:	**References Included:** 10

Additional Notes: Gene-environment interactions were the primary focus of the meta-analyses

18.2. Result(s)

18.2.A Colorectal cancer, Folate

Studies (10), Total Subjects (16843)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
Dietary folate	Colorectal cancer	0.81	(0.68, 0.95)	

Notes: P-value = 0.01

18.3. Statistical Method(s)

Results: Colorectal cancer, Folate
Adjustment factors: Research center, age, sex
Statistical metric description: Unless otherwise indicated, we adjusted all regression analyses described below for age, center, and sex, as appropriate. We used fixed effects meta-analysis methods to obtain summary ORs and 95% CIs across studies. The P values from the meta-analysis, unadjusted for multiple comparisons, are termed nominal P values. We report the P value for heterogeneity and examine forest plots for results showing evidence for heterogeneity. For PLCO, we used inverse sampling fractions as weights in all analyses to account for study design; for all other studies, we used equal weights. Inadequate modeling of the marginal association can bias interaction testing (35). Therefore, for each SNP and environmental factor, we employed a screening method, based on logistic regression main-effect associations, to find a reason- able form to use for GxE testing. Nested models were compared using likelihood ratio tests, with a $P < 0.05$ indicating significantly better performance. For SNPs, we considered assumptions of log-additive (SNPs coded 0/1/2, representing counts of the minor allele) and recessive (SNPs coded 0/1 in which 0 represents homozygous for common allele or heterozygous and 1

represents homozygous for the minor allele) modes of inheritance in comparison with an unrestricted model with indicator variables for heterozygote and homozygote minor alleles. We did not consider a dominant mode of inheritance, because the log-additive model usually does not lose power if the true model is dominant. If the unrestricted model did not significantly outperform the log-additive model, we used the log-additive model. If the unrestricted model performed significantly better than the log-additive model, but not the recessive model, we used the recessive model. If the unrestricted model performed significantly better than the log-additive and the recessive, we used the unrestricted model. Under this procedure, we selected the recessive model for rs6983267, and the log-additive model for the other 9 SNPs. Dichotomous environmental variables were coded 0/1 and did not require model selection. For the continuous variables, BMI and height, we compared main-effects models with and without a quadratic term. In both cases, the model with the quadratic term did not perform significantly better, so we modeled these variables using only a linear term. For the categorical variables (alcohol, pack years, and the quartile version of the dietary variables), we compared a model using a group-linear variable to a saturated model with indicator variables for each non- reference category. For alcohol, the saturated model per- formed significantly better, so we modeled alcohol with indicator variables. In contrast, for the other variables, the saturated model was not significantly better than a model with a single group-linear term. Thus, we modeled these variables with their sex- and study-specific medians, as described above in the section on data harmonization. To test for interactions between SNPs and environmental risk factors, we used an efficient empirical-Bayes (EB) shrink- age method (36). This method creates a weighted average of the standard case-only and case–control estimators, which is weighted toward the unbiased case–control estimator when the assumption of gene–environment independence in the population is suspect and toward the more efficient case-only estimator when the assumption is supported by the data. We modeled both the main effect and interaction based on the model selected from the main effects, as described above. Subjects missing data for a particular SNP or environmental factor were dropped from the analysis for that SNP factor interaction test. Because we carried out 180 tests (10 SNPs 18 versions of the environmental risk factors), with correlation among some tests, we used permutations to account for multiple testing. We ran the analysis 1,000 times using a permuted case–control status in each run. Then, we used the Westfall & Young step down procedure (37) to derive the adjusted P value for each GxE interaction based on the permuted P values. We term these the adjusted P values and used them to evaluate the statistical significance of a given interaction at the 0.05 level. For situations in which the EB interaction-term adjusted $P < 0.05$, we also examined the results from the traditional logistic regression case–control estimate and examined results adjusting for additional covariates (smoking history, BMI, alcohol consumption, and red meat consumption). As follow-up analysis, we examined the main effect for the SNP in strata defined by the environmental risk factor. We also pooled the data across studies and examined (i) the main effect of the environmental factor in strata defined by the SNP; and (ii) the combined effect in strata defined by both the SNP and the environmental factor. As a supplemental analysis, we examined all 180 SNP environmental factor GxE interactions in substratum analyses restricted to colon only and rectal only cases. Data harmonization was carried out with SAS and T-SQL. All other analyses were conducted with the R programming language.

19. IBRAHIM, 2010

Full citation: Ibrahim EM, Zekri JM. 2010. Folic acid supplementation for the prevention of recurrence of colorectal adenomas: metaanalysis of interventional trials. Med Oncol 27(3): 915-918.
Funding: None reported

19.1. Folic acid and colorectal adenoma recurrence

Protocol: Folic acid and colorectal adenoma recurrence	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
We did a comprehensive search of citations from PubMed, EMBASE, Cochrane databases, and abstracts of relevant proceedings. We selected for analysis only those prospective phase II and III randomized clinical trials that directly compared folic acid supplementation given in a defined dose and a planned duration versus placebo to prevent recurrence of colorectal adenomas among those who had previous resection. Individual studies were evaluated for quality and potential bias using the Downs and Black quality assessment method.	**Inclusion Criteria:** Examine folic acid supplementation for prevention of recurrence of colorectal adenomas, has a placebo control, Phase II and III clinical trials, Prospective, Randomized clinical trials **Exclusion Criteria:**
Starting date:	**Ending date:**
Total references from search:	**References Included:** 5

Additional Notes:

19.2. Result(s)

19.2.A Colorectal adenomas, 0.5mg/day folic acid supplementation, random effects

Studies (1), Total Subjects (419)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
Folic acid supplementation	Recurrence of colorectal adenomas	1.15	(0.75, 1.75)	n/a

Notes: P = 0.53

19.2.B Colorectal adenomas, 1mg/day folic acid supplementation, random effects

Studies (2), Total Subjects (1041)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
Folic acid supplementation	Recurrence of colorectal adenomas	0.62	(0.48, 0.8)	I2 = 0%, p = 0.64

Notes: P = 0.0002

19.2.C Colorectal adenomas, 5mg/day folic acid supplementation, random effects

Studies (1), Total Subjects (20)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
Folic acid supplementation	Recurrence of colorectal adenomas	1.78	(0.13, 23.52)	n/a

Notes: P = 0.66

19.2.D Colorectal adenomas, folic acid supplementation, fixed effects

Studies (4), Total Subjects (1486)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
Folic acid supplementation	Recurrence of colorectal adenomas	1.08	(0.87, 1.33)	I2 = 0%, p = 0.53

Notes: P = 0.49

19.2.E Colorectal adenomas, folic acid supplementation, random effects

Studies (4), Total Subjects (1480)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
Folic acid supplementation	Recurrence of colorectal adenomas	0.78	(0.49, 1.24)	I2 = 55%, p = 0.08

Notes: P = 0.30

19.3. Statistical Method(s)

Results: Colorectal adenomas, 0.5mg/day folic acid supplementation, random effects; Colorectal adenomas, 1mg/day folic acid supplementation, random effects; Colorectal adenomas, 5mg/day folic acid supplementation, random effects; Colorectal adenomas, folic acid supplementation, fixed effects; Colorectal adenomas, folic acid supplementation, random effects

Adjustment factors:

Statistical metric description: Data were analyzed using Review Manager Version 5.0.17 (Cochrane Collaboration, Software Update, Oxford, United Kingdom). In this meta-analysis, both fixed and random effect models were tested as appropriate. A two- tailed P value of <0.05 was considered statistically significant. Publication bias was explored through visual inspection of the funnel plots. Findings of the meta-analysis were depicted in classical Forest plots.

20. KANTOR, 2014

Full citation: Kantor ED, Hutter CM, Minnier J, Berndt SI, Brenner H, Caan BJ, Campbell PT, Carlson CS, Casey G, Chan AT, Chang-Claude J, Chanock SJ, Cotterchio M, Du M, Duggan D, Fuchs CS, Giovannucci EL, Gong J, Harrison TA, Hayes RB, Henderson BE, Hoffmeister M, Hopper JL, Jenkins MA, Jiao S, Kolonel LN, Le Marchand L, Lemire M, Ma J, Newcomb PA, Ochs-Balcom HM, Pflugeisen BM, Potter JD, Rudolph A, Schoen RE, Seminara D, Slattery ML, Stelling DL, Thomas F, Thornquist M, Ulrich CM, Warnick GS, Zanke BW, Peters U, Hsu L, White E. 2014. Gene-environment interaction involving recently identified colorectal cancer susceptibility Loci. Cancer Epidemiol Biomarkers Prev 23(9): 1824-1833.

Funding: C.S. Carlson, M. Du, J. Gong, T.A. Harrison, L. Hsu, C.M. Hutter, S. Jiao, J. Minnier, B.M. Pflugeisen, U. Peters, D.L. Stelling,M. Thornquist, G.S. Warnick, and C.M. Ulrich are affiliated with GECCO, which is supported by the following grants from the National Cancer Institute, NIH, U.S. Department of Health and Human Services: U01 CA137088 and R01 CA059045. L. Le Marchand is affiliated with Colo2&3, which is supported by the NIH (R01 CA60987). G. Casey, J.L. Hopper, M.A. Jenkins, and P.A. Newcomb are affiliated with CCFR, which is supported by the NIH (RFA #CA-95-011) and through cooperative agreements with members of the CCFR and P.I.s. This genome wide scan was supported by the National Cancer Institute, NIH by U01 CA122839. The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the CFRs, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government or the CFR. The following Colon CFR centers contributed data to this manuscript and were supported by NIH: Australasian Colorectal Cancer Family Registry (U01 CA097735), Ontario Registry for Studies of Familial Colorectal Cancer (U01 CA074783), and Seattle Colorectal Cancer Family Registry (U01 CA074794). H. Brenner, J. Chang-Claude, M. Hoffmeister, and A. Rudolph are affiliated with DACHS, which was supported by grants from the German Research Council (Deutsche Forschungsgemeinschaft, BR 1704/6-1, BR 1704/6-3, BR 1704/6-4, and CH 117/1-1), and the German Federal Ministry of Education and Research (01KH0404 and 01ER0814). B.J. Caan, J.D. Potter, and M.L. Slattery are affiliated with DALS, which was supported by theNIH (R01 CA48998 toM.L. Slattery).A.T. Chan, C.S. Fuchs, E.L. Giovannucci, and J. Ma are affiliated with HPFS, NHS, and PHS. HPFS was supported by the NIH (P01 CA 055075, UM1 CA167552, R01 137178, and P50 CA 127003), NHS by the NIH (R01 CA137178, P01 CA 087969, and P50 CA 127003) and PHS by the NIH (CA42182). B.E. Henderson, L.N. Kolonel, and L. Le Marchand are affiliated with MEC, which is supported by the following grants from the NIH: R37 CA54281, P01 CA033619, and R01 CA63464. M. Cotterchio, M. Lemire, and B.W. Zanke are affiliated with OFCCR, which is supported by the NIH, through funding allocated to the Ontario Registry for Studies of Familial Colorectal Cancer (U01 CA074783); see CCFR section above. Additional funding toward genetic analyses of OFCCR includes the Ontario Research Fund, the Canadian Institutes of Health Research, and the Ontario Institute for Cancer Research, through generous support from the Ontario Ministry of Research and Innovation. S. I. Berndt, S.J. Chanock, R.B. Hayes, and R.E. Schoen are affiliated with PLCO, which was supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics and supported by contracts from the Division of Cancer Prevention, National Cancer Institute, NIH, DHHS. Funding for the Lung Cancer and Smoking study was provided by NIH, Genes, Environment and Health Initiative (GEI) Z01 CP 010200, NIH U01 HG004446, and NIH GEI U01 HG 004438. P.A. Newcomb is affiliated with PMH, which is supported by the NIH (R01 CA076366 to P.A. Newcomb). E. White is affiliated with VITAL, which is supported in part by the NIH (K05 CA154337) from the National Cancer Institute and Office of Dietary Supplements. H.M. Ochs-Balcom and F. Thomas are affiliated with WHI. The WHI program is funded by the National Heart, Lung, and Blood Institute, NIH, U.S. Department of Health and Human Services through contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C. P. Campbell is at the American Cancer Society (ACS)

and supported through ACS. M. Du is supported by the National Cancer Institute, NIH (R25CA94880). D. Duggan is affiliated with TGEN and funded through a subaward with GECCO (R01 CA059045). E.D. Kantor is supported by the National Cancer Institute, NIH (R25CA94880 and T32CA009001). D. Seminara is a Senior Scientist and Consortia Coordinator at the Epidemiology and Genetics Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, NIH.

20.1. GECCO and CCFR studies

Protocol: GECCO and CCFR studies	
Literature Search Strategy: Other	**Protocol type:** Meta-analysis
Study participants were drawn from either case–control studies [Ontario Familial Colorectal Cancer Registry (OFCCR), Darmkrebs: Chancen der Verhuetung durch Screening (DACHS), Diet, Activity and Lifestyle Survey (DALS), CCFR, Colorectal Cancer Studies 2&3 (Colo2&3), and the PMH study within the CCFR (PMH-CCFR)] or from case–control studies nested within prospective cohorts: Health Professionals Follow-up Study (HPFS), Nurses' Health Study (NHS), Physicians' Health Study (PHS), Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO), Women's Health Initiative (WHI), Multiethnic Cohort Study (MEC), and the VITamins And Lifestyle (VITAL) study. More detailed information on these studies can be found in Table 1 and in the Supplementary Methods. All participants gave informed consent and studies were approved by their respective Institutional Review Boards.	**Inclusion Criteria:** data from the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) or Colon Cancer Family Registry (CCFR), Nested case-control or case-control designs **Exclusion Criteria:**
Starting date:	**Ending date:**
Total references from search:	**References Included:** 13

Additional Notes:

20.2. Result(s)

20.2.A colorectal cancer, dietary folate

Studies (13), Total Subjects (18440)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	colorectal cancer	0.7	(0.59, 0.83)	p = 0.45

Notes: p = 5.3 x 10^(-5) Table 3 title indicates results are only from GECCO, but methods/results/discussion do not mention excluding CCFR from the analysis.

20.2.B colorectal cancer, dietary folate, case–control studies

Studies (6), Total Subjects (10798)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	colorectal cancer	0.44	(0.29, 0.66)	p = 0.44

Notes: p = 8.4 x 10^(-5)

20.2.C colorectal cancer, dietary folate, nested case–control studies

Studies (7), Total Subjects (7642)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	colorectal cancer	0.78	(0.64, 0.94)	p = 0.96

Notes: p = 8.0 x 10^(-3)

20.3. Statistical Method(s)

Results: colorectal cancer, dietary folate; colorectal cancer, dietary folate, case–control studies; colorectal cancer, dietary folate, nested case–control studies

Adjustment factors: age, energy intake, sex, study

Statistical metric description: Analyses of main effects of SNPs and environmental factors and GxE interaction were adjusted for age, sex, and study center, and analyses involving genetic data were further adjusted for population substructure (first 3 principal components using EIGENSTRAT; ref. 37). Analyses corresponding to the following dietary variables were further adjusted for energy intake if available: calcium, fiber, folate, fruit consumption, and vegetable consumption. As PHS participants were matched on smoking status, analyses corresponding to this study were further adjusted for smoking. To assess the best model fit for each SNP, we compared an unrestricted model to log-additive, dominant, and recessive models using a likelihood ratio test (19). All SNPs were best modeled using a log-additive model, except for rs59336; this SNP was modeled dominantly, given that the unrestricted model outperformed both the additive and recessive models. The model form of environmental variables was also assessed. The best mode lform for the alcohol variable and 4-level dietary variables was assessed using a likelihood ratio test to compare a model with unrestricted categorical variables to a reduced model with a single linear variable. The likelihood ratio test indicated that modeling alcohol categorically significantly outperformed the linear alcohol variable; therefore, alcohol was modeled using unrestricted categorical variables. However, all of the 4-level dietary variables (fruit consumption, vegetable consumption, red meat consumption, processed meat consumption, fiber intake, folate intake, and calcium intake) were modeled as single linear variables, given that the unrestricted categorical variable did not outperform the linear variable. To assess the best model form for BMI [(kg/m2)/10] and pack-years smoked (5-level variable), we used a likelihood ratio test to compare a model with and without a quadratic term; the addition of the quadratic term did not improve the model fit for either of these variables, and therefore both BMI [(kg/m2)/10] and smoking (5-level variable) were modeled linearly. To test for interaction, an efficient Empirical Bayes (EB) shrinkage method was used, which is a weighted sum of the case-only test and the traditional case–control method. In the event that the assumption of GxE independence seems to hold, more weight is given to the more powerful case-only method; if this assumption is violated, more weight is given to the case–control estimate, which does not assume GxE independence. This approach affords the greater power of the case-only analysis, while protecting against bias in the event of GxE dependence. All results for meta-analyses were obtained using a fixed-effects model, and for each meta-analysis performed, we examined the corresponding P-value for heterogeneity across studies (Supplementary Table S2). Given that 288 tests were performed (16 SNPs*18 environmental factors) and some of the environmental variables were correlated with one another, permutation was used to account for multiple testing and correlations among variables. Each analysis was performed 2,000 times using a permuted case–control status in each run, after which the Westfall and Young step-down procedure was applied to derive an adjusted P-value for each interaction. These adjusted P-values were then used to assess the presence of

interaction at the alpha=0.05 level. All other P values are termed nominal P values. Data harmonization was performed in SAS and T-SQL, whereas all other analyses were performed in R.

21. KENNEDY, 2011

Full citation: Kennedy DA, Stern SJ, Moretti M, Matok I, Sarkar M, Nickel C, Koren G. 2011. Folate intake and the risk of colorectal cancer: a systematic review and meta-analysis. Cancer Epidemiol 35(1): 2-10.
Funding: none reported

21.1. Folate intake and the risk of colorectal cancer

Protocol: Folate intake and the risk of colorectal cancer	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
The databases MEDLINE, Embase and Scopus were searched from inception to October 2009, both database specific subject headings and textwords were searched using the terms ''folic acid'' OR ''folate'' AND ''colorectal cancer'' and ''colorectal neoplasms'' limiting the results to humans only. The results of the search in each of the three databases were placed in a bibliography tool and, in order to ensure blinding, an extract of the author, journal and year was made into a spreadsheet for the purposes of title review. Title review was conducted by one reviewer (DAK) blinded to the journal of publication, place of research and results, to determine which studies articles to retrieve. The methods section of the selected journal articles were retrieved by other team members (IM, MS) not responsible for reviewing the journal articles. These were reviewed by two independent reviewers (DAK, SS) blinded to the journal of publication, place of research and results, as to their meeting the inclusion criteria. In case of disagreement between the two reviewers, a third reviewer served as a tiebreaker (GK). Fig. 1 details the search strategy flow.	**Inclusion Criteria:** exposure is folate (dietary or total) with at least two levels of folate intake, observational studies, outcome is colorectal, colon, or rectal cancer incidence **Exclusion Criteria:**
Starting date:	**Ending date:** 2009-10-01
Total references from search: 6427	**References Included:** 27

Additional Notes:

21.2. Result(s)

21.2.A **colorectal cancer, dietary folate, case control**

Studies (12), Total Subjects (3276)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	colorectal cancer	0.87	(0.74, 1.02)	I2 = 63%, p = 0.0002

Notes: P=0.09

21.2.B **colorectal cancer, dietary folate, case control, men only**

Studies (5), Total Subjects (695)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	colorectal cancer	0.89	(0.66, 1.19)	I2 = 65%, p = 0.02

Notes: Not all Ns were available.

21.2.C colorectal cancer, dietary folate, case control, women only

Studies (4), Total Subjects (691)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	colorectal cancer	0.74	(0.55, 1.01)	I2 = 59%, p = 0.05

Notes: P=0.06

21.2.D colorectal cancer, dietary folate, cohort

Studies (9), Total Subjects (472531)

Exposure	Assessed Outcome	hazard ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	colorectal cancer	0.92	(0.81, 1.05)	I2 = 42%, p = 0.07

Notes: P=0.21 The N for this result was not given in the paper. Ns for each study in this section were extracted from the corresponding papers and summed.

21.2.E colorectal cancer, dietary folate, cohort, women only

Studies (7), Total Subjects (291720)

Exposure	Assessed Outcome	hazard ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	colorectal cancer	0.93	(0.8, 1.08)	I2 = 31%, p = 0.19

Notes: P=0.34 The N for this result was not given in the paper. Ns for each study in this section were extracted from the corresponding papers and summed.

21.2.F colorectal cancer, total folate, case control

Studies (8), Total Subjects (1679)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
total folate	colorectal cancer	0.85	(0.74, 0.99)	I2 = 11%, p = 0.34

Notes: P=0.03

21.3. Statistical Method(s)

Results: colorectal cancer, dietary folate, case control; colorectal cancer, dietary folate, case control, men only; colorectal cancer, dietary folate, case control, women only; colorectal cancer, dietary folate, cohort; colorectal cancer, dietary folate, cohort, women only; colorectal cancer, total folate, case control

Adjustment factors:

Statistical metric description: The meta-analysis was performed using the inverse variance method under a random effect model. Adjusted odds ratios along with 95% confidence intervals were used for the case control studies while adjusted risk ratios/hazard ratios and 95% confidence intervals for the cohort studies. In all instances the ratios used compared the incidence between the lowest ‘‘quantile’’ of folate intake versus the highest. One case control reported relative risk without 95% confidence intervals. The paper did not publish the number of case and controls nor the covariates in the regression for each quintile so it was not possible to derive the adjusted odds ratio. For this reason, this study was not included in the meta analysis. Publication bias was assessed via visual inspection of the funnel plots created by plotting the OR to SE(log[OR]) for case control studies and RR to SE([RR]) for cohort studies. Assessment of heterogeneity was performed using both x2 and I2. The x2 test assesses whether the differences in results are due to chance only. Heterogeneity exists when the P value is low. The I2 assess the percentage of variability in the effect estimates that is due to heterogeneity rather than chance. I2 values over 50% indicate that substantial heterogeneity may be present. The analysis was performed using Review Manager 5.0 software. Mann–Whitney U was performed on the quality of the studies to determine whether or not there were differences in the quality of the studies based on the directionality of the outcome. IBM’s SPSS for Windows version 17 was used for the analysis (IBM SPSS, Version 17, Chicago). Two small modifications were made to the forest plot output generated by Revman. The raw data input on log[odds ratio] or log[hazard ratio] and SE information was eliminated from Figs. 2 to 4 to simplify the presentation of the forest plots. A dash (-) in the forest plot was used to indicate that the number of people in the specific quantile was not reported on in journal article.

22. KIM, 2010

Full citation: Kim DH, Smith-Warner SA, Spiegelman D, Yaun SS, Colditz GA, Freudenheim JL, Giovannucci E, Goldbohm RA, Graham S, Harnack L, Jacobs EJ, Leitzmann M, Mannisto S, Miller AB, Potter JD, Rohan TE, Schatzkin A, Speizer FE, Stevens VL, Stolzenberg-Solomon R, Terry P, Toniolo P, Weijenberg MP, Willett WC, Wolk A, Zeleniuch-Jacquotte A, Hunter DJ. 2010. Pooled analyses of 13 prospective cohort studies on folate intake and colon cancer. Cancer Causes Control 21(11): 1919-1930.
Funding: Supported by research grant CA55075 from the National Institutes of Health and by the National Colorectal Cancer Research Alliance.

22.1. Pooled analyses of folate intake and colon cancer

Protocol: Pooled analyses of folate intake and colon cancer	
Literature Search Strategy: Other	**Protocol type:** Pooled-analysis
The Pooling Project of Prospective Studies of Diet and Cancer has been described previously. For the present analysis, we included prospective studies that met the following predefined criteria: (1) at least 50 incident colorectal cancer cases; (2) assessment of usual dietary intake; and (3) a validation study of the dietary assessment method or a closely related instrument (Table 1). The Adventist Health Study, included in the Pooling Project, was excluded from this analysis because folate intake was not assessed at baseline. The Nurses' Health Study was divided into two parts (1980–1986 and 1986–2000 follow-up periods). Following the underlying theory of survival data, blocks of person-time in different time periods are asymptotically uncorrelated, regardless of the extent to which they are derived from the same people, so pooling estimates from these two time periods provide the same information as using a single time period but takes advantage of the updated dietary assessment in 1986. In addition to the exclusion criteria originally applied in each individual study, we excluded participants whose log(e)-transformed energy intakes were beyond three standard deviations from the log(e)-transformed mean intake of the baseline population of each study or who had a history of cancer (except non-melanoma skin cancer) at baseline.	**Inclusion Criteria:** assessed the validity of their dietary assessment method or a closely related instrument, at least 50 incident cases, include folate intake data, outcome is colorectal cancer, Prospective **Exclusion Criteria:** history of cancer other than nonmelanoma skin cancer at baseline, log(e)-transformed energy intakes beyond 3 standard deviations from the study-specific log(e)-transformed mean energy intake of the baseline population
Starting date:	**Ending date:**
Total references from search:	**References Included:** 13

Additional Notes:

22.2. Result(s)

22.2.A colon cancer, folate intake, dietary

Studies (13), Total Subjects (725134)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
dietary folate intake	colon cancer	0.92	(0.84, 1.0)	test for between-studies heterogeneity = 0.85

Notes:

22.2.B colon cancer, folate intake, total

Studies (8), Total Subjects (526166)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
total folate intake	colon cancer	0.85	(0.77, 0.95)	test for between-studies heterogeneity = 0.42

Notes:

22.3. Statistical Method(s)

Results: colon cancer, folate intake, dietary; colon cancer, folate intake, total

Adjustment factors:

Statistical metric description: Each study was analyzed using the Cox proportional hazards model with SAS PROC PHREG. The Canadian National Breast Screening Study and the Netherlands Cohort Study were analyzed as case–cohort studies. We evaluated associations with energy-adjusted dietary and total folate intake. Study- and sex-specific quintiles or deciles were based on the distributions for the subcohort in the two case–cohort studies and on the baseline populations for the remaining studies. The Canadian National Breast Screening Study, Prospective Study on Hormones, Diet and Breast Cancer, and Swedish Mammography Cohort were not included in the total folate analyses because information on multivitamin use was not available at baseline in these studies. Although total folate intake was estimated in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, this study also was not included in the quantile analyses for total folate intake because only 8% of the participants in this study reported using multivitamins, the main source of supplemental intake. Thus, the total folate intake in the higher categories in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study was not comparable to the other studies in which more than 30% of the study participants used multivitamins. Further, the Netherlands Cohort Study was not included in the quantile analyses for total folate intake because the multivitamins that were used in the Netherlands when the study was initiated did not include folate, so the folate intake in this study only comes from food sources. We also analyzed total folate intake using absolute intake cutpoints, which were identical across studies. These analyses included both the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study and Netherlands Cohort Study because their lower total folate intake levels compared to the other studies could be taken into account using identical absolute intake cutpoints. If no participants diagnosed with colon cancer were in the highest intake category in a study, the relative risk could not be estimated for the highest category in that study and the noncases in the highest category in that study were included in the second highest intake category. To calculate the p-value for the test for trend across categories, participants were

assigned the median value of their study's category of intake, and this variable was entered as a continuous variable in the regression model. For all studies, we included age at baseline and the year that the baseline questionnaire was returned as stratification variables. Person-years of follow-up were calculated from the date the baseline questionnaire was returned until the date of colon cancer diagnosis, loss to follow-up, if available, death, or end of follow-up, whichever came first. The Cancer Prevention Study II Nutrition Cohort, Netherlands Cohort Study, and the New York State Cohort were each analyzed as two separate cohorts of men and women. If there were missing data for a measured covariate within a study, an indicator variable was created for missing responses for that covariate, if applicable. Two-sided 95% CIs and p-values were calculated. To combine the study-specific effects, we used the random-effects model; the study-specific effects were weighted by the inverse of the sum of their variance and the estimated between-studies variance component. We tested for the statistical significance of between-studies heterogeneity among the study-specific estimates using the Q statistic. We tested for effect modification by sex and smoking status using a meta-regression model. We also evaluated whether the association between total folate intake and colon cancer risk varied by levels of alcohol and methionine intake. For these analyses, a cross-product term of total folate intake expressed as a continuous variable and the ordinal score of alcohol or methionine intake was included in the model. We tested the null hypothesis of no effect modification using a Wald test. When evaluating associations by tumor site (proximal colon vs distal colon cancer), we assessed the statistical significance of differences in the natural logarithm of the RRs by tumor site with a contrast test.

23. LARSSON, 2006

Full citation: Larsson SC, Giovannucci E, Wolk A. 2006. Folate intake, MTHFR polymorphisms, and risk of esophageal, gastric, and pancreatic cancer: a meta-analysis. Gastroenterology 131(4): 1271-1283.
Funding: None reported

23.1. Folate intake and esophageal, gastric, and pancreatic cancer

Protocol: Folate intake and esophageal, gastric, and pancreatic cancer	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
A computerized literature search was conducted in MEDLINE for studies published in any language from 1966 to March 2006 using the key words folate, folic acid, or MTHFR in combination with cancer, neoplasm, or the individual cancer sites. We also reviewed the reference lists of the relevant articles to identify additional studies. Because folate intake frequently was only one of several dietary factors studied, reports that had fruit, vegetables, vitamins, or nutrients as key words were scrutinized for findings on folate. Studies were included if they (1) presented original data from case-control or cohort studies and (2) provided odds ratios (ORs) or rate ratios with their confidence intervals (CIs) for the association of dietary folate intake (ie, folate from foods), total folate intake (ie, folate from foods and dietary supplements), blood folate levels, or polymorphisms in the MTHFR gene with esophageal, gastric, or pancreatic cancer risk. Studies were excluded if they provided only a risk estimate with no means by which to calculate the CI or if the risk estimate was not adjusted by age. When there were multiple publications from the same population, only the most recently published report was included.	**Inclusion Criteria:** case-control or cohort study, exposure is dietary folate intake (ie, folate from foods), total folate intake (ie, folate from foods and dietary supplements), blood folate levels, or polymorphisms in the MTHFR gene, outcome is esophageal, gastric, or pancreatic cancer **Exclusion Criteria:** provided only a risk estimate with no means by which to calculate the CI, risk estimate was not adjusted by age
Starting date: 1966-01-01	**Ending date:** 2006-03-01
Total references from search:	**References Included:** 20

Additional Notes:

23.2. Result(s)

23.2.A esophageal cancer, adenocarcinoma, folate intake

Studies (3), Total Subjects (1769)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folate intake	esophageal cancer, adenocarcinoma	0.5	(0.39, 0.65)	I2 = 0%, p = 0.74

Notes:

23.2.B esophageal cancer, squamous cell carcinoma, folate intake

Studies (4), Total Subjects (3408)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folate intake	esophageal cancer, squamous cell carcinoma	0.66	(0.53, 0.83)	I2 = 0%, p = 0.85

Notes:

23.2.C gastric cancer, folate intake, all studies

Studies (11), Total Subjects (73335)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folate intake	gastric cancer	0.9	(0.72, 1.13)	I2 = 58.8%, p = 0.007

Notes:

23.2.D gastric cancer, folate intake, case-control

Studies (9), Total Subjects (8341)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folate intake	gastric cancer	0.88	(0.67, 1.14)	I2 = 64.7%, p = 0.004

Notes:

23.2.E gastric cancer, folate intake, cohort

Studies (2), Total Subjects (64994)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folate intake	gastric cancer	1.01	(0.72, 1.42)	I2 = 0%, p = 0.91

Notes:

23.2.F pancreatic cancer, folate intake, all studies

Studies (5), Total Subjects (237510)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folate intake	pancreatic cancer	0.49	(0.35, 0.67)	I2 = 17.1%, p = 0.31

Notes:

23.3. Statistical Method(s)

Results: esophageal cancer, adenocarcinoma, folate intake; esophageal cancer, squamous cell carcinoma, folate intake; gastric cancer, folate intake, all studies; gastric cancer, folate intake, case-control; gastric cancer, folate intake, cohort; pancreatic cancer, folate intake, all studies

Adjustment factors:

Statistical metric description: We weighted the study-specific log ORs for case-control studies and log rate ratios for cohort studies by the inverse of the variance to compute summary relative risk (RR) estimates with 95% CIs. Because the absolute risk of the cancers considered in this meta-analysis is low, ORs in case-control studies and rate ratios in cohort studies yield similar estimates of RR. Studies were pooled with the DerSimonian and Laird random-effects model, which considers both within- and between-study variability. When separate RRs were provided for the intestinal and diffuse types of gastric cancer, for cardia and noncardia gastric cancer, or for men and women, we pooled the RRs (weighted by the inverse of their variance) to obtain one RR from each study. Statistical heterogeneity among studies was assessed with the Q and I2 statistics. For the Q statistic, heterogeneity was considered present if P<.1. I2 is the proportion of total variation contributed by between-study variability. We used random-effects meta-regression to investigate sources of heterogeneity and to provide an estimate of unexplained heterogeneity, T2. Study characteristics examined included study design (case-control vs cohort), type of controls in case-control studies (population-based vs hospital-based), and geographical area (United States, Europe, other). We used funnel plots and Egger's regression asymmetry test to evaluate publication bias (P<.1 was considered representative of statistically significant publication bias). The potential influence that unpublished studies could have on the summary estimate was examined using trim and fill analysis. All analyses were performed with Stata statistical software (version 9.0; StataCorp, College Station, TX).

24. LARSSON, 2007

Full citation: Larsson SC, Giovannucci E, Wolk A. 2007. Folate and risk of breast cancer: A meta-analysis. Journal of the National Cancer Institute 99(1): 64-76.
Funding: This study was supported by research grants from the Swedish Cancer Society and the Swedish Research Council/Longitudinal Studies. The study sponsors had no role in the design, collection, analysis, or interpretation of the data or in the writing or decision to submit the manuscript.

24.1. Folate and risk of breast cancer

Protocol: Folate and risk of breast cancer	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
Studies were identified by a literature search of MEDLINE (from January 1, 1966, through November 1, 2006) by use of the search terms "folate" or "folic acid" in combination with "breast cancer" or "breast neoplasm." We also reviewed the reference lists of retrieved articles to identify additional studies. No language restrictions were imposed.	**Inclusion Criteria:** case-control or prospective cohort studies, present data on breast cancer incidence or mortality, provide relative risk estimates (or odds ratios in case-control studies) with confidence intervals or sufficient data to allow calculation of these effect measures, report results on dietary folate intake, total folate intake, or serum or plasma folate levels **Exclusion Criteria:**
Starting date: 1966-01-01	**Ending date:** 2006-11-01
Total references from search:	**References Included:** 23

Additional Notes:

24.2. Result(s)

24.2.A breast cancer, dietary folate increments, case-control

Studies (13), Total Subjects (19370)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	breast cancer	0.8	(0.72, 0.89)	I2 = 18.1%, p = 0.26

Notes:

24.2.B breast cancer, dietary folate increments, postmenopausal, case-control

Studies (7), Total Subjects (11667)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	breast cancer	0.75	(0.58, 0.96)	I2 = 71.1%, p = 0.002

Notes:

24.2.C breast cancer, dietary folate increments, postmenopausal, prospective

Studies (6), Total Subjects (194857)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
dietary folate increments	breast cancer	0.92	(0.82, 1.03)	I2 = 40.4%, p = 0.14

Notes: Studies with both pre- and postmenopausal women are not reported with separate Ns for the two groups, so the N here is not accurate.

24.2.D breast cancer, dietary folate increments, premenopausal, case-control

Studies (6), Total Subjects (13084)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	breast cancer	0.8	(0.68, 0.96)	I2 = 22.4%, p = 0.27

Notes:

24.2.E breast cancer, dietary folate increments, premenopausal, prospective

Studies (2), Total Subjects (96037)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
dietary folate increments	breast cancer	1.16	(0.96, 1.41)	I2 = 3.7%, p = 0.31

Notes: Studies with both pre- and postmenopausal women are not reported with separate Ns for the two groups, so the N here is not accurate.

24.2.F breast cancer, dietary folate increments, prospective

Studies (8), Total Subjects (302959)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
dietary folate increments	breast cancer	0.97	(0.88, 1.07)	I2 = 50.1%, p = 0.05

Notes:

24.2.G breast cancer, dietary folate, case-control

Studies (13), Total Subjects (19370)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	breast cancer	0.73	(0.64, 0.83)	I2 = 27.8%, p = 0.17

Notes:

24.2.H breast cancer, dietary folate, prospective

Studies (8), Total Subjects (302959)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
dietary folate	breast cancer	0.96	(0.87, 1.05)	I2 = 44.6%, p = 0.08

Notes:

24.2.I breast cancer, total folate increments, case-control

Studies (3), Total Subjects (5417)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
total folate	breast cancer	0.93	(0.81, 1.07)	I2 = 68.1%, p = 0.04

Notes:

24.2.J breast cancer, total folate increments, prospective

Studies (6), Total Subjects (306209)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
total folate increments	breast cancer	1.01	(0.97, 1.05)	I2 = 48.4%, p = 0.08

Notes:

24.2.K breast cancer, total folate, case-control

Studies (3), Total Subjects (5417)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
total folate	breast cancer	0.87	(0.61, 1.23)	I2 = 67.4%, p = 0.05

Notes:

24.2.L breast cancer, total folate, prospective

Studies (6), Total Subjects (306209)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
total folate	breast cancer	1.0	(0.87, 1.14)	I2 = 57.0%, p = 0.04

Notes:

24.3. Statistical Method(s)

Results: breast cancer, dietary folate, case-control; breast cancer, dietary folate increments, case-control; breast cancer, dietary folate increments, postmenopausal, case-control; breast cancer, dietary folate increments, postmenopausal, prospective; breast cancer, dietary folate increments, premenopausal, case-control; breast cancer, dietary folate increments, premenopausal, prospective; breast cancer, dietary folate increments, prospective; breast cancer, dietary folate, prospective; breast cancer, total folate, case-control; breast cancer, total folate increments, case-control; breast cancer, total folate increments, prospective; breast cancer, total folate, prospective

Adjustment factors:

Statistical metric description: We weighted the study-specific log relative risks for cohort studies and log odds ratios for case–control studies by the inverse of their variance to calculate a summary estimate and its 95% confidence interval. Studies were combined by use of the DerSimonian and Laird random-effects model, which considers both within- and between-study variation. For the dose–response meta-analysis of folate intake, we used the method proposed by Greenland and Longnecker and Orsini et al.

to compute study-specific slopes (linear trends) from the correlated log risk estimates across categories of folate intake. This method requires that the distributions of case patients and control subjects (or person-time) and the risk estimates with their variance estimates for three or more quantitative exposure categories be known. For three studies that did not provide the distribution of case patients and control subjects by exposure category, we estimated the slopes by use of variance-weighted least squares regression models. For each study, the median or mean level of folate intake for each category of intake was assigned to each corresponding relative risk estimate. When the median or mean intake per category was not provided in the article, we assigned the midpoint of the upper and lower boundaries in each category as the average intake. If the lower boundary of the lowest category or the upper boundary of the highest category was not provided, we assumed that both boundaries had the same amplitude as the closest category. We used the Q and I2 statistics to examine statistical heterogeneity among studies. For the Q statistic, a P value of less than .1 was considered representative of statistically significant heterogeneity. I2 is the proportion of total variation contributed by between-study variation. Publication bias was evaluated with the use of funnel plots and with Egger's regression asymmetry test (P<.1 was considered representative of statistically significant publication bias). All statistical analyses were performed with Stata, version 9.0 (StataCorp, College Station, TX). All statistical tests were two-sided.

25. LEWIS, 2006

Full citation: Lewis SJ, Harbord RM, Harris R, Smith GD. 2006. Meta-analyses of observational and genetic association studies of folate intakes or levels and breast cancer risk. J Natl Cancer Inst 98(22): 1607-1622.
Funding: None reported

25.1. Folate intakes or levels and breast cancer

Protocol: Folate intakes or levels and breast cancer	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
We searched the Medline and ISI Web of Knowledge databases for studies on folate intake or biomarkers of folate levels and breast cancer and on the MTHFR C677T polymorphism and breast cancer that were published through May 31, 2006. The following search algorithm was used for the review on folate intake or level and breast cancer: (breast) AND (cancer OR malignancy OR tumour OR tumor) AND (folate OR folic acid). The following search algorithm was used for the review on MTHFR polymorphism and breast cancer: (breast) AND (cancer OR malignancy OR tumour OR tumor) AND (MTHFR OR methylenetetrahydrofolate reductase). Publications were also identified by reviewing the bibliographies of retrieved articles. No studies were excluded on the basis of language; non – English language publications were translated into English. When multiple publications reported on the same population, we used the most recent publication only. For studies that did not provide raw data or give point estimates (odds ratios [ORs] or relative risks [RRs]) in the initial publication, we attempted to obtain this information by correspondence with the authors. When such information could not be obtained, the studies were excluded.	**Inclusion Criteria:** **Exclusion Criteria:**
Starting date:	**Ending date:** 2006-05-31
Total references from search:	**References Included:** 25

Additional Notes:

25.2. Result(s)

25.2.A breast cancer, dietary folate, case-control

Studies (13), Total Subjects (19400)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	breast cancer	0.91	(0.87, 0.96)	

Notes:

25.2.B breast cancer, dietary folate, cohort

Studies (9), Total Subjects (335066)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
dietary folate	breast cancer	0.99	(0.98, 1.01)	

Notes:

25.2.C breast cancer, dietary folate, postmenopausal, case-control

Studies (4), Total Subjects (6970)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	breast cancer	0.92	(0.83, 1.02)	

Notes:

25.2.D breast cancer, dietary folate, postmenopausal, cohort

Studies (6), Total Subjects (223351)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	breast cancer	1.01	(0.98, 1.05)	

Notes:

25.2.E breast cancer, dietary folate, premenopausal, case-control

Studies (5), Total Subjects (10379)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	breast cancer	0.87	(0.78, 0.97)	

Notes:

25.2.F breast cancer, dietary folate, premenopausal, cohort

Studies (3), Total Subjects (186201)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
dietary folate	breast cancer	1.01	(0.98, 1.04)	

Notes:

25.3. Statistical Method(s)

Results: breast cancer, dietary folate, case-control; breast cancer, dietary folate, cohort; breast cancer, dietary folate, postmenopausal, case-control ; breast cancer, dietary folate, postmenopausal, cohort; breast cancer, dietary folate, premenopausal, case-control ; breast cancer, dietary folate, premenopausal, cohort

Adjustment factors:

Statistical metric description: Published odds ratios and relative risks are presented for the observational studies of folate intake and breast cancer in Table 1. To make comparisons across studies, we calculated the odds ratios for case – control studies or relative risks for cohort studies for a 100-µg/d increase in folate intake by using either continuous odds ratios (or relative risks) or odds ratios (or relative risks) across categories of folate intake for each study. For these comparisons, we considered

dietary folate intake only because this variable was reported by all studies, whereas folate intake from both diet and from supplement use was not. We did not include studies of biomarkers of folate. When data were presented according to quantiles or other categories of exposure, we used the median or mean exposure in each group when they were reported. When the median or mean exposures were not reported (as was the case for the majority of reports included in the meta-analyses), we estimated the mean exposure in each group based on the distribution of exposures among subjects across groups, as described by Chene and Thompson. This method addresses the problem of unbounded upper and/or lower categories by assuming a normal distribution of the exposure in the population. When the number of individuals in each quantile was not reported, we assumed that the quantile groups were of equal size. When the number of individuals in each group was presented in the paper but no odds ratios or relative risks were given, the unadjusted log odds ratio or relative risk per 100-µg/d increase in folate intake was estimated directly using logistic regression. When either unadjusted or adjusted odds ratios or relative risks comparing quantiles or groups were presented, these were used to calculate odds ratios or relative risks for a 100-µg/d increase in folate intake as follows: If no confidence intervals, standard errors, or Pvalues were reported, we estimated the standard error of the log odds ratio (or relative risk) from the number of subjects withand without disease in each group using the formula described by Woolf. We then estimated the log odds ratio (or relative risk) per 100-µg/d increase in folate intake using the method of Greenland and Longnecker. This method accounts for the correlations between estimates of odds ratios/relative risks for different folate levels that have been compared with the same reference level and preserves adjustments for confounders in the reported odds ratios and relative risks. We performed one sub- group analysis of menopausal status at diagnosis of breast cancer. We used published genotype frequencies to calculate unadjusted odds ratios for the studies of MTHFR genotype associations. For one study, which was stratified by ethnic group, a different effect estimate was used for each group. In the analyses of all studies, random- effects meta-analysis was used to calculate summary odds ratio estimates. Each summary estimate was a weighted average of the estimates from each study, where the weight for each study is the inverse of the sum of the within-study variance for that study and the between-study variance, which was estimated by the method of moments. All statistical analyses were carried out with the use of Stata statistical software (version 9; Stata Corporation, College Station, TX). All statistical tests were two-sided. We assessed small-study effects, including publication bias, for studies of dietary folate intake and of the MTHFR polymorphism by computing both the Egger and Begg tests. To assess whether there was an interaction between MTHFR genotype and folate intake, we extracted or calculated the odds ratio for TT versus CC genotype in high and in low folate conditions separately, where possible.

26. LI, 2013

Full citation: Li C, Chen P, Hu P, Li M, Li X, Guo H, Li J, Chu R, Zhang W, Wang H. 2013. Folate intake and MTHFR polymorphism C677T is not associated with ovarian cancer risk: evidence from the meta-analysis. Mol Biol Rep 40(12): 6547-6560.

Funding: This study was supported by grants from the Ministry of Science and Technology of China (2012BAK01B00 and 2011BAK10B00), the National Nature Science Foundation (81125020, 31101261 and 31200569), the Key Research Program (KSZD-EW-Z-021) of the Chinese Academy of Sciences, the Science and Technology Commission of Shanghai Municipality (12XD140 7000, 12431900500 and 10391902100), Director Foundation (20090 101) and the Food Safety Research Center and Key Laboratory of Food Safety Research of INS, SIBS, CAS. Peizhan Chen was partially supported by the SA-SIBS scholarship program.

26.1. Folate intake and ovarian cancer

Protocol: Folate intake and ovarian cancer	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
A comprehensive literature search was conducted on MEDLINE and PubMed databases by two independent researchers to identify relevant studies published prior to 31 December 2012. The search flowchart was shown in Fig. 1. We used the term ‘‘ovarian cancer’’, along with ‘‘folate’’, ‘‘folic acid’’ or ‘‘MTHFR’’ for the search without any other restrictions. The reference lists of the retrieved publications were checked to identify any missing studies in the database search. We selected eligible studies that examined the correlation between folate intake and ovarian cancer risk with the folate intake data in quantiles together with the risk estimates (RR or odds ratio [OR]) and 95 % CIs, or with the results of the highest quantile in contrast with the lowest quantile, or with data that could be used to calculate the risk estimate and its 95 % CI. Studies that examined the association of MTHFR single nucleotide polymorphism (SNP) C677T and ovarian cancer risk should provide sufficiency data for the frequency of the genotypes. We included case–control, cohort or cross-sectional studies that were reported in English.	**Inclusion Criteria:** case-control, cohort, or cross-sectional studies, English language article, exposure is folate intake, outcome is ovarian cancer, population-based, provide relative risk estimates (or odds ratios in case-control studies) with confidence intervals or sufficient data to allow calculation of these effect measures **Exclusion Criteria:**
Starting date:	**Ending date:** 2012-12-31
Total references from search: 373	**References Included:** 8

Additional Notes:

26.2. Result(s)

26.2.A <u>ovarian cancer, dietary folate intake</u>

Studies (8), Total Subjects (227859)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
dietary folate intake	ovarian cancer	0.88	(0.75, 1.05)	I2 = 42.6%, p-value = 0.094

Notes: p-value for random effects model = 0.158

26.2.B **ovarian cancer, total folate intake**

Studies (4), Total Subjects (114135)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
total folate intake	ovarian cancer	1.04	(0.87, 1.23)	I2 = 37.2%, p-value = 0.189

Notes: p-value for random effects model = 0.681

26.3. Statistical Method(s)

Results: ovarian cancer, dietary folate intake; ovarian cancer, total folate intake

Adjustment factors:

Statistical metric description: The standard inverse variance weighting method was used to calculate the pooled estimate and its 95 % CI that concerning the effect of folate intake and ovarian cancer risk. Due to the relative negligible difference between ORs from case–control studies and RRs from prospective studies numerically, the ORs were assumed as the estimates of RRs for further analysis. Each study was assigned with appropriate weighting using the inverse square of SE for each logRR. Statistical heterogeneity among studies was evaluated by Q test and I2 statistics. We considered significant heterogeneity existing when p value was less than 0.05 for the Q test or I2 > 25 % in I2 statistics. Results from random-effects model were acceptable for interpretation when significant heterogeneity among studies was detected; otherwise, the results from the fixed-effects model were used. Publication bias was assessed by the Egger's linear regression test and a p value less than 0.05 indicated significant publication bias. For the sensitivity test, we excluded a single study from the meta-analysis each time to evaluate the influence of individual study on the overall estimate. All the statistical analysis was conducted with the R software and the Meta package for R.

27. LIN, 2013

Full citation: Lin HL, An QZ, Wang QZ, Liu CX. 2013. Folate intake and pancreatic cancer risk: an overall and dose-response meta-analysis. Public Health 127(7): 607-613.
Funding: None

27.1. Folate intake and pancreatic cancer risk

Protocol: Folate intake and pancreatic cancer risk	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
The literature search was conducted before November 2011 in the Pubmed and Embase databases without restrictions in terms of publication language and format and included articles ahead of publication. The following keywords were used in searching: folate, folic acid or Vitamin B9, in combination with pancreatic cancer or cancer of the pancreas. Moreover, the reference lists of the relevant articles were reviewed to identify additional studies. Because folate intake frequently was only one of several dietary factors studied, reports that had fruit, vegetables, vitamins, or nutrients as key words were scrutinized for findings on folate.	**Inclusion Criteria:** case-control or cohort study, exposure is dietary folate intake (ie, folate from foods), total folate intake (ie, folate from foods and dietary supplements), or blood folate levels, provide relative risk estimates (or odds ratios in case-control studies) with confidence intervals or sufficient data to allow calculation of these effect measures **Exclusion Criteria:**
Starting date:	**Ending date:** 2011-11-01
Total references from search:	**References Included:** 13

Additional Notes:

27.2. Result(s)

27.2.A pancreatic cancer, blood folate level

Studies (3), Total Subjects ()

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
blood folate level	pancreatic cancer	0.8	(0.44, 1.45)	I2 = 71.5%, p = 0.030

Notes: N is not reported

27.2.B pancreatic cancer, dietary folate intake

Studies (10), Total Subjects ()

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
dietary folate intake	pancreatic cancer	0.66	(0.49, 0.88)	I2 = 76.4%, p = 0.000

Notes: N is not reported

27.2.C pancreatic cancer, folate intake overall

Studies (14), Total Subjects ()

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folate intake overall	pancreatic cancer	0.78	(0.65, 0.93)	I2 = 66.2%, p = 0.000

Notes: N is not reported

27.2.D pancreatic cancer, incremental dietary folate intake, all studies

Studies (7), Total Subjects ()

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
incremental dietary folate intake	pancreatic cancer	0.93	(0.9, 0.97)	I2 = 81.14% p-value = 0.13

Notes: N is not reported.

27.2.E pancreatic cancer, incremental dietary folate intake, case-control

Studies (2), Total Subjects ()

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
incremental dietary folate intake	pancreatic cancer	0.92	(0.87, 0.97)	I2 = 56.90% p-value = 0.89

Notes: N is not reported.

27.2.F pancreatic cancer, incremental dietary folate intake, cohort

Studies (5), Total Subjects ()

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
incremental dietary folate intake	pancreatic cancer	0.94	(0.9, 0.99)	I2 = 86.11% p-value = 0.04

Notes: N is not reported.

27.2.G pancreatic cancer, supplemental folate intake

Studies (5), Total Subjects ()

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
supplemental folate intake	pancreatic cancer	1.08	(0.82, 1.41)	I2 = 13.6%, p = 0.328

Notes: N is not reported

27.2.H pancreatic cancer, total folate intake

Studies (4), Total Subjects ()

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
total folate intake	pancreatic cancer	0.75	(0.5, 1.13)	I2 = 64.4%, p = 0.038

Notes: N is not reported

27.3. Statistical Method(s)

Results: pancreatic cancer, blood folate level; pancreatic cancer, dietary folate intake; pancreatic cancer, folate intake overall; pancreatic cancer, incremental dietary folate intake, all studies; pancreatic cancer, incremental dietary folate intake, case-control; pancreatic cancer, incremental dietary folate intake, cohort; pancreatic cancer, supplemental folate intake; pancreatic cancer, total folate intake
Adjustment factors:
Statistical metric description: The measure of effect of interest is the relative risk (RR) and the corresponding 95% confidence interval (CI). Because the incidence and mortality rate of pancreatic cancer is relatively low (12.1 and 10.8 per 100,000 person-years in US), OR from case-control studies accurately estimate RR. For simplicity, all results are reported as RR. Study-specific risk estimates were combined using a random-effects model, which considers both within-study and between-study variation and provides more conservative estimates compared with the fixed effects model. For dose-response meta-analyses of the association between folate intake and pancreatic cancer risk, the method proposed by Greenland and Longnecker was used to compute study-specific slopes from the correlated natural logarithm of the risk estimates across exposurecategories. For each study, the median level of folate intake for each category was assigned to each corresponding risk estimate. When the highest category was open ended, the midpoint was calculated as 1.2 times its lower boundary. Statistical heterogeneity between studies was assessed with the I2 statistic, which was a quantitative measurement of the percentage of total variation across studies that were attributable to heterogeneity rather than to chance. A significant heterogeneity was defined as a P value <0.10. An estimation of potential publication bias was executed by the funnel plot, in which ln(RR) of each study was plotted against the standard error of ln(RR). An asymmetrical plot suggests a possible publication bias. Funnel plot asymmetry was assessed by the method of Egger's linear regression test, a linear regression approach to measure funnel plot asymmetry on the natural logarithm scale of the RR. The significance of the intercept was determined by the t-test suggested by Egger (P<0.10 was considered representative of statistically significant publication bias). All analyses were performed with Stata statistical software (version 12.0; StataCorp, College Station, TX).

28. LIU, 2011

Full citation: Liu YX, Wang B, Wan MH, Tang WF, Huang FK, Li C. 2011. Meta-analysis of the Relationship between the Metholenetetrahydrofolate Reductase C677T Genetic Polymorphism, Folate Intake and Esophageal Cancer. Asian Pac J Cancer Prev 12(1): 247-252.
Funding: This work was funded from grants of the National 973 Project Foundation of China, no. 2009CB522401.

28.1. Folate intake and esophageal cancer

Protocol: Folate intake and esophageal cancer	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
We searched MEDLINE, EMBASE and the Chinese Biomedical Database. The data of the last search was February 2011. We designed a comprehensive and exhaustive search strategy for MEDLINE, EMBASE and the Chinese Biomedical Database databases to identify all relevant studies. Two reviewers (Liu YX and Li CW) independently extracted the following data from each publication: the first author's last name, year of publication, country where the study was conducted, sample size, measure of exposure and prevalence of the variant genotype in the study population.	**Inclusion Criteria:** case-control, exposure is folate intake, outcome is esophageal cancer, provide relative risk estimates (or odds ratios in case-control studies) with confidence intervals or sufficient data to allow calculation of these effect measures **Exclusion Criteria:**
Starting date:	**Ending date:** 2011-02-28
Total references from search: 86	**References Included:** 6

Additional Notes:

28.2. Result(s)

28.2.A esophageal cancer, folate intake

Studies (6), Total Subjects (9495)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
folate intake	esophageal cancer	0.6	(0.5, 0.7)	p = 0.009

Notes:

28.2.B esophageal cancer, folate intake, smokers

Studies (6), Total Subjects ()

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
folate intake	esophageal cancer	0.75	(0.56, 0.94)	

Notes: N is not given in the paper.

28.3. Statistical Method(s)

Results: esophageal cancer, folate intake; esophageal cancer, folate intake, smokers
Adjustment factors:
Statistical metric description: The Stata SE version 9.0 software package (version 9, STATA, College Station, TX) was used for all of the statistical analysis. The lowest category of dietary folate intake was regarded as reference for the highest category. Statistical analysis was performed for the case-control studies. We used both the adjusted data (adjusted OR with 95% CI) and crude data (unadjusted). The heterogeneity was tested with a Q-statistics with p-values <0.05, and its possible sources were assessed by subgroup analysis as described below. Fixed-effect model was applied to obtain the summaried ORs and their 95% confidence interval if there is no heterogeneity between studies, otherwise random-effect model was used. The Hardy-Weinberg equilibrium in the controls in each study was assessed by using the x2 test, and Egger's regression asymmetry test was taken to evaluate publication bias ($p<0.1$ was considered representative of statistically significant publication bias). A subgroup analysis was taken regarding tobacco, alcohol consumption and folate intake as well as ethnicity. A random-effects meta-regression was conducted to investigate sources of heterogeneity and to provide an estimate of unexplained heterogeneity (Stern et al., 2001). In addition, a sensitivity analysis was performed to explore robustness of results.

29. LIU, 2014

Full citation: Liu M, Cui LH, Ma AG, Li N, Piao JM. 2014. Lack of effects of dietary folate intake on risk of breast cancer: an updated meta-analysis of prospective studies. Asian Pac J Cancer Prev 15(5): 2323-2328.
Funding: This work was supported by the Chinese Nutrition Society Research Fund - DSM Specialized Research Fund.

29.1. Dietary folate intake and breast cancer

Protocol: Dietary folate intake and breast cancer	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
We conducted a comprehensive English literature search up to August 2013 by two independent researchers on PUBMED, MEDLINE and EMBASE databases. Search terms "dietary folate intake" or "dietary folic acid consumption" in combination with "breast cancer" or "breast neoplasm" were used. Eligible studies have to meet the following inclusion criteria: 1) prospective study design; 2) the exposure of interest was dietary folate intake; 3) number of incident breast cancer cases and total participants; 4) provided relative risk (RR) or hazard ratio(HR) with 95% confidence interval (CI).	**Inclusion Criteria:** breast cancer outcome, exposure is dietary folate intake, Prospective, provide relative risk (RR) or hazard ratio (HR) with 95% confidence interval (CI) **Exclusion Criteria:**
Starting date:	**Ending date:** 2013-08-01
Total references from search:	**References Included:** 15

Additional Notes:

29.2. Result(s)

29.2.A <u>breast cancer, dietary folate intake, estrogen receptor + / progesterone receptor +</u>

Studies (3), Total Subjects ()

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
dietary folate intake	breast cancer	1.05	(0.95, 1.5)	I2 = 0%, p value = 0.987

Notes: N is not given in the paper.

29.2.B <u>breast cancer, dietary folate intake, estrogen receptor - / progesterone receptor -</u>

Studies (4), Total Subjects ()

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
dietary folate intake	breast cancer	0.91	(0.8, 1.03)	I2 = 0%, p value = 0.795

Notes: N is not given in the paper.

29.2.C **breast cancer, dietary folate intake, overall**

Studies (15), Total Subjects (1836566)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
dietary folate intake	breast cancer	0.98	(0.9, 1.05)	I2 = 53.8%, p value = 0.007

Notes:

29.2.D **breast cancer, dietary folate intake, postmenopausal**

Studies (10), Total Subjects ()

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
dietary folate intake	breast cancer	0.98	(0.89, 1.07)	I2 = 56.6%, p value = 0.014

Notes: N is not given in the paper.

29.2.E **breast cancer, dietary folate intake, premenopausal**

Studies (4), Total Subjects ()

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
dietary folate intake	breast cancer	1.06	(0.96, 1.16)	I2 = 0%, p value = 0.645

Notes: N is not given in the paper.

29.3. Statistical Method(s)

Results: breast cancer, dietary folate intake, estrogen receptor - / progesterone receptor -; breast cancer, dietary folate intake, estrogen receptor + / progesterone receptor +; breast cancer, dietary folate intake, overall; breast cancer, dietary folate intake, postmenopausal; breast cancer, dietary folate intake, premenopausal

Adjustment factors:

Statistical metric description: Since the incidence and mortality rate of breast cancer is relatively low, RR and HR will be approximately equal, and the measure of effect-estimates is referred to as RR in our meta-analysis (Lin et al., 2013). Cochrane Q test and Higgins I-square (I2) statistics were used to assess heterogeneity among studies. The p-value of 0.1 was used for the Cochrane Q test on testing the heterogeneity, and the values of 25, 50 and 75% of I2 statistic were used as low, moderate and high heterogeneity, respectively. Based on the test on heterogeneity, the fixed-effects model (Mantel et al., 1959) or random effects mode (DerSimonian et al., 1986) was used to obtain pooled estimates. In addition, we performed meta-regression, subgroup and sensitivity. For the dose–response analysis, we used the generalized least-squares trend estimation (GLST) method developed by Greenland and Orsini (Greenland et al., 1992; Orsini et al., 2006).The method requires that the average categories of dietary folate dose, number of breast cancer cases, person-years or noncases, and adjusted logarithm of the RR with its SE (Greenland et al., 1992; Berlin et al., 1993). The median value of dietary folate intake in each category was assigned to the corresponding RR for each study when provided in the paper. For studies that reported the range of dietary folate, the midpoint of the interval was chosen. For the lowest category was open ended, the lowest boundary was considered to be zero. For the open-ended upper interval, the value arbitrarily assigned was 20% higher than the low end of the interval (Berlin et al.,

1993; Aune et al., 2012) .The does-response results are presented for a 220ug/d increment. The publication bias among studies was examined with Funnel plots, Eggeŕs liner regression test (Egger et al., 1997) and Begǵs test (Begg et al., 1994) with a significance level of 0.1. Sensitivity analyses were conducted to assess the stability of individual studies, by excluding any single study each time. In addition, we also performed subgroup analysis based on menstrual status, hormonal status and the consumption of alcohol, methionine and vitamin B12. All statistical analyses were conducted with STATA software (version 12.0; College Station, TX). All statistical tests were two sided and considered statistically significant when <0.05.

30. MARTÍ-CARVAJAL, 2013

Full citation: Marti-Carvajal AJ, Sola I, Lathyris D, Karakitsiou DE, Simancas-Racines D. 2013. Homocysteine-lowering interventions for preventing cardiovascular events. Cochrane Database of Systematic Reviews 1(1): CD006612.
Funding:

30.1. Cochrane review of homocysteine-lowering interventions for preventing cancer

Protocol: Cochrane review of homocysteine-lowering interventions for preventing cancer	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
We searched The Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library (2012, Issue 2), MEDLINE (1950 to Feb week 2 2012), EMBASE (1980 to 2012 week 07), and LILACS (1986 to February 2012). We also searched ISI Web of Science (1970 to February 2012). We handsearched the reference lists of included papers. We also contacted researchers in the field. There was no language restriction in the search.	**Inclusion Criteria:** adults (age > 18 years), at risk of, or with established cardiovascular disease, follow-up period of one year or longer, randomized controlled trials **Exclusion Criteria:** Studies with patients with end-stage renal disease
Starting date:	**Ending date:** 2012-02-29
Total references from search: 1393	**References Included:** 12

Additional Notes:

30.2. Result(s)

30.2.A **cancer, homocysteine-lowering treatment**

Studies (7), Total Subjects (32869)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
homocysteine-lowering treatment	cancer	1.06	(0.98, 1.13)	I2 = 0.0%, p = 0.68

Notes: P for overall effect = 0.13

30.3. Statistical Method(s)

Results: cancer, homocysteine-lowering treatment
Adjustment factors:
Statistical metric description: We pooled the risk ratios (RR) with 95% confidence interval (CI) for the following binary outcomes: non-fatal or fatal myocardial infarction, non-fatal or fatal stroke (Ischaemic or haemorrhagic), first unstable angina pectoris episode requiring hospitalisation, hospitalisation for heart failure, mortality due to any cause and serious or non-serious adverse events as recommended by

Higgins 2011. For all included trials, we noted the levels of attrition. We contacted the first author of the paper if data were missing. We extracted data on the number of participants by allocated treatment group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow-up. If we were not able to do so, we recorded for each study whether the results pertained to an intention-to-treat analysis or to available-cases analysis. We quantified statistical heterogeneity using I2, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003). We considered statistical heterogeneity to be present if the I2 was greater than 50% (Higgins 2011). When a significant heterogeneity was detected (I2> 50%), we attempted to identify the possible causes of heterogeneity. Assessment of reporting biases We assessed publication bias for myocardial infarction, stroke, and death by any cause using the Comphrensive Meta-Analysis software (CMA 2005).

31. METAYER, 2014

Full citation: Metayer C, Milne E, Dockerty JD, Clavel J, Pombo-de-Oliveira MS, Wesseling C, Spector LG, Schuz J, Petridou E, Ezzat S, Armstrong BK, Rudant J, Koifman S, Kaatsch P, Moschovi M, Rashed WM, Selvin S, McCauley K, Hung RJ, Kang AY, Infante-Rivard C. 2014. Maternal supplementation with folic acid and other vitamins and risk of leukemia in offspring: a childhood leukemia international consortium study. Epidemiology 25(6): 811-822.

Funding: The pooled analyses were supported by the National Cancer Institute (NCI), USA (R03CA132172). Childhood Leukemia International Consortium (CLIC) administration is supported by the National Institute of Environmental Health Sciences (NIEHS), USA (P01 ES018172), the Environmental Protection Agency, USA (USEPA, RD83451101), and the CHILDREN with CANCER, UK. The NCI provided support for teleconferences among CLIC Members.

31.1. Vitamins and folic acid and risk of leukemia in offspring

Protocol: Vitamins and folic acid and risk of leukemia in offspring	
Literature Search Strategy: Other	**Protocol type:** Pooled-analysis
Twelve case-control studies conducted in 10 countries from 1980 to 2012 and participating in the childhood leukemia international consortium contributed data to the current pooled analyses (Table 1); this included 8 studies with published data from Australia, Canada, France, Germany, New Zealand, and the United States and 4 studies from Brazil, Costa Rica, Egypt, and Greece with unpublished data at the time of this report. Study design and characteristics of participants in individual studies have been described previously. A total of 19,183 children were available for analysis (6,963 cases of ALL, 585 cases of AMI, and 11,635 controls). Information on immunophenotype was available for 84% of all, including 5,193 children diagnosed with the precursor B-cell type and 678 with the T-cell type.	**Inclusion Criteria:** case-control, exposure is prenatal intake of folic acid and vitamins, outcome is childhood acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) **Exclusion Criteria:**
Starting date: 1980-01-01	**Ending date:** 2012-12-31
Total references from search:	**References Included:** 12

Additional Notes:

31.2. Result(s)

31.2.A **ALL, folic acid, any time**

Studies (8), Total Subjects (8590)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
vitamins	ALL	0.8	(0.71, 0.89)	

Notes:

31.2.B ALL, folic acid, preconception

Studies (7), Total Subjects (7767)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
vitamins	ALL	0.82	(0.7, 0.96)	

Notes:

31.2.C ALL, folic acid, pregnancy

Studies (7), Total Subjects (7683)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
vitamins	ALL	0.77	(0.67, 0.88)	

Notes:

31.2.D ALL, vitamins, any time

Studies (12), Total Subjects (18311)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
vitamins	ALL	0.85	(0.78, 0.92)	

Notes:

31.2.E ALL, vitamins, preconception

Studies (8), Total Subjects (11497)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
vitamins	ALL	0.88	(0.79, 0.99)	

Notes:

31.2.F ALL, vitamins, pregnancy

Studies (10), Total Subjects (14258)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
vitamins	ALL	0.81	(0.74, 0.88)	

Notes:

31.2.G AML, folic acid, any time

Studies (6), Total Subjects (4409)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
vitamins	AML	0.68	(0.48, 0.96)	

Notes:

31.2.H AML, folic acid, preconception

Studies (5), Total Subjects (3813)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
vitamins	AML	0.88	(0.59, 1.32)	

Notes:

31.2.I AML, folic acid, pregnancy

Studies (5), Total Subjects (3853)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
vitamins	AML	0.52	(0.31, 0.89)	

Notes:

31.2.J AML, vitamins, any time

Studies (8), Total Subjects (8096)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
vitamins	AML	0.92	(0.75, 1.14)	

Notes:

31.2.K AML, vitamins, preconception

Studies (5), Total Subjects (3745)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
vitamins	AML	0.96	(0.66, 1.39)	

Notes:

31.2.L AML, vitamins, pregnancy

Studies (6), Total Subjects (5005)

Exposure	Assessed Outcome	adjusted odds ratio	95% CI (low, high)	Test of Heterogeneity
vitamins	AML	0.85	(0.64, 1.14)	

Notes:

31.3. Statistical Method(s)

Results: ALL, folic acid, any time; ALL, folic acid, preconception; ALL, folic acid, pregnancy; ALL, vitamins, any time; ALL, vitamins, preconception; ALL, vitamins, pregnancy; AML, folic acid, any time; AML, folic acid, preconception; AML, folic acid, pregnancy; AML, vitamins, any time; AML, vitamins, preconception; AML, vitamins, pregnancy

Adjustment factors: age, ethnicity, parental education, sex, study

Statistical metric description: Study-specific and pooled odds ratios (ORs), as well as approximate 95% confidence intervals (CIs), were estimated from unconditional logistic regression models, separately for all and a Ml, and by immunophenotype for all (B- and t-cell lineage). All variables except mother's age at delivery, child's age at diagnosis (and corresponding age for controls), and birth weight were categorical. Models were adjusted for child's age, sex, ethnicity, and parental education level, as these variables were either matching factors in the individually matched studies or treated as confounders. We present models without and with adjustment for study center (Models 1 and 2, respectively) for the main analyses on use of vitamin/folic acid supplements any time, preconception, and during pregnancy; only study-adjusted models (Model 2) are presented for additional analyses. Overall, adjusting for study center improved the fit of all models (P values for log-likelihood ratio test <0.001). Other variables (child's birth weight, maternal age at delivery, maternal alcohol intake, and child born before/after folic acid food fortification) were not included in the final models, as the ORs changed by less than 10%. We

conducted stratified analyses by sex, age at diagnosis (infants 0–1 year vs. older children), parental education (none/primary, secondary, and tertiary), maternal alcohol consumption (drinkers vs. nondrinkers), and folic acid food fortification (child born before vs. after). P values for heterogeneity between strata were obtained from the log-likelihood ratio test or Woolf 's test. In order to characterize the heterogeneity in vitamin and folic acid supplementation between participating childhood leukemia international consortium studies and to account for it in the analysis, we assessed between-study and within-study variability. Total variability N(p)(1–p) was partitioned into between-study variability (which represents the deviation of study-specific prevalence from the mean prevalence for all studies combined, weighted by the number of subjects in individual studies, V(B)=∑(Ni)(p(i)-p)^2) and within-study variability (which represents the deviation of individual subjects from the study-specific mean prevalence, weighted by the number of subjects in their corresponding study, V(W) = n(i)p(i)∑(1-p(i)), where N is the total number of cases and controls across all studies, n is the total number of subjects in each study, p is the proportion of women taking vitamins across all studies, and pi is the proportion of women taking vitamins in each study. For use of vitamins and folic acid any time and during pregnancy, VB accounted for approximately 33% to 44% of the total variability, whereas for preconception vitamin and folic acid intake VB accounted for about 16% of the total variability. Subsequently, we grouped the study sites into those contributing to either the lowest between-study variability (VB < 30% of total variability)or the highest between-study variability (VB ≥30% of total variability) and conducted stratified analyses for each group to assess the impact of study heterogeneity in Models 1 versus 2. The cut point for grouping studies with low versus high VB was driven by the data. Lastly, we conducted sensitivity analyses by systematically excluding 2 studies (out of 12) at a time, which resulted in 66 sets of 10 studies. For each set, we then computed the ORs and 95% CIs for each type and period of maternal supplementation. Out of a total of 66 ORs, we calculated the minimum, mean and maximum ORs, and the corresponding 95% CIs.

32. MILNE, 2010

Full citation: Milne E, Royle JA, Miller M, Bower C, de Klerk NH, Bailey HD, van Bockxmeer F, Attia J, Scott RJ, Norris MD, Haber M, Thompson JR, Fritschi L, Marshall GM, Armstrong BK. 2010. Maternal folate and other vitamin supplementation during pregnancy and risk of acute lymphoblastic leukemia in the offspring. Int J Cancer 126(11): 2690-2699.
Funding: Australian National Health and Medical Research Council (NHMRC), NHMRC, NBN Children's Cancer Research Fund, Cancer Institute NSW, Cancer Council NSW and the Leukaemia Foundation

32.1. Maternal folate and risk of ALL, with Aus-ALL Participants 2003-2007

Protocol: Maternal folate and risk of ALL, with Aus-ALL Participants 2003-2007	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
We searched PubMed for original studies of maternal folate and/or vitamin supplementation before and during pregnancy and risk of childhood ALL published from 1966 to 2008. The following search terms were used: pregnancy, leukemia, maternal, diet, dietary supplements, folic acid and medication. We also referred to 2 recent meta-analyses to ensure that we had identified all relevant articles.	**Inclusion Criteria:** case-control or cohort study, childhood ALL is an outcome, contain relevant information on the association between ALL and maternal folate supplementation and/or vitamin use, population-based **Exclusion Criteria:** hypothesis-generating study, restricted to any specific subgroup
Starting date: 1966-01-01	**Ending date:** 2008-01-01
Total references from search: 45	**References Included:** 7

Additional Notes: 6 identified from search, 1 included in this same publication.

32.2. Result(s)

32.2.A Acute Lymphoblastic Leukemia, Folate supplementation, Vitamins before pregnancy

Studies (2), Total Subjects (1918)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
Vitamins before pregnancy	Acute Lymphoblastic Leukemia	0.95	(0.77, 1.18)	I2 = 0.0%, p=0.455

Notes:

32.2.B Acute Lymphoblastic Leukemia, Folate supplementation, Vitamins during pregnancy

Studies (5), Total Subjects (8839)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
Vitamins during pregnancy	Acute Lymphoblastic Leukemia	0.83	(0.73, 0.94)	I2 = 42.6%, p=0.137

Notes:

32.2.C Acute Lymphoblastic Leukemia, Folate supplementation, Vitamins only before pregnancy

Studies (2), Total Subjects (5470)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
Vitamins only before pregnancy	Acute Lymphoblastic Leukemia	1.05	(0.55, 2.01)	I2 = 0.0%, p=0.611

Notes:

32.2.D Acute Lymphoblastic Leukemia, Folate supplementation, Vitamins with folate vs no folate during pregnancy

Studies (2), Total Subjects (2042)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
Vitamins with folate versus no folate during pregnancy	Acute Lymphoblastic Leukemia	1.06	(0.77, 1.46)	I2 = 0.0%, p=0.920

Notes:

32.2.E Acute Lymphoblastic Leukemia, Folate supplementation, Vitamins with folate vs no vitamins during pregnancy

Studies (2), Total Subjects (3220)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
Vitamins with folate versus no vitamins during pregnancy	Acute Lymphoblastic Leukemia	1.02	(0.86, 1.21)	I2 = 0.0%, p=0.722

Notes:

32.3. Statistical Method(s)

Results: Acute Lymphoblastic Leukemia, Folate supplementation, Vitamins before pregnancy; Acute Lymphoblastic Leukemia, Folate supplementation, Vitamins during pregnancy; Acute Lymphoblastic Leukemia, Folate supplementation, Vitamins only before pregnancy; Acute Lymphoblastic Leukemia, Folate supplementation, Vitamins with folate vs no folate during pregnancy; Acute Lymphoblastic Leukemia, Folate supplementation, Vitamins with folate vs no vitamins during pregnancy

Adjustment factors:

Statistical metric description: We extracted the most appropriate adjusted ORs from each study and used fixed effects, precision-based weighting to calculate the summary ORs with data from our study. Statistical heterogeneity among studies was assessed using the Cochrane Q test and the I2 statistic.

33. MYUNG, 2011

Full citation: Myung SK, Ju W, Kim SC, Kim H, Korean Meta-analysis Study G. 2011. Vitamin or antioxidant intake (or serum level) and risk of cervical neoplasm: a meta-analysis. BJOG 118(11): 1285-1291.

Funding: We received no funding.

33.1. Vitamin intake and risk of cervical neoplasm

Protocol: Vitamin intake and risk of cervical neoplasm	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
We searched MEDLINE (PubMed), EMBASE, and the Cochrane Library in November 2008 using selected common keywords regarding vitamin or antioxidant intake (or serum level) and cervical neoplasm (cervical dysplasia, carcinoma in situ [CIS], and cervical cancer) in case–control studies. We also scanned the bibliographies of relevant articles to identify additional studies. As the keywords for the literature search, we selected 'vitamin', 'antioxidant', 'retinol (vitamin A)', 'beta-carotene', 'carotenoids', 'ascorbic acid (vitamin C)', 'alpha-tocopherol (vitamin E)', 'folate', 'selenium' and 'lycopene' for the exposure factors; 'cervical cancer', 'cervical neoplasm' and 'cervical intraepithelial neoplasia', for the outcome factors; and 'case–control studies' for the study design.	**Inclusion Criteria:** case-control, English language article, exposure is vitamin or antioxidant intake, outcome is cervical neoplasm risk, report adjusted odds ratios (ORs) and 95% CIs **Exclusion Criteria:** studies reporting disease not confirmed by biopsy
Starting date:	**Ending date:** 2008-11-01
Total references from search: 240	**References Included:** 22

Additional Notes:

33.2. Result(s)

33.2.A cervical neoplasm, carcinoma in situ, folate intake

Studies (5), Total Subjects (2775)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
folate intake	cervical neoplasm, carcinoma in situ	0.47	(0.21, 1.09)	I2 = 71.8%

Notes: Random effects model

33.2.B cervical neoplasm, folate intake

Studies (9), Total Subjects (5203)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
folate intake	cervical neoplasm	0.6	(0.41, 0.88)	I2 = 59.8%

Notes: Fixed effects model

33.2.C cervical neoplasm, folate intake, studies adjusted for HPV

Studies (5), Total Subjects (2692)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
folate intake	cervical neoplasm	0.86	(0.64, 1.16)	I2 = 45.7%

Notes: Fixed effects model

33.2.D cervical neoplasm, folate intake, studies unadjusted for HPV

Studies (4), Total Subjects (2511)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
folate intake	cervical neoplasm	0.45	(0.25, 0.8)	I2 = 59.8%

Notes: Random effects model

33.2.E cervical neoplasm, invasive cancer, folate intake

Studies (4), Total Subjects (2428)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
folate intake	cervical neoplasm, invasive cancer	0.75	(0.57, 0.98)	I2 = 33.7%

Notes: Fixed effects model

33.3. Statistical Method(s)

Results: cervical neoplasm, carcinoma in situ, folate intake; cervical neoplasm, folate intake; cervical neoplasm, folate intake, studies adjusted for HPV; cervical neoplasm, folate intake, studies unadjusted for HPV; cervical neoplasm, invasive cancer, folate intake

Adjustment factors:

Statistical metric description: We used an adjusted OR with 95% CI of the highest intake (or serum level) group for the disease outcome variable compared with the lowest intake (or serum level) group reported in each study, whenever possible. The main analysis was to investigate the association between individual vitamin or antioxidant intake (or serum level) and risk of cervical neoplasm. We also conducted subgroup analyses by type of cervical neoplasm, i.e. CIS and invasive cervical cancer. A summary OR with 95% CI was estimated by using both fixed-effects and random-effects models. For assessing heterogeneity, we used the Higgins I2, which is calculated as follows: I2 = 100% x (Q-df)/Q; where Q is Cochran's heterogeneity statistic and df is degrees of freedom. Negative values of I2 are considered as zero. Values of I2 range from 0% (no heterogeneity) to 100% (maximal heterogeneity). We considered an I2 > 50% as having substantial heterogeneity. Woolfe's method (inverse variance method) was used in a fixed-effects model and the DerSimonian and Laird method was used in a random-effects model. We used Stata SE version 10.0 software package (StataCorp, College Station, TX, USA) for statistical analysis.

34. QIN, 2013

Full citation: Qin X, Cui Y, Shen L, Sun N, Zhang Y, Li J, Xu X, Wang B, Xu X, Huo Y, Wang X. 2013. Folic acid supplementation and cancer risk: A meta-analysis of randomized controlled trials. Int J Cancer 133(5): 1033-1041.
Funding: Major State Basic Research Development Program of China; Grant number: 973 programe; 2012CB517703;

34.1. Folic acid supplementation and cancer risk

Protocol: Folic acid supplementation and cancer risk	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
This report followed the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines. We searched the MEDLINE database (via PubMed) from January 1966 to October 2012, with the MeSH terms “cancer,” “adenoma,” “malignancy,” “tumor” and “folic acid,” “folate,” “homocysteine.” Manual searches of bibliographies from all of the relevant trials and review articles also were conducted. The searches were restricted to human studies and clinical trials, but there were no language restrictions. A team of experts in the relevant field was assembled.	**Inclusion Criteria:** assessed cancer incidence and/or cancer mortality, intervention consisted of folic acid supplementation (with or without additional B vitamins), intervention duration at least 6 months, Randomized clinical trials **Exclusion Criteria:**
Starting date: 1966-01-01	**Ending date:** 2012-10-01
Total references from search: 517	**References Included:** 15

Additional Notes:

34.2. Result(s)

34.2.A breast cancer, folic acid

Studies (4), Total Subjects (19800)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid treatment	breast cancer incidence	0.82	(0.63, 1.07)	not significant (p>0.10 and I2<50%)

Notes: P = 0.15

34.2.B cancer, folic acid, <= 1 mg/day, low median

Studies (6), Total Subjects (11972)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid treatment	hematological malignancy	1.23	(1.06, 1.43)	

Notes: P = 0.007

34.2.C cancer, folic acid, > 1 mg/day, high median

Studies (7), Total Subjects (37434)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid treatment	hematological malignancy	1.02	(0.95, 1.09)	

Notes: P = 0.64

34.2.D colorectal cancer, folic acid

Studies (7), Total Subjects (33824)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid treatment	colorectal cancer incidence	1.01	(0.82, 1.23)	not significant (p>0.10 and I2<50%)

Notes: P = 0.95

34.2.E hematological malignancy, folic acid

Studies (3), Total Subjects (25670)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid treatment	hematological malignancy	0.87	(0.64, 1.17)	not significant (p>0.10 and I2<50%)

Notes: P = 0.35

34.2.F lung cancer, folic acid

Studies (5), Total Subjects (31864)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid treatment	lung cancer incidence	1.0	(0.84, 1.21)	not significant (p>0.10 and I2<50%)

Notes: P = 0.97

34.2.G melanoma, folic acid

Studies (3), Total Subjects (19128)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid treatment	melanoma incidence	0.47	(0.23, 0.94)	not significant (p>0.10 and I2<50%)

Notes: P = 0.03

34.2.H other gastrointestinal cancer, folic acid

Studies (2), Total Subjects (20228)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid treatment	other gastrointestinal cancer incidence	1.0	(0.75, 1.33)	not significant (p>0.10 and I2<50%)

Notes: P = 0.99

34.2.I other genitourinary cancer, folic acid

Studies (2), Total Subjects (20228)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid treatment	other genitourinary cancer incidence	0.97	(0.75, 1.27)	not significant (p>0.10 and I2<50%)

Notes: P = 0.84

34.2.J prostate cancer, folic acid

Studies (5), Total Subjects (27065)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid treatment	prostate cancer incidence	1.17	(0.84, 1.62)	p = 0.07; I2 = 54.3%

Notes: P = 0.35

34.2.K total cancer incidence, folic acid, fortified, fixed effects

Studies (6), Total Subjects (13377)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid treatment	total cancer incidence	1.01	(0.89, 1.15)	I2 = 2.8%, p = 0.3984

Notes:

34.2.L total cancer incidence, folic acid, fortified, random effects

Studies (6), Total Subjects (13377)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid treatment	total cancer incidence	1.02	(0.89, 1.16)	I2 = 2.8%, p = 0.3984

Notes:

34.2.M total cancer incidence, folic acid, overall, fixed effects

Studies (13), Total Subjects (49406)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid treatment	total cancer incidence	1.05	(0.99, 1.11)	I2 = 0%, p = 0.5273

Notes:

34.2.N total cancer incidence, folic acid, overall, random effects

Studies (13), Total Subjects (49406)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid treatment	total cancer incidence	1.05	(0.99, 1.11)	I2 = 0%, p = 0.5273

Notes:

34.2.O total cancer incidence, folic acid, unfortified, fixed effects

Studies (6), Total Subjects (30507)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid treatment	total cancer incidence	1.06	(0.98, 1.15)	I2 = 9.7%, p = 0.354

Notes:

34.2.P total cancer incidence, folic acid, unfortified, random effects

Studies (6), Total Subjects (30507)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid treatment	total cancer incidence	1.06	(0.97, 1.17)	I2 = 9.7%, p = 0.354

Notes:

34.3. Statistical Method(s)

Results: breast cancer, folic acid; cancer, folic acid, > 1 mg/day, high median; cancer, folic acid, <= 1 mg/day, low median; colorectal cancer, folic acid; hematological malignancy, folic acid; lung cancer, folic acid; melanoma, folic acid; other gastrointestinal cancer, folic acid; other genitourinary cancer, folic acid; prostate cancer, folic acid; total cancer incidence, folic acid, fortified, fixed effects; total cancer incidence, folic acid, fortified, random effects; total cancer incidence, folic acid, overall, fixed effects; total cancer incidence, folic acid, overall, random effects; total cancer incidence, folic acid, unfortified, fixed effects; total cancer incidence, folic acid, unfortified, random effects

Adjustment factors:

Statistical metric description: Relative risk (RR) with a 95% confidence interval (95% CI) was used to measure the effect of folic acid supplementation on cancer incidence and cancer mortality. All RRs reflect the risk in the group allocated to folic acid supplementation relative to the control group. Heterogeneity between studies was assessed by Cochran's Q test with a significance level set at 0.10. The I2 statistic was also examined, and we considered I2 >50% to indicate relevant heterogeneity. As it is unlikely that all of the heterogeneity in the results is due to the treatment itself, summary estimates of RR and 95% CIs were obtained by using random-effect (DerSimonian and Laird) models. We used the following approaches to evaluate potential effect modification. First of all, we performed subgroup analyses according to cancer types, folic acid fortification (fortified, unfortified and partly fortified), sex, the dose of folic acid, intervention duration, percent baseline current smoker, percent baseline diabetes, percent use of antiplatelet agents, percent use of lipid-lowering drugs and percent baseline hypertension. For the continuous variables, subgroups were defined based on above or below the median values. Second, we used meta-regression analyses to further quantify and test statistical

significance of the effect modification. In the regression models, we considered mean age, sex, the dose of folic acid, intervention duration, mean body mass index (BMI), percent baseline current smoker, percent baseline diabetes, percent use of antiplatelet agents, percent use of lipid-lowering drugs and percent baseline hypertension. This meta-regression was performed with these factors specified as random effects (mixed models). Estimation of the residual between-trial variance was based on a restricted maximum likelihood method. The potential for publication bias was examined using a funnel plot, Peter's test and Egger regression test. We also conducted a sensitivity analysis by removing each individual trial from the meta-analysis. All of the analyses were done using R software, version 2.13.0 (http://www.R-project.org/).

35. SANJOAQUIN, 2005

Full citation: Sanjoaquin MA, Allen N, Couto E, Roddam AW, Key TJ. 2005. Folate intake and colorectal cancer risk: a meta-analytical approach. Int J Cancer 113(5): 825-828.
Funding: Cancer Research U.K.

35.1. Folate intake and colorectal cancer

Protocol: Folate intake and colorectal cancer	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
We conducted electronic searches of the PubMed database, which includes articles back to the 1950s and up to January 2004, using both MeSH headings and text words including the terms "folate," "folic acid," "colorectal," "colon," "rectum," "bowel," "cancer" and exploded variants. All full articles that matched the inclusion criteria were retrieved and the reference lists in those articles were hand-searched for other relevant publications.	**Inclusion Criteria:** English language article, exposure is folate intake, outcome is colorectal cancer, provide relative risk estimates (or odds ratios in case-control studies) with confidence intervals or sufficient data to allow calculation of these effect measures **Exclusion Criteria:**
Starting date: 1950-01-01	**Ending date:** 2004-01-31
Total references from search:	**References Included:** 16

Additional Notes:

35.2. Result(s)

35.2.A colorectal cancer, dietary folate, case-control

Studies (7), Total Subjects (15842)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
dietary folate intake	colorectal cancer	0.76	(0.6, 0.96)	x2 = 23.10, p = 0.01

Notes:

35.2.B colorectal cancer, dietary folate, cohort

Studies (5), Total Subjects (2394)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
dietary folate intake	colorectal cancer	0.75	(0.64, 0.89)	x2 = 4.96, p = 0.67

Notes: N reflects the number of cases; total N was not given.

35.2.C colorectal cancer, total folate, case-control

Studies (3), Total Subjects (2467)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
total folate intake	colorectal cancer	0.81	(0.62, 1.05)	x2 = 2.39, p = 0.50

Notes:

35.2.D colorectal cancer, total folate, cohort

Studies (3), Total Subjects (2689)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
total folate intake	colorectal cancer	0.95	(0.81, 1.11)	x2 = 4.57, p = 0.33

Notes: N reflects the number of cases; total N was not given.

35.3. Statistical Method(s)

Results: colorectal cancer, dietary folate, case-control; colorectal cancer, dietary folate, cohort; colorectal cancer, total folate, case-control; colorectal cancer, total folate, cohort

Adjustment factors:

Statistical metric description: The studies mostly reported relative risks according to quintiles (cohort studies) or quartiles (case-control studies) of folate intake; therefore, for this analysis, they were transformed using an established method so that all the meta-analyses are based on the relative risk in the top vs. bottom quintiles of intake for cohort studies and top vs. bottom quartiles for case-control studies. Summary estimates of the standardized RRs were derived using random- and fixed-effect models; both yielded similar results and only estimates from random-effect models are presented. The 95% CIs from the original publications were used to calculate the standard errors of the standardized RRs, and the weighted average of the RRs was calculated by giving each study a weight proportional to its precision (i.e., the inverse of the variance). Thus, larger studies, with more precise estimates and narrower confidence intervals, were given greater weight than smaller ones. We tested for heterogeneity using Cochran's Q-test to evaluate the consistency of findings. Separate analyses were performed for cohort and case-control studies. A metaregression analysis was performed to investigate whether the association between folate intake and risk differed according to sex, endpoint (colon or rectum) and source of folate (from foods only or foods plus supplements). The results are presented graphically, whereby squares represent study-specific estimates and diamonds represent pooled estimates. The area of each square is proportional to the inverse of the variance of the natural logarithm of the RR; 95% CIs for individual RRs are represented by horizontal lines and for the pooled estimates by the width of the diamonds. All the analyses were performed using the statistical package Stata 8.0 (StataCorp, College Station, TX).

36. TIO, 2014A

Full citation: Tio M, Andrici J, Cox MR, Eslick GD. 2014a. Folate intake and the risk of upper gastrointestinal cancers: a systematic review and meta-analysis. J Gastroenterol Hepatol 29(2): 250-258.
Funding: None

36.1. Folate intake and upper gastrointestinal cancers

Protocol: Folate intake and upper gastrointestinal cancers	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
We followed the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines in performing our systematic review. Relevant articles were identified by two reviewers (M.T. and J.A.) by systematically searching through MEDLINE (from 1950), PubMed (from 1946), EMBASE (from 1949), and Current Contents Connect (from 1998) through to July 26, 2013. The search was performed using the terms folate, folic acid, or vitamin B9, and esophageal, gastric, stomach, or pancreatic cancer, neoplasm, squamous cell carcinoma, or adenocarcinoma. The search terms used were searched as text word and as exploded medical subject headings where possible. The reference lists of relevant articles were also searched for appropriate studies. No language restrictions were used in either the search or study selection. A search for unpublished literature was not performed. Disagreement on article inclusion between the two reviewers was resolved via a third reviewer (G.E.).	**Inclusion Criteria:** case-control or cohort study, exposure is dietary folate intake (ie, folate from foods), total folate intake (ie, folate from foods and dietary supplements), or blood folate levels, outcome is esophageal, gastric, or pancreatic cancer, report the 95% confidence interval (CI), report the risk point estimate as an odds ratio (OR), hazard ratio, or relative risk that compared a higher level of folate intake with a lower level of folate intake, use an internal comparison when calculating the risk estimate **Exclusion Criteria:** meta-analyses of studies
Starting date: 1946-01-01	**Ending date:** 2013-07-26
Total references from search: 3477	**References Included:** 36

Additional Notes:

36.2. Result(s)

36.2.A esophageal adenocarcinoma, retrospective, dietary folate intake

Studies (3), Total Subjects (3546)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate intake	esophageal adenocarcinoma	0.57	(0.43, 0.76)	I2 = 44.9%, P = 0.16

Notes:

36.2.B esophageal cancer, dietary folate intake

Studies (9), Total Subjects (11537)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate intake	esophageal cancer	0.59	(0.51, 0.69)	

Notes: p-value = 0.00

36.2.C esophageal squamous cell carcinoma, retrospective, dietary folate intake

Studies (4), Total Subjects (3977)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate intake	esophageal squamous cell carcinoma	0.63	(0.44, 0.89)	I2 = 47.7%, P = 0.13

Notes:

36.2.D gastric cancer, dietary folate intake

Studies (16), Total Subjects (209689)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate intake	gastric cancer	0.98	(0.81, 1.19)	

Notes: p-value = 0.83

36.2.E gastric cancer, prospective, dietary folate intake

Studies (3), Total Subjects (197159)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate intake	gastric cancer	1.19	(0.92, 1.54)	I2 = 0.0%, P = 0.70

Notes:

36.2.F gastric cancer, retrospective, dietary folate intake

Studies (8), Total Subjects (12530)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate intake	gastric cancer	0.87	(0.7, 1.09)	I2 = 56.2%, P = 0.01

Notes:

36.2.G pancreatic cancer, dietary folate intake

Studies (8), Total Subjects (295526)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate intake	pancreatic cancer	0.66	(0.49, 0.89)	

Notes: p-value = 0.01

36.2.H pancreatic cancer, prospective and retrospective, plasma folate

Studies (4), Total Subjects (2215)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
plasma folate	pancreatic cancer	0.73	(0.47, 1.13)	I2 = 67.1%, p = 0.03

Notes:

36.2.I pancreatic cancer, prospective and retrospective, total folate intake

Studies (4), Total Subjects (261727)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
total folate intake	pancreatic cancer	0.69	(0.47, 1.03)	I2 = 62.7%, p = 0.04

Notes:

36.2.J pancreatic cancer, prospective, dietary folate intake

Studies (5), Total Subjects (291958)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate intake	pancreatic cancer	0.65	(0.38, 1.11)	I2 = 80.1%, p <0.0001

Notes:

36.2.K pancreatic cancer, retrospective, dietary folate intake

Studies (3), Total Subjects (3568)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate intake	pancreatic cancer	0.67	(0.49, 0.91)	I2 = 42.0%, p = 0.18

Notes:

36.3. Statistical Method(s)

Results: esophageal adenocarcinoma, retrospective, dietary folate intake; esophageal cancer, dietary folate intake; esophageal squamous cell carcinoma, retrospective, dietary folate intake; gastric cancer, dietary folate intake; gastric cancer, prospective, dietary folate intake; gastric cancer, retrospective, dietary folate intake; pancreatic cancer, dietary folate intake; pancreatic cancer, prospective and retrospective, plasma folate; pancreatic cancer, prospective and retrospective, total folate intake; pancreatic cancer, prospective, dietary folate intake; pancreatic cancer, retrospective, dietary folate intake

Adjustment factors:

Statistical metric description: Pooled estimates of the OR and 95% CI for the risk of esophageal cancer, gastric cancer, and pancreatic cancer in association with folate were calculated using the random effects model of DerSimonian and Laird. Heterogeneity was assessed using the I2 statistic, which determines the proportion of variability across studies that is due to heterogeneity as opposed to sampling error. Sensitivity analyses were performed when statistically significantly heterogeneity was detected.

Subgroup analyses stratified by either study design or histological subtype were also performed. We pre-specified analyses of meta-regression of log OR versus highest absolute folate intake level, lowest absolute folate intake level, and difference between highest and lowest absolute folate intake level. Publication bias was assessed with Egger's regression model. If publication bias was detected, the additional publication bias methods consisting of the fail-safe number method and the trim-and-fill method were employed to quantify the effect of the bias. The fail-safe number method calculates the number of unpublished studies needed to convert the observed result to statistical non-significance at the alpha level of significance $P<0.05$ level. Publication bias is considered to be an issue if the fail-safe number is less than $5n+10$, where n is the number of studies included in the meta-analysis. The trim-and-fill method simulates unpublished studies in the meta-analysis to calculate a new pooled OR, which is then compared with the original pooled OR. If the new pooled OR is similar to the original pooled OR, this indicates that publication bias has little effect on the meta-analysis results. Results were regarded as statistically significant if $P<0.05$. All analyses were done with Comprehensive Meta-analysis (version 2.0; Biostat, Englwood, NJ, USA).

37. TIO, 2014B

Full citation: Tio M, Andrici J, Cox MR, Eslick GD. 2014b. Folate intake and the risk of prostate cancer: a systematic review and meta-analysis. Prostate cancer and prostatic diseases 17(3): 213-219.
Funding: None reported

37.1. Folate intake and risk of prostate cancer

Protocol: Folate intake and risk of prostate cancer	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
We followed the Meta-Analysis of Observational Studies in Epidemiology guidelines in performing our systematic review. 14 Relevant articles were identified by two reviewers (MT and JA) by systematically searching through MEDLINE (from 1950), PubMed (from 1946), EMBASE (from 1949) and Current Contents Connect (from 1998) through to 11 October 2013. A third reviewer (GE) adjudicated any disagreement on study inclusion. The search used the terms 'folate' OR 'folic acid' OR 'vitamin B9' AND 'prostate cancer' OR 'prostate neoplasms'. The search terms used were searched as text word and as exploded medical subject headings where possible. The reference lists of relevant articles were also searched for appropriate studies. No language restrictions were used in either the search or study selection. A search for unpublished literature was not performed.	**Inclusion Criteria:** case-control or cohort study, exposure is dietary folate intake (ie, folate from foods), total folate intake (ie, folate from foods and dietary supplements), or blood folate levels, outcome is risk of prostate cancer, report the 95% confidence interval (CI), report the risk point estimate as an odds ratio (OR), hazard ratio, or relative risk, or incidence rate ratio that compared a higher level of folate intake with a lower level of folate intake, use an internal comparison when calculating the risk estimate **Exclusion Criteria:**
Starting date: 1946-01-01	**Ending date:** 2013-10-11
Total references from search: 1115	**References Included:** 19

Additional Notes:

37.2. Result(s)

37.2.A prostate cancer, blood folate

Studies (7), Total Subjects (13232)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
blood folate	prostate cancer	1.43	(1.06, 1.93)	I2 = 79.5%, P <0.01

Notes: p-value = 0.02; N given in text (10,232) differs from N calculated by hand (13,232)

37.2.B prostate cancer, dietary folate

Studies (11), Total Subjects (146782)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	prostate cancer	0.97	(0.89, 1.06)	I2 = 41.9%, P = 0.07

Notes: p-value = 0.50

37.2.C **prostate cancer, total folate**

Studies (5), Total Subjects (93781)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
total folate	prostate cancer	0.99	(0.82, 1.19)	I2 = 48.2%, P = 0.10

Notes: p-value = 0.89

37.3. Statistical Method(s)

Results: prostate cancer, blood folate; prostate cancer, dietary folate; prostate cancer, total folate

Adjustment factors:

Statistical metric description: Pooled estimates of the OR and 95% CI for the risk of prostate cancer in association with folate were calculated using the random-effects model of DerSimonian and Laird. Heterogeneity was assessed using the I2 statistic, which determines the proportion of variability across studies that is due to heterogeneity as opposed to sampling error.16 Sensitivity analyses were performed when statistically significantly heterogeneity was detected. Subgroup analyses stratified by either study design or population group were also performed. Meta-regression was performed when heterogeneity remained after sensitivity and subgroup analysis. Our pre-specified metaregression analyses compared the log ORs versus the highest absolute folate level, lowest absolute folate level and difference between the highest and lowest absolute folate level. Publication bias was assessed with Egger's regression model. Results were regarded as statistically significant if $P<0.05$. All analyses were done with Comprehensive Metaanalysis (version 2.0).

38. TIO, 2014C

Full citation: Tio M, Andrici J, Eslick GD. 2014c. Folate intake and the risk of breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat 145(2): 513-524.
Funding: None reported

38.1. Folate intake and breast cancer

Protocol: Folate intake and breast cancer	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
We followed the meta-analysis of observational studies in epidemiology (MOOSE) guidelines in performing our systematic review. Relevant articles were identified by two reviewers (M.T. and J.A.) by systematically searching through MEDLINE (from 1950), PubMed (from 1946), EMBASE (from 1949) and Current Contents Connect (from 1998) through to March 2nd, 2014. The search used the terms ''folate'' or ''folic acid'' or ''vitamin B9'' and ''breast cancer'' or ''breast neoplasms.'' The search terms used were searched as text word and as exploded medical subject headings where possible. The reference lists of relevant articles were also searched for appropriate studies. No language restrictions were used in either the search or study selection. A search for unpublished literature was not performed. Disagreement on article inclusion between the two reviewers was resolved via a third reviewer (G.E.).	**Inclusion Criteria:** breast cancer outcome, case-control or cohort study, exposure is dietary folate intake (ie, folate from foods), total folate intake (ie, folate from foods and dietary supplements), or blood folate levels, report the 95% confidence interval (CI), report the risk point estimate as an odds ratio (OR), hazard ratio, or relative risk, or incidence rate ratio that compared a higher level of folate intake with a lower level of folate intake, use an internal comparison when calculating the risk estimate **Exclusion Criteria:** meta-analyses of studies
Starting date: 1950-01-01	**Ending date:** 2014-03-02
Total references from search: 3716	**References Included:** 49

Additional Notes:

38.2. Result(s)

38.2.A breast cancer, blood folate level

Studies (7), Total Subjects (5226)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
blood folate level	breast cancer	0.86	(0.6, 1.25)	I2 = 70.3%, p < 0.01

Notes:

38.2.B breast cancer, blood folate level, ER+

Studies (2), Total Subjects (2100)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
blood folate level	breast cancer	1.59	(1.19, 2.12)	I2 = 0.0%, p = 0.45

Notes:

38.2.C breast cancer, blood folate level, ER-

Studies (2), Total Subjects (2100)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
blood folate level	breast cancer	1.02	(0.52, 2.0)	I2 = 0.0%, p = 0.48

Notes:

38.2.D breast cancer, dietary folate

Studies (36), Total Subjects (607625)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	breast cancer	0.84	(0.77, 0.91)	I2 = 71.2%, p < 0.01

Notes: Calculated N (607,625) does not match N reported in text (608,265).

38.2.E breast cancer, dietary folate , ER+

Studies (6), Total Subjects (214606)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	breast cancer	0.91	(0.77, 1.08)	I2 = 67.8%, p < 0.01

Notes:

38.2.F breast cancer, dietary folate , ER+/PR+

Studies (6), Total Subjects (183322)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	breast cancer	0.92	(0.69, 1.22)	I2 = 78.8%, p < 0.01

Notes:

38.2.G breast cancer, dietary folate , ER+/PR-

Studies (4), Total Subjects (89329)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	breast cancer	0.89	(0.72, 1.1)	I2 = 0.0%, p = 0.68

Notes:

38.2.H breast cancer, dietary folate , ER-

Studies (9), Total Subjects (379382)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	breast cancer	0.96	(0.83, 1.11)	I2 = 8.95%, p = 0.36

Notes:

38.2.I breast cancer, dietary folate , ER-/PR+

Studies (2), Total Subjects (27100)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	breast cancer	0.49	(0.17, 1.42)	I2 = 55.9%, p = 0.13

Notes:

38.2.J breast cancer, dietary folate , ER-/PR-

Studies (6), Total Subjects (183322)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	breast cancer	0.97	(0.81, 1.17)	I2 = 0.0%, p = 0.82

Notes:

38.2.K breast cancer, dietary folate , PR+

Studies (4), Total Subjects (150237)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	breast cancer	0.81	(0.53, 1.24)	I2 = 86.2%, p < 0.01

Notes:

38.2.L breast cancer, dietary folate , PR-

Studies (6), Total Subjects (212466)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
dietary folate	breast cancer	1.01	(0.9, 1.13)	I2 = 0.0%, p = 0.80

Notes:

38.2.M breast cancer, total folate intake

Studies (15), Total Subjects (544460)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
total folate intake	breast cancer	0.98	(0.91, 1.07)	I2 = 71.2%, p < 0.01

Notes: Calculated N (544,460) does not match N reported in text (521,474).

38.2.N breast cancer, total folate intake, ER+

Studies (5), Total Subjects (189234)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
total folate intake	breast cancer	1.0	(0.97, 1.04)	I2 = 0.0%, p = 0.69

Notes:

38.2.O breast cancer, total folate intake, ER+/PR-

Studies (2), Total Subjects (87657)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
total folate intake	breast cancer	0.83	(0.68, 1.02)	I2 = 0.0%, p = 0.71

Notes:

38.2.P breast cancer, total folate intake, ER-

Studies (6), Total Subjects (279897)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
total folate intake	breast cancer	0.93	(0.82, 1.05)	I2 = 60.5%, p = 0.02

Notes:

38.2.Q breast cancer, total folate intake, PR+

Studies (3), Total Subjects (149361)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
total folate intake	breast cancer	1.01	(0.97, 1.04)	I2 = 0.0%, p = 0.69

Notes:

38.2.R breast cancer, total folate intake, PR-

Studies (3), Total Subjects (149361)

Exposure	Assessed Outcome	crude odds ratio	95% CI (low, high)	Test of Heterogeneity
total folate intake	breast cancer	1.0	(0.94, 1.05)	I2 = 0.0%, p = 0.57

Notes:

38.3. Statistical Method(s)

Results: breast cancer, blood folate level; breast cancer, blood folate level, ER-; breast cancer, blood folate level, ER+; breast cancer, dietary folate ; breast cancer, dietary folate , ER-; breast cancer, dietary folate , ER+; breast cancer, dietary folate , ER-/PR-; breast cancer, dietary folate , ER-/PR+; breast cancer, dietary folate , ER+/PR-; breast cancer, dietary folate , ER+/PR+; breast cancer, dietary folate , PR-; breast cancer, dietary folate , PR+; breast cancer, total folate intake; breast cancer, total folate intake, ER-; breast cancer, total folate intake, ER+; breast cancer, total folate intake, ER+/PR-; breast cancer, total folate intake, PR-; breast cancer, total folate intake, PR+

Adjustment factors:

Statistical metric description: Pooled estimates of the OR and 95 % CI for the risk of breast cancer in association with folate were calculated using the random-effects model of DerSimonian and Laird. Heterogeneity was assessed using the I2 statistic, which determines the proportion of variability across studies that is due to heterogeneity as opposed to sampling error. Sensitivity analyses were performed when statistically significantly heterogeneity was detected. Subgroup analyses stratified by either study design or population group were also performed. Meta-regression was performed when heterogeneity remained after sensitivity and subgroup analysis. Our pre-specified meta-regression analyses compared the log odd ratios versus highest absolute folate level, lowest absolute folate level, and difference between highest and lowest absolute folate level. Publication bias was assessed with Egger's regression model. If publication bias was detected, then the additional publication bias methods consisting of the fail-safe number method and the trim-and-fill method were employed to quantify the effect of the bias. The fail-safe number method calculates the number of unpublished studies needed to convert the observed result to statistical non-significance at the alpha level of significance $p < 0.05$ level. Publication bias is considered to be an issue if the fail-safe number is less than $5 n + 10$, where n is the number of studies included in the meta-analysis. The trim-and-fill method simulates unpublished studies in the meta-analysis to calculate a new pooled OR, which is then compared to the original pooled OR. If the new pooled OR is similar to the original pooled OR, then this indicates that publication bias has little effect on the meta-analysis results. Results were regarded as statistically significant if $p < 0.05$. All analyses were done with Comprehensive Meta-analysis (version 2.0), Englewood, NJ, USA (2005).

39. VOLLSET, 2013

Full citation: Vollset SE, Clarke R, Lewington S, Ebbing M, Halsey J, Lonn E, Armitage J, Manson JE, Hankey GJ, Spence JD, Galan P, Bonaa KH, Jamison R, Gaziano JM, Guarino P, Baron JA, Logan RF, Giovannucci EL, den Heijer M, Ueland PM, Bennett D, Collins R, Peto R, Collaboration BVTT. 2013. Effects of folic acid supplementation on overall and site-specific cancer incidence during the randomised trials: meta-analyses of data on 50,000 individuals. Lancet 381(9871): 1029-1036.
Funding: British Heart Foundation, Medical Research Council, Cancer Research UK, Food Standards Agency

39.1. Folic acid supplementation and site-specific cancer incidence

Protocol: Folic acid supplementation and site-specific cancer incidence	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
We identified trials by searching PubMed using the search terms "randomized trials", "folic acid", "B-vitamins" or "homocysteine-lowering treatment", and by scanning reference lists of trial reports (appendix p 3). Trials were eligible for inclusion if (1) at least one randomised comparison was folic acid versus placebo with scheduled treatment duration of at least 1 year (irrespective of whether any other treatment was tested factorially); (2) the trial included at least 500 participants; and (3) data on cancer incidence had been recorded. We sought for unpublished trials completed before 2011 through electronic searches and discussions with other experts in the field, but did not find any. (As of Jan 1, 2013, we still know of no such trials completed since 2010.) We obtained individual participant datasets for all 49 621 participants in the 13 trials completed by the end of 2010 (table 1, appendix p 6). Information about cancer incidence was not recorded in two other trials with a total of 5992 participants. The protocol for trial identification, analysis and involvement of trialists was agreed following discussion with all collaborators before any cancer results emerged.	**Inclusion Criteria:** data on cancer incidence was recorded, exposure is folate intake, has a placebo control, randomized controlled trials, scheduled treatment duration of at least 1 year, trial included at least 500 participants **Exclusion Criteria:**
Starting date:	**Ending date:** 2013-01-01
Total references from search:	**References Included:** 13

Additional Notes:

39.2. Result(s)

39.2.A **cancer incidence at 1 year follow-up; folic acid**

Studies (13), Total Subjects (49621)

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity
folic acid	cancer incidence at 1 year follow-up	0.89	(0.74, 1.07)	

Notes:

39.2.B cancer incidence at 2 year follow-up; folic acid

Studies (13), Total Subjects (49621)

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity
folic acid	cancer incidence at 2 year follow-up	1.16	(0.96, 1.4)	

Notes:

39.2.C cancer incidence at 3 year follow-up; folic acid

Studies (13), Total Subjects (49621)

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity
folic acid	cancer incidence at 3 year follow-up	1.13	(0.92, 1.39)	

Notes:

39.2.D cancer incidence at 4 year follow-up; folic acid

Studies (13), Total Subjects (49621)

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity
folic acid	cancer incidence at 4 year follow-up	1.11	(0.88, 1.4)	

Notes:

39.2.E cancer incidence at 5 year follow-up; folic acid

Studies (13), Total Subjects (49621)

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity
folic acid	cancer incidence at 5 year follow-up	1.09	(0.85, 1.4)	

Notes:

39.2.F cancer incidence at 6+ year follow-up; folic acid

Studies (13), Total Subjects (49621)

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity
folic acid	cancer incidence at 6+ year follow-up	1.01	(0.82, 1.24)	

Notes:

39.2.G cancer incidence; bladder; folic acid

Studies (13), Total Subjects (49621)

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity
folic acid	bladder cancer incidence	0.97	(0.68, 1.39)	

Notes: p = 1.00

39.2.H cancer incidence; brain; folic acid

Studies (13), Total Subjects (49621)

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity
folic acid	brain cancer incidence	1.27	(0.6, 2.69)	

Notes: p = 1.00

39.2.I cancer incidence; breast; folic acid

Studies (13), Total Subjects (49621)

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity
folic acid	breast cancer incidence	0.89	(0.66, 1.2)	

Notes: p = 1.00

39.2.J cancer incidence; colorectal; folic acid

Studies (13), Total Subjects (49621)

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity
folic acid	colorectal cancer incidence	1.07	(0.83, 1.37)	

Notes: p = 1.00

39.2.K cancer incidence; haematological; folic acid

Studies (13), Total Subjects (49621)

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity
folic acid	haematological cancer incidence	1.01	(0.72, 1.42)	

Notes: p = 1.00

39.2.Lcancer incidence; kidney; folic acid

Studies (13), Total Subjects (49621)

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity
folic acid	kidney cancer incidence	1.12	(0.68, 1.85)	

Notes: p = 1.00

39.2.M cancer incidence; larynx; folic acid

Studies (13), Total Subjects (49621)

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity
folic acid	larynx cancer incidence	0.89	(0.25, 3.11)	

Notes: p = 1.00

39.2.N cancer incidence; lip, mouth, pharynx; folic acid

Studies (13), Total Subjects (49621)

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity
folic acid	lip, mouth, pharynx cancer incidence	1.38	(0.66, 2.86)	

Notes: p = 1.00

39.2.O cancer incidence; liver or gall bladder; folic acid

Studies (13), Total Subjects (49621)

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity
folic acid	liver or gall bladder cancer incidence	1.01	(0.47, 2.15)	

Notes: p = 1.00

39.2.P cancer incidence; lung; folic acid

Studies (13), Total Subjects (49621)

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity
folic acid	lung cancer incidence	1.08	(0.86, 1.35)	

Notes: p = 1.00

39.2.Q cancer incidence; melanoma; folic acid

Studies (13), Total Subjects (49621)

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity
folic acid	melanoma incidence	1.04	(0.66, 1.64)	

Notes: p = 1.00

39.2.R cancer incidence; oesophagus; folic acid

Studies (13), Total Subjects (49621)

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity
folic acid	oesophagus cancer incidence	0.72	(0.36, 1.44)	

Notes: p = 1.00

39.2.S cancer incidence; ovary; folic acid

Studies (13), Total Subjects (49621)

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity
folic acid	ovary cancer incidence	0.88	(0.37, 2.15)	

Notes: p = 1.00

39.2.T cancer incidence; pancreas; folic acid

Studies (13), Total Subjects (49621)

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity
folic acid	pancreas cancer incidence	1.07	(0.59, 1.93)	

Notes: p = 1.00

39.2.U cancer incidence; prostate; folic acid

Studies (13), Total Subjects (49621)

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity
folic acid	prostate cancer incidence	1.15	(0.94, 1.41)	

Notes: p = 1.00

39.2.V cancer incidence; stomach; folic acid

Studies (13), Total Subjects (49621)

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity
folic acid	stomach cancer incidence	1.01	(0.58, 1.75)	

Notes: p = 1.00

39.2.W cancer incidence; uterus; folic acid

Studies (13), Total Subjects (49621)

Exposure	Assessed Outcome	relative risk	99% CI (low, high)	Test of Heterogeneity
folic acid	uterus cancer incidence	1.23	(0.63, 2.41)	

Notes: p = 1.00

39.2.X **overall first cancer incidence; folic acid**

Studies (13), Total Subjects (49621)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid	first cancer incidence	1.06	(0.99, 1.13)	X2 = 15.26; p = 0.23

Notes: p = 0.10

39.3. Statistical Method(s)

Results: cancer incidence at 1 year follow-up; folic acid; cancer incidence at 2 year follow-up; folic acid; cancer incidence at 3 year follow-up; folic acid; cancer incidence at 4 year follow-up; folic acid; cancer incidence at 5 year follow-up; folic acid; cancer incidence at 6+ year follow-up; folic acid; cancer incidence; bladder; folic acid; cancer incidence; brain; folic acid; cancer incidence; breast; folic acid; cancer incidence; colorectal; folic acid; cancer incidence; haematological; folic acid; cancer incidence; kidney; folic acid; cancer incidence; larynx; folic acid; cancer incidence; lip, mouth, pharynx; folic acid; cancer incidence; liver or gall bladder; folic acid; cancer incidence; lung; folic acid; cancer incidence; melanoma; folic acid; cancer incidence; oesophagus; folic acid; cancer incidence; ovary; folic acid; cancer incidence; pancreas; folic acid; cancer incidence; prostate; folic acid; cancer incidence; stomach; folic acid; cancer incidence; uterus; folic acid; overall first cancer incidence; folic acid

Adjustment factors:

Statistical metric description: We based comparisons of cancer rates by allocated treatment on intention-to-treat analyses of first events during the scheduled treatment period to calculate the event rate ratio (RR). The log-rank observed minus expected (o–e) statistics from each trial and their variances (v) were separately summed to produce, respectively, a grand total o–e statistic (G) and its variance (V). The one-step estimate of the log of the RR is then G/V with variance 1/V (and 95% CI G/V±1·96/√V). For n trials, a χ^2 statistic for heterogeneity with n–1 degrees of freedom (χ^2 n–1) is $S–G^2/V$, where S is the sum over all trials of $(o–e)^2/v$. We assessed the eff ects on cancer incidence in subgroups of year of follow-up (fi rst 3 years or later), age, sex, plasma folate concentration, plasma homocysteine concentration, and whether or not there was a nationwide folic acid fortifi cation programme. We investigated heterogeneity of the RRs in these subgroups by a global χ^2 test to reduce the chance of misinterpreting any false positive results arising from multiple com parisons. We used 99% CIs for individual trials or subgroups (again to avoid misinterpreting false positive results), but used 95% CIs for the overall findings. To correct for multiple comparisons, p values for particular types of cancer were multiplied by the number of types investigated (to a maximum corrected p value of 1·0). To help reassess the hypotheses of increased incidence of colorectal adenoma and prostate cancer raised by AFPPS, we assessed the effects of folic acid on colorectal and prostate cancer with and without exclusion of the AFPPS trial. The provision of (o–e) for each trial facilitates sensitivity analyses that exclude or include particular trials. Folate reduces homocysteine, and the mean reduction in all trials was the weighted mean of study-specific percent reductions in homocysteine, with weights proportional to the variances of the log-rank statistics for overall cancer incidence. We used Statistical Analysis System (SAS) version 9.2.

40. WIEN, 2012

Full citation: Wien TN, Pike E, Wisloff T, Staff A, Smeland S, Klemp M. 2012. Cancer risk with folic acid supplements: a systematic review and meta-analysis. BMJ open 2(1): e000653.
Funding: This work was supported by the Norwegian Knowledge Centre for the Health Services.

40.1. Cancer risk with folic acid supplements

Protocol: Cancer risk with folic acid supplements	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
To identify all relevant published reports, we performed a systematic literature search using medical subject headings (MeSH) and free-text search terms for folate, folic acid, cancer and neoplasm. We searched the following electronic databases and web pages from inception to present: Embase, Ovid Medline, Cochrane Library, Centre for Reviews and Dissemination, NHS evidence, Clinical evidence and ISI Web of Knowledge, AHRQ, INAHTA, SBU, DACEHTA and FINOHTA. The searches were conducted in March 2010, with supplementary searches in Embase, Medline and Cochrane Library on 6 May 2010. A filter for controlled studies was used in order to reduce number of hits. There were no limits by language, and non-English papers with a relevant English abstract were translated. The full search strategy including the search terms for the various databases is supplied at the web pages of the Norwegian Knowledge Centre for the Health Services. In addition, we manually searched reference lists of review articles and conducted limited updated non-systematic literature searches in the same electronic databases up to 31 January 2011. For ongoing studies, we searched WHO's International clinical trials registry platform and http://www.clinicaltrials.org, up to 10 February 2011. Study authors were not contacted for additional non-published studies.	**Inclusion Criteria:** assessed cancer incidence and/or cancer mortality, population taking folic acid supplements >=0.4 mg/day by oral route for any indication, systematic review, randomised controlled trial (RCT), or controlled observational study design **Exclusion Criteria:** folic acid given as part of high-dose cytostatic regimen of cancer treatment
Starting date:	**Ending date:** 2011-01-31
Total references from search: 3629	**References Included:** 21

Additional Notes: Additional hand retrievals and conducted through Jan 2011, and Cochrane search through February 2011. Folic acid could be taken with or without other B vitamins and compared with any control.

40.2. Result(s)

40.2.A <u>breast cancer incidence, cohorts, folic acid >=400ug/day</u>

Studies (2), Total Subjects (60423)

Exposure	Assessed Outcome	adjusted relative risk	95% CI (low, high)	Test of Heterogeneity

Exposure	Assessed Outcome	adjusted relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid intervention	breast cancer	1.02	(0.75, 1.39)	

Notes: results in text

40.2.B breast cancer incidence, RCTs, folic acid >=400ug/day vs. placebo/control

Studies (3), Total Subjects (11636)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid intervention	breast cancer	0.86	(0.65, 1.14)	

Notes: results in text

40.2.C colon and rectum cancer incidence, RCTs, folic acid >=400ug/day vs. placebo/control

Studies (8), Total Subjects (32639)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid intervention	colon and rectum cancer	1.0	(0.83, 1.21)	

Notes: results in text; states 9 RCTs included, but lists only 8

40.2.D haematological cancer incidence, RCTs, folic acid >=400ug/day vs. placebo/control

Studies (3), Total Subjects (24343)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid intervention	haematological cancer	1.16	(0.76, 1.78)	

Notes: results in text; states 4 RCTs included, but lists only 3

40.2.E lung cancer incidence, RCTs, folic acid >=400ug/day vs. placebo/control

Studies (5), Total Subjects (30537)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid intervention	haematological cancer	1.11	(0.92, 1.33)	

Notes: results in text; states 6 RCTs included, but lists only 5

40.2.F pancreas cancer incidence, cohorts, folic acid >=400ug/day

Studies (2), Total Subjects (234655)

Exposure	Assessed Outcome	adjusted relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid intervention	pancreas cancer	1.12	(0.9, 1.4)	

Notes: results in text

40.2.G prostate cancer incidence, RCTs, folic acid >=400ug/day vs. placebo/control

Studies (5), Total Subjects (25738)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid intervention	prostate cancer	1.24	(1.03, 1.49)	I2=17%, p=0.31

Notes: Test for overall effect Z=2.29 (p=0.02). (Favors control)

40.2.H total cancer incidence, RCTs, folic acid 400ug-1mg/day (sensitivity analysis)

Studies (4), Total Subjects (9469)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid intervention, 400ug-1mg/day	total cancer incidence	1.21	(1.06, 1.38)	

Notes:

40.2.I total cancer incidence, RCTs, folic acid >1mg/day (sensitivity analysis)

Studies (5), Total Subjects (28764)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid intervention, >1mg/day	total cancer incidence	1.03	(0.96, 1.11)	

Notes:

40.2.J total cancer incidence, RCTs, folic acid >=400ug/day vs. placebo/control

Studies (9), Total Subjects (38233)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid intervention	total cancer incidence	1.07	(1.0, 1.14)	I2=0%, p=0.45

Notes: Test for overall effect Z=2.10 (p=0.04). (Favors control)

40.2.K total cancer incidence, RCTs, folic acid in fortified countries (sensitivity analysis)

Studies (2), Total Subjects (7498)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid intervention, 400ug-1mg/day	total cancer incidence	0.95	(0.81, 1.13)	

Notes:

40.3. Statistical Method(s)

Results: prostate cancer incidence, RCTs, folic acid >=400ug/day vs. placebo/control; total cancer incidence, RCTs, folic acid >1mg/day (sensitivity analysis); total cancer incidence, RCTs, folic acid 400ug-1mg/day (sensitivity analysis); total cancer incidence, RCTs, folic acid >=400ug/day vs. placebo/control; total cancer incidence, RCTs, folic acid in fortified countries (sensitivity analysis)

Adjustment factors:
Statistical metric description: When feasible, we pooled data by meta-analyses with Cochrane Collaboration software (RevMan5) and used random-effects model calculating RRs with 95% CIs. For trials with factorial design, we compared all groups that received folic acid supplements >=0.4 mg/day with groups that did not. Analyses were conducted for both crude data and adjusted data when possible. For RCT's, analyses of crude data are presented in this article, and for observational data, adjusted analyses are presented. In our analyses of adjusted data, we used the analyses with the most explanatory variables if there were alternatives. These analyses were combined using generic inverse variance in RevMan5.

Results: breast cancer incidence, cohorts, folic acid >=400ug/day; breast cancer incidence, RCTs, folic acid >=400ug/day vs. placebo/control; colon and rectum cancer incidence, RCTs, folic acid >=400ug/day vs. placebo/control; haematological cancer incidence, RCTs, folic acid >=400ug/day vs. placebo/control; lung cancer incidence, RCTs, folic acid >=400ug/day vs. placebo/control; pancreas cancer incidence, cohorts, folic acid >=400ug/day
Adjustment factors:
Statistical metric description: When feasible, we pooled data by meta-analyses with Cochrane Collaboration software (RevMan5) and used random-effects model calculating RRs with 95% CIs. For trials with factorial design, we compared all groups that received folic acid supplements >0.4 mg/day with groups that did not. Analyses were conducted for both crude data and adjusted data when possible. For RCT's, analyses of crude data are presented in this article, and for observational data, adjusted analyses are presented. In our analyses of adjusted data, we used the analyses with the most explanatory variables if there were alternatives. These analyses were combined using generic inverse variance in RevMan5.

41. ZHANG, 2014A

Full citation: Zhang YF, Shi WW, Gao HF, Zhou L, Hou AJ, Zhou YH. 2014a. Folate intake and the risk of breast cancer: a dose-response meta-analysis of prospective studies. PLoS One 9(6): e100044.
Funding: This study was funded by the academic pacemaker programming in health systems, Pudong New Area, Shanghai (PWRD2012-12), Fund being innovative of science and technology development fund, Pudong New Area, Shanghai (PKJ2012-Y04) and the medicant project of Shuguang foundation of Chinese medical development office in Shanghai (2012JJHM012). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

41.1. Folate intake and risk of breast cancer

Protocol: Folate intake and risk of breast cancer	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement issued in 2009 (Checklist S1). Any prospective study that examined the relationship between folate intake and breast cancer was eligible for inclusion in our study, and no restrictions were placed on the publication language or status (published, in press, or in progress). We searched the PubMed, EmBase, and Cochrane Library electronic databases for articles published through June 2013 using the following search terms (''folate'' OR ''folic acid'') AND (''cancer'' OR ''neoplasm'' OR ''carcinoma'') AND (''cohort'' OR ''cohort studies'' OR ''nest case-control studies''). We also conducted manual searches of the reference lists from all relevant original and review articles to identify additional eligible studies. The medical subject headings, methods, patient populations, designs, exposures, and outcome variables of these articles were used to identify the relevant studies. Two of the authors (HFG and YFZ) conducted this literature search independently, according to a standardized approach. Any inconsistencies between the 2 authors were settled by the primary author (YHZ) until a consensus was reached. and included >2 folate intake categories. We excluded all case-control studies because various confounding factors could have biased the results.	**Inclusion Criteria:** authors reported the effect estimates (risk ratio [RR], hazard ratio [HR], or odds ratio [OR]) and 95% confidence intervals (CIs) for comparisons of highest and lowest category folate intake, breast cancer outcome, exposure is folate intake, included 2 or more folate intake categories, prospective cohort or nested prospective case-control study **Exclusion Criteria:** case-control
Starting date:	**Ending date:** 2013-06-30
Total references from search: 640	**References Included:** 19

Additional Notes:

41.2. Result(s)

41.2.A **breast cancer, folate intake, highest versus lowest**

Studies (14), Total Subjects (677858)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folate intake, highest versus lowest	breast cancer	0.97	(0.9, 1.05)	I = 57.5%, P = 0.004

Notes: P = 0.451

41.2.B **breast cancer, folate intake, per 100 ug/day**

Studies (14), Total Subjects (677858)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folate intake, per 100 ug/day	breast cancer	0.99	(0.98, 1.01)	I = 66.2%, P < 0.001

Notes: P = 0.361

41.3. Statistical Method(s)

Results: breast cancer, folate intake, highest versus lowest; breast cancer, folate intake, per 100 ug/day
Adjustment factors:
Statistical metric description: We examined the relationship between folate intake and the risk of breast cancer on the basis of the effect estimates (RR or HR) and 95% CI published in each study. We first used the random-effects model [10,11] to calculate the summary RRs and 95% CIs for highest versus lowest category folate intake levels. Second, we transformed category-specific risk estimates into RR estimates associated with an increase in folate intake of 100mg/day by using the method of generalized least squares for trend estimation [12]. These estimates were calculated by assuming a linear relationship between the natural logarithm of RR and increasing folate intake. The value assigned to each folate category was the mid-point for closed categories and the median for open categories (assuming a normal distribution for folate intake). We combined the RRs for each 100mg/day increase in folate intake by using the results of a random-effect meta-analysis [10]. Third, We conducted a dose-response random-effects meta-analysis of the correlated natural logs of the RRs or HRs across all folate intake categories [12,13]. To derive the dose-response curve, we modeled folate using restricted cubic splines with 3 knots at fixed distribution percentiles of 10%, 50%, and 90% [12]. This method required knowledge of the distributions of cases and persons or person-years and effect estimates (RRs or HRs) along with the variance estimates for at least 3 quantitative exposure categories. Inter-study heterogeneity was investigated with the Q statistic, and we considered P-values, 0.10 as indicative of significant heterogeneity [14,15]. Breast cancer subgroup analyses were conducted on the basis of the country, study design, sample size, effect estimate (HR or RR), follow-up duration, adjusted alcohol intake, and alcohol intake. We also performed a sensitivity analysis by removing each individual study from the meta-analysis. Several methods were used to evaluate the potential publication bias. Funnel plots for the risk of breast cancer were visually inspected. The Egger [16] and Begg [17] tests were also used to statistically assess the publication bias with respect to the breast cancer incidence. All reported P values were 2-sided, and P values, 0.05 were considered statistically significant for all included studies. STATA software (version 12.0; Stata Corporation, College Station, TX, USA) was used to perform the statistical analyses.

42. ZHANG, 2014B

Full citation: Zhang YF, Zhou L, Zhang HW, Hou AJ, Gao HF, Zhou YH. 2014b. Association between folate intake and the risk of lung cancer: a dose-response meta-analysis of prospective studies. PLoS One 9(4): e93465.
Funding: This study was funded by Shanghai Natural Science Foundation (Grant No. 12ZR1422800) and Talents Training Program of Shanghai Seventh People's Hospital (Grant No. QMX2014-01). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

42.1. Folate intake and risk of lung cancer

Protocol: Folate intake and risk of lung cancer	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement issued in 2009 (Checklist S1) [11]. Any prospective study that examined the relationship between folate intake and incidence of lung cancer was eligible for inclusion in our study, and no restrictions were placed on language or publication status (published, in press, or in progress). We searched PubMed, Embase, and the Cochrane Library electronic databases for articles published until September 2013, and used ''(''folate'' OR ''folic acid'') AND (''cancer'' OR ''neoplasm'' OR ''carcinoma'') AND (''cohort'' OR ''cohort studies'' OR ''nest case-control studies'')'' as the search terms. We also conducted manual searches of reference lists from all the relevant original and review articles to identify additional eligible studies. The medical subject heading, methods, patient population, design, exposure, and outcome variables of these articles were used to identify the relevant studies. The literature search was independently undertaken by 2 authors (YFZ and HFG) with a standardized approach. Any inconsistencies between these 2 authors were settled by the primary author (YHZ) until a consensus was reached.	**Inclusion Criteria:** authors reported the effect estimates (risk ratio [RR], hazard ratio [HR], or odds ratio [OR]) and 95% confidence intervals (CIs) for comparisons of highest and lowest category folate intake, exposure is folate intake, outcome is risk of lung cancer, prospective cohort or nested prospective case-control study **Exclusion Criteria:** case-control
Starting date:	**Ending date:** 2013-09-30
Total references from search: 1173	**References Included:** 9

Additional Notes:

42.2. Result(s)

42.2.A lung cancer, high versus low folate intake

Studies (9), Total Subjects (566921)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
high versus low folate intake	lung cancer	0.92	(0.84, 1.01)	I2 = 0.0%, P = 0.495

Notes: P = 0.076

42.2.B **lung cancer, per 100 ug/day increment in folate intake**

Studies (9), Total Subjects (566921)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
per 100 ug/day increment in folate intake	lung cancer	0.99	(0.97, 1.01)	I2 = 33.6%, P = 0.139

Notes: P = 0.318

42.3. Statistical Method(s)

Results: lung cancer, high versus low folate intake; lung cancer, per 100 ug/day increment in folate intake

Adjustment factors:

Statistical metric description: We examined the relationship between folate intake and the risk of lung cancer on the basis of the effect estimates (RR, OR, or HR) and 95% CIs published in each study. First, we used the random-effects model [14–15] to calculate summary RRs and 95% CIs for high versus low folate intake. Second, we transformed category-specific risk estimates into RR estimates associated with an increase in folate intake of 100 mg/day by using the method of generalized least squares for trend estimation [16]. These estimates were calculated by assuming a linear relationship between the natural logarithm of RR and increasing folate intake. The value assigned to each folate category was the mid-point for closed categories and the median for open categories (assuming a normal distribution for folate intake). We combined the RRs for each 100mg/day increase in folate intake by using the results of a random-effect meta-analysis [14]. Third, we conducted a dose-response random-effects meta-analysis from the correlated natural logarithm of RRs or HRs across the folate intake categories [16–17]. To derive the dose-response curve, we modeled folate by using restricted cubic splines with 3 knots at fixed percentiles, 10%, 50%, and 90%, of the distribution [16]. This method requires knowledge about the distribution of cases and persons or person-years as well as effect estimates (RRs, OR, or HRs) with the variance estimates for at least 3 quantitative exposure categories. Fourth, folate intake was also analyzed by considering a study-specific dose, and the lowest intake category was used as the reference throughout the analyses. If no participants were diagnosed with lung cancer in a study's highest intake category, the participants in the highest category were included in the second highest intake category. Heterogeneity between studies was investigated by using the Q statistic, and we considered P-values, 0.10 indicative of significant heterogeneity [18–19]. Subgroup analyses were conducted according to the country, sex, and duration of follow-up. In addition, we performed a sensitivity analysis by removing each individual study from the meta-analysis. Several methods were used to check for potential publication bias. Visual inspections of funnel plots for incidence of lung cancer were conducted. The Egger [20] and Begg [21] tests were also used to statistically assess the publication bias for the incidence of lung cancer. All reported P-values are 2-sided, and P-values, 0.05 were considered statistically significant for all included studies. Statistical analyses were performed by using STATA software (version 12.0; Stata Corporation, College Station, TX, USA).

43. ZHOU, 2011

Full citation: Zhou YH, Tang JY, Wu MJ, Lu J, Wei X, Qin YY, Wang C, Xu JF, He J. 2011. Effect of folic acid supplementation on cardiovascular outcomes: a systematic review and meta-analysis. PLoS One 6(9): e25142.
Funding: Funding was provided by the National Nature Science Foundation of China (30872186, 81072388), a grant from the leading talents of science in Shanghai 2010 (022) and a grant sponsored by the Program of Shanghai Subject Chief Scientist (09XD1405500). The funders had no role in the study design, data collection, analysis, decision to publish, or preparation of the manuscript.

43.1. Effect of Folic Acid Supplementation on Cardiovascular Outcomes

Protocol: Effect of Folic Acid Supplementation on Cardiovascular Outcomes

Protocol: Effect of Folic Acid Supplementation on Cardiovascular Outcomes	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
We searched the electronic databases Medline, EmBase, and the Cochrane Central Register of Controlled Trials for articles to a time limit of Nov. 20, 2010, using ''folic acid'', ''folate'', 'cardiovascular disease'', ''coronary disease'', ''coronary thrombosis'', ''ischemic heart disease'', ''stroke'', ''coronary stenosis'', ''coronary restenosis'', and ''randomized controlled trial'' as the search terms. All reference lists from reports on non-randomized controlled trials were searched manually for additional eligible studies. We contacted authors to obtain any possible additional published or unpublished data, and searched the proceedings of annual meetings in the Cochrane Cardiovascular Disease Group Specialized Register. In addition, we searched for ongoing randomized controlled trials, which had been registered as completed but not yet published, in the metaRegister of Controlled Trials. Medical subject headings and methods, patient population, and intervention were used to identify relevant trials. This review was conducted and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) Statement issued in 2009 (Checklist S1). The literature search was undertaken independently by 2 authors (Chao Wang and Ying-Yi. Qin) with a standardized approach, and any disagreement between these 2 authors was settled by a third author (Yu-Hao. Zhou) until a consensus was reached. All completed randomized controlled trials assessing the effects of folic acid therapy compared with the effects of a placebo, and reporting at least 1 outcome of major cardiovascular events were included as eligible trials. Randomized controlled trials to be included in the analysis were limited to those with at least 100 patients and at least 6 months follow-up, to ensure that only high-quality studies were incorporated.	**Inclusion Criteria:** contains relevant information on the effects of folic acid supplementation on cardiovascular outcomes, English, has a placebo control, randomized controlled trials, sample size of at least 100 **Exclusion Criteria:** affiliated trials, cross-over study, ongoing trials, patients with other therapies
Starting date:	**Ending date:** 2010-11-20
Total references from search: 1594	**References Included:** 16

Additional Notes:

43.2. Result(s)

43.2.A cancer, folic acid supplementation, compared to placebo

Studies (6), Total Subjects (26544)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
folic acid supplementation	incidence of cancer	1.08	(0.98, 1.21)	I2 = 26.7%, p=0.234

Notes: No N is given for studies 16 and 17. These are both methods papers but they are listed as studies included in the analysis for this outcome. The overall N listed in the text of the paper is 26,544 (included above) but the sum of the N's provided in the paper is 4147. The papers included, but not detailed is 22,397(84%).

43.3. Statistical Method(s)

Results: cancer, folic acid supplementation, compared to placebo
Adjustment factors:
Statistical metric description: We assessed the overall effect of folic acid supplementation on all data from the included trials. The outcomes were reported using relative risks (RR) with 95% confidence intervals (CIs) to estimate the effect of folic acid on major cardiovascular events, stroke, myocardial infarction, total mortality, and possible drug-correlated adverse reactions. After this, a subgroup analysis was carried out based on the number of patients, duration of folic acid supplementation, mean age, baseline total plasma homocysteine, pre-existing disease, and Jadad score. The statistical estimates of effect were derived using a random-effects model with Mantel–Haenszel statistics. Heterogeneity of treatment effects between studies was investigated visually by scatter plot analysis and statistically by the heterogeneity I2 statistic. I2 statistic of 0%–40% indicates unimportant heterogeneity, 30%–60% indicates moderate heterogeneity, 50%–90% indicates substantial heterogeneity, and 75%–100% indicates considerable heterogeneity. P values were calculated by x2tests. All the reported P values are two-sided and value of P less than 0.05 was regarded as statistically significant for all included studies. All analyses were calculated using STATA (version 10.0).