

**Supplementary Table 2: Studies identified by systematic review of the literature included in meta-analysis**

First author	Year	Country	Cases & controls	Metabolite(s)	Measure(s)	Adjustment(s)	Reference
Weinstein	2003	Finland	29,133 male smokers ages 50-69 years recruited to the Alpha-Tocopherol Beta-Carotene (ATBC) Lung Cancer Prevention study from 1985-1988. Subjects were provided $\alpha$ -tocopherol and/or $\beta$ -carotene supplements or placebo for 5-8 years, with follow-up continuing through the Finnish Cancer Registry. Cases were defined as incident prostate cancers diagnosed through 1994 with available serum (n=232). Two controls were matched to each case on clinic, intervention group, date of baseline blood draw ( $\pm$ 45 days), age ( $\pm$ 5 years), and serum availability (n=464).	Folate B <sub>12</sub> Homocysteine (all from serum)	Odds ratios (quartiles)	BPH	7
Hultdin	2005	Sweden	Case-control study nested within the Northern Sweden Health and Disease Cohort, which for men includes the Västerbotten Intervention Project (VIP) and the WHO Northern Sweden Monitoring Trends and Determinants of Cardiovascular Disease (MONICA) study. As of July 2001, 37,776 men had been recruited to these 2 subcohorts. Incident cases (n=254) of prostate cancer were identified through linkage with the regional cancer registry. Two controls were matched to each case on subcohort, recruitment date ( $\pm$ 2 months), and age ( $\pm$ 6 years) (n=514).	Folate B <sub>12</sub> Homocysteine (all from plasma)	Odds ratios (quartiles)	[all metabolites, BMI, smoking]*	13
Rossi	2006	Australia	Cross-sectional health surveys of adults listed on the electoral roll (compulsory enrolment) were undertaken at intervals of 3 years from 1966 to 1981 in the town of Busselton, Western Australia. A subcohort of men who attended the 1969 and 1978 surveys, excluding those with a history of cancer in 1978, were followed for the period from December 1978 to December 2001 (N=466). Prostate cancer events (cancer registration, hospital admission for cancer, or cancer death) were identified by linkage (n=52). As an individual could have more than one event, subsequent events were censored at the time of the first event.	Serum folate Red cell folate	Hazard ratios (quartiles and per SD)	age, BMI, smoking, alcohol	19
Johansson	2008	Germany, Greece, Italy, the Netherlands, Spain, Sweden, and the United	The European Prospective Investigation into Cancer and Nutrition study recruited 519,978 individuals across Europe between 1992 and 2006, including 153,457 men of whom 137,001 provided a baseline blood sample. In Italy, the Netherlands, Spain, Sweden, and the United Kingdom, incident cancer cases were identified through record linkage with regional or national cancer registries. In Germany and Greece, follow-up was based on a combination of methods, including health insurance records, cancer and pathology registries, and active follow-up	Folate B <sub>12</sub> (both from serum)	Odds ratios (quartiles and per doubling)	BMI, smoking, alcohol, physical activity, marital status, education	15

		Kingdom	through study subjects and their next-of-kin. This study was based on 869 cases (Italy 61, Germany 182, Greece 9, the Netherlands 24, Spain 94, Sweden 321, United Kingdom 177) each matched to one control (two in Sweden) chosen at random from appropriate risk sets comprising all cohort members alive and free of cancer (except non-melanoma skin cancer) at the time of diagnosis of the index case. Matching criteria were study center, age at enrollment ( $\pm 6$ months), time of day of blood collection ( $\pm 1$ hour), and time between blood draw and last consumption of food or drink ( $<3, 3-6, >6$ h).				
Figueiredo	2009	USA	A secondary analysis of prostate cancer incidence within the Aspirin/Folate Polyp Prevention Study, a placebo-controlled randomized trial of aspirin and folic acid supplementation for the chemoprevention of colorectal adenomas conducted between 1994 and 2006. Participants were followed for up to 10.8 (median 7.0, interquartile range 6.0-7.8) years and asked periodically to report all illnesses and hospitalizations. The results included in our meta-analysis were based on 319 men (mean age $57.3 \pm 9.2$ years) with no diagnosed prostate cancer prior to trial entry, allocated to receive placebo with aspirin (215 men (67.4%)) or without aspirin (104 men (32.6%)), of whom 24 (7.2%) were African-American; 9 men were diagnosed with prostate cancer (mean Gleason score $6.8 \pm 1.7$ ).	Plasma folate** Red cell folate B <sub>12</sub> **	Hazard ratio per SD	Age, alcohol, aspirin and folic acid treatment allocation, baseline multivitamin use, plasma levels of B <sub>2</sub> , B <sub>6</sub> , and B <sub>12</sub>	18
Ebbing	2009	Norway	A secondary analysis of cancer incidence within the Norwegian Vitamin Trial (NORVIT) and Western Norway B Vitamin Intervention Trial (WENBIT), two placebo-controlled double-blind randomized trials of folic acid, vitamin B <sub>12</sub> (cyanocobalamin) and vitamin B <sub>6</sub> (pyridoxine hydrochloride) for lowering of homocysteine among 6,837 patients (76.5% male) with ischaemic heart disease, conducted between 1998 and 2005. Participants were followed for up to 9 years (median 6.5 years). The results included in our meta-analysis were based on the 2,502 men (mean age $60.8 \pm 10.6$ years) with no diagnosed cancer prior to trial entry, allocated to treatment with vitamin B <sub>6</sub> alone or with placebo; 81 prostate cancer cases were identified by linkage to the Cancer Registry of Norway, of which 80 cases had valid values of baseline serum folate, serum cobalamin and plasma total homocysteine.	Serum folate*** Serum B <sub>12</sub> *** Plasma homocysteine***	Hazard ratio per quartile	Age and treatment allocation	21

\* results adjusted for these covariates were reported by the authors but unadjusted results were used in our meta-analysis

\*\* for the purpose of our meta-analysis, we obtained unpublished data by correspondence with the authors, excluding men allocated to folic acid supplementation, and without adjustment for plasma levels of B<sub>2</sub> and B<sub>6</sub>

\*\*\* for the purpose of our meta-analysis, we used unpublished data, excluding men allocated to folic acid and B<sub>12</sub> supplementation