Food Fortification Initiative
Enhancing Grains for Healthier Lives

No evidence to link folate status or folate intake to prostate cancer risk

Evaluating results from a meta-analysis assessing folate exposure and prostate cancer

Does folate increase prostate cancer risk? This brief breaks down the science.

A meta-analysis by Wang et al., 2014[1] examined about 200,000 individuals from 10 prospective studies and found no significant association between folate intake and prostate cancer risk (pooled risk ratio=1.02, non-significant p-value). The paper also evaluated the risk of prostate cancer based on serum folate levels. The study reported that "high serum folate levels" resulted in a 21% increase in the risk of prostate cancer (pooled risk ratio=1.21; 95% confidence intervals (1.05, 1.39) and P=0.008).

Is consuming more folate associated with prostate cancer risk?

No. The study found no significant association, meaning there was no positive link between folate intake and prostate cancer risk. The studied populations had relatively low supplement exposure; the highest levels of folate intake across the studies were 260-640+ micrograms/day, which generally reflects intake from dietary folate sources (except in one study, which took place in the US post-fortification[6]). In these populations, the highest levels of folate intake were generally under, or close to, the Recommended Nutrient Intake of dietary folate equivalents for adults (400 micrograms/day).[4]

How much folic acid is usually provided through fortification?

Food fortification, when following World Health Organization (WHO) fortification guidelines,[2,3] adds about 30-50% of the recommended intake of folic acid (400 mcg/day) to staple foods. Women of reproductive age are advised to consume 400 mcg/day of folic acid to prevent birth defects.[4] **When designed appropriately, fortification programs will never contribute folic acid amounts that exceed the upper tolerable nutrient intake level (UL) for adults, or 1000 mcg/day).** Regularly exceeding the UL is far more likely when multiple supplements containing folic acid are consumed. A nationally representative analysis of diets found that no-one in the US exceeded the folic acid UL through fortified foods alone.[5]

Are serum folate levels associated with prostate cancer risk?

Wang et al. 2014[1] compared populations with the highest serum folate levels from each study and found a slightly increased risk. But let's reassess how each study defined its highest level. Serum folate levels are closely linked to folate intake and reflect recent folate intake. However, the studies included in meta-analysis had wide differences in their population's highest serum folate levels: one study's highest serum folate levels is considered borderline deficient (>8.03 nmol/L[7]), while another had such a wide range of exposures that their highest serum folate level ranged between 14.3-102.4 nmol/L[8]). Combining such wide-ranging definitions of "high serum folate" makes the meta-analysis's pooled risk ratio estimate problematic to interpret.

In comparison, folate deficiency is defined as serum/plasma folate concentrations <6.8 nmol/L. Possible deficiency is defined as 6.8-13.4 nmol/L and a normal range for serum/plasma folate is 13.5-45.3 nmol/L.[9] Proposed optimal serum folate levels to prevent neural tube defects range from 24-28 nmol/L.[10] Four of the five studies included in the Wang, et al. 2014 meta-analysis included individuals who would have been considered folate insufficient. Although these individuals had the highest levels of serum folate for their population, their levels were still quite low. Thus, it may be more accurate to say that the Wang et al., 2014 meta-analysis found an increased risk of prostate cancer in a broad range of individuals with low, normal, and elevated serum folate levels.

Studies in Wang et al. 2014	*Definitions for "high" folate intake or status**	*Adjusted odds ratios or relative risks (95% confidence intervals)*	*P-trend*
Exposure: "High" folate intake			
Stevens et al. 2006 (US†)	>640 micrograms/day	1.11 (1.01-1.22)	0.35
Weinstein et al. 2006 (Finland)	>378 micrograms/day	0.96 (0.81-1.15)	0.84
Bassett et al. 2012 (Australia)	>444 micrograms/day**	1.00 (0.83-1.22)	0.62
Verhage et al. 2012 (Netherlands)	>259 micrograms/day**	1.05 (0.87-1.26)	0.913
Roswall et al. 2013 (Denmark)	>468 micrograms/day	0.87 (0.71-1.07)	0.23
Exposure: "High" folate status			
Hultdin et al. 2005 (Sweden)	>10.30 nmol/L POSSIBLE DEFICIENCY LEVELS	1.60 (1.03-2.49)	0.02
Johansson et al. 2008 (pan-Europe)	≥8.03 nmol/L POSSIBLE DEFICIENCY LEVELS	1.30 (0.88-1.93)	0.41
Beilby et al. 2010 (Australia)	14.3-102.0 nmol/L	1.09 (0.48-2.46)	0.83
de Vogel et al. (2013) (Norway)	≥39.7 nmol/L	1.15 (0.97-1.37)	0.04
Weinstein et al. (2003) (Finland)	≥10.79 nmol/L POSSIBLE DEFICIENCY LEVELS	1.2 (0.74-1.94)	0.52

All of these p-values are larger than 0.05, indicating there is no relationship between high intake and prostate cancer. The overall meta-analysis also found no relationship.

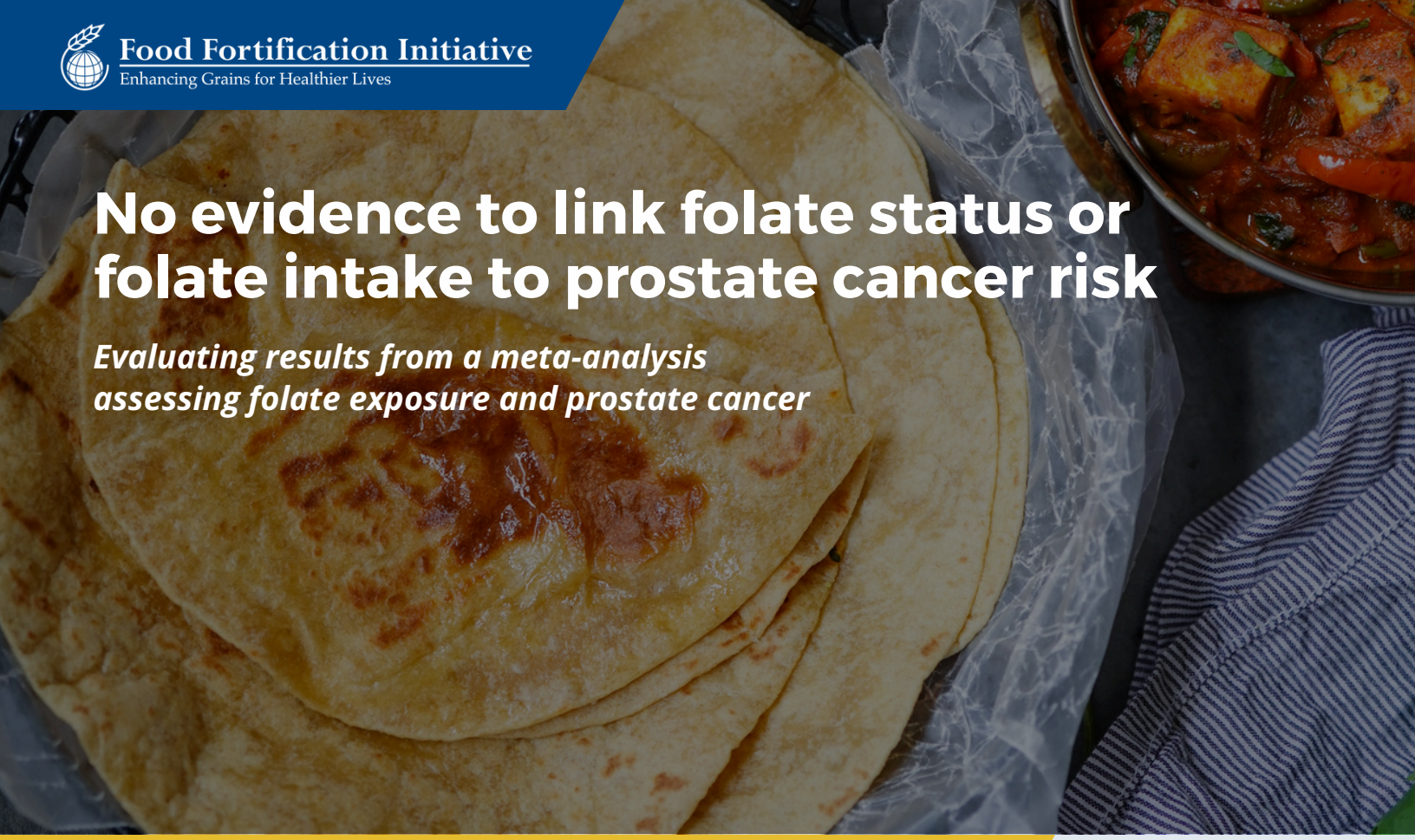
These populations included a mix of individuals with possibly deficient, normal, and elevated folate status. It is extremely difficult to interpret what the increased risk is when the exposure is not well defined.

*Where relevant, converted from ug/L to nmol/L using 1 ug/L = 2.266 nmol/L
**Study design did not measure supplement intake, so folate intake does not account for folic acid from supplements.
† Fortification with folic acid is mandatory in the country at the time of the study.

Multiple independent safety panels have reached consensus that there are no proven adverse effects related to consuming folic acid at levels below the upper tolerable level, as intended through food fortification.

There is no consensus that folate intake or blood folate status is related to prostate cancer risk. On the other hand, there is scientific consensus that low folate intake is linked to cancer,[11] and that folate is important for health and development.[4]

More recent reviews and national safety panels[11,12,13,14] have concluded that there are no adverse effects related to the consumption of folic acid in the context of food fortification. Wang et al., 2014's results are difficult to interpret considering the wide range in folate status included in the study. Food fortification is designed to provide safe amounts of vitamins and minerals, not supplement-level quantities.



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