Food Fortification with Folic Acid is Safe: Global Evidence

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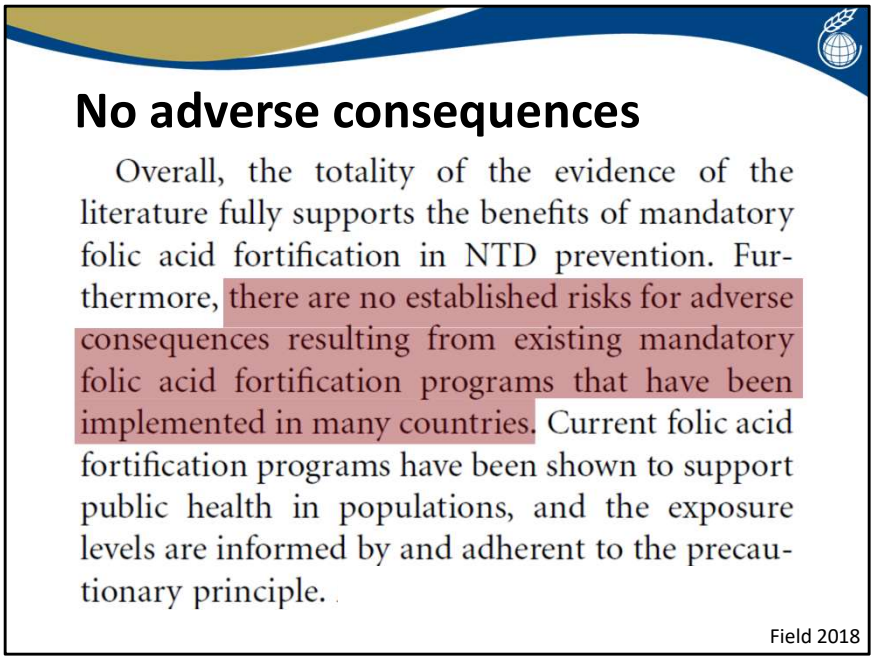
Food Fortification Initiative

Enhancing Grains for Healthier Lives



Last year, researchers published a review of the evidence on the safety of fortification with folic acid. Here is what they concluded:

"there are no established risks for adverse consequences resulting from existing mandatory folic acid fortification programs that have been implemented in many countries."

In this presentation, I will show you evidence that has led these and other researchers to conclude that fortification with folic acid is safe.

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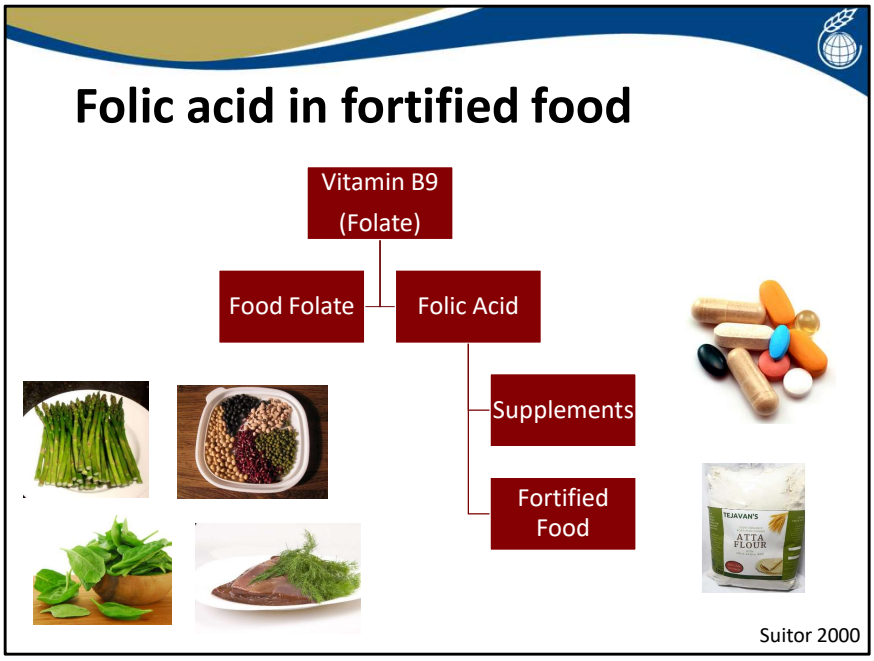
Source:
Martha S. Field, Patrick J. Stover. Safety of folic acid. Annals of the New York Academy of Sciences. 1414:59–71, 2018.

Main messages

- Fortifying food with folic acid does not mask vitamin B12 deficiency
- Fortifying food with folic acid does not cause cancer or increase deaths from cancer
- Free folic acid in blood does not increase cancer or adenoma risk
- Fortifying food with folic acid is safe



Vitamin B9 is also known as folate.

We can consume two types of vitamin B9.

One is food folate which is naturally found in food such as these vegetables, legumes and meat products.

The second type is folic acid which is a synthetic form of the nutrient.

Folic acid can be added to supplements and fortified food.

In this presentation, we are going to focus on folic acid, and mainly on folic acid in fortified food.

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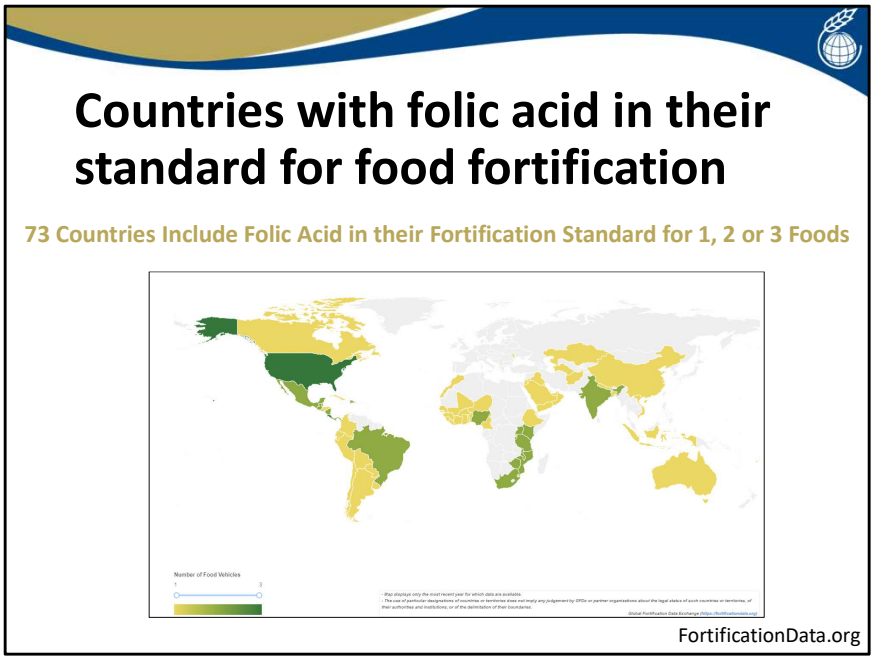
Source:
Suitor CW & Bailey LB (2000) Dietary folate equivalents: interpretation and application. Journal of the American Dietetic Association 100: 88–94.

Source for images:

Asparagus: https://recipemashups.files.wordpress.com/2008/12/asparagus.jpg
Legumes: http://yang-sheng.com/wp-content/uploads/2012/07/beans.jpg
Green leafy vegetables: https://ljayhealth.files.wordpress.com/2012/02/spinach.jpg
Meat: http://popsgrassfedbeef.org/images/bigstock_Beef_Liver_With_Dill_On_White__3599062.jpg
Supplements: www.jebkinnison.com
Fortified wheat flour: https://my-live-02.slatic.net/p/18/tejavan39s-fortified-chakki-atta-flour-in-1kg-packing-6907-552779651-ff29e643b0b4a6f2504a2d027cd4eefd.jpg



Currently, 73 countries include folic acid in their fortification standards for up to 3 foods, including wheat flour, rice and maize flour.

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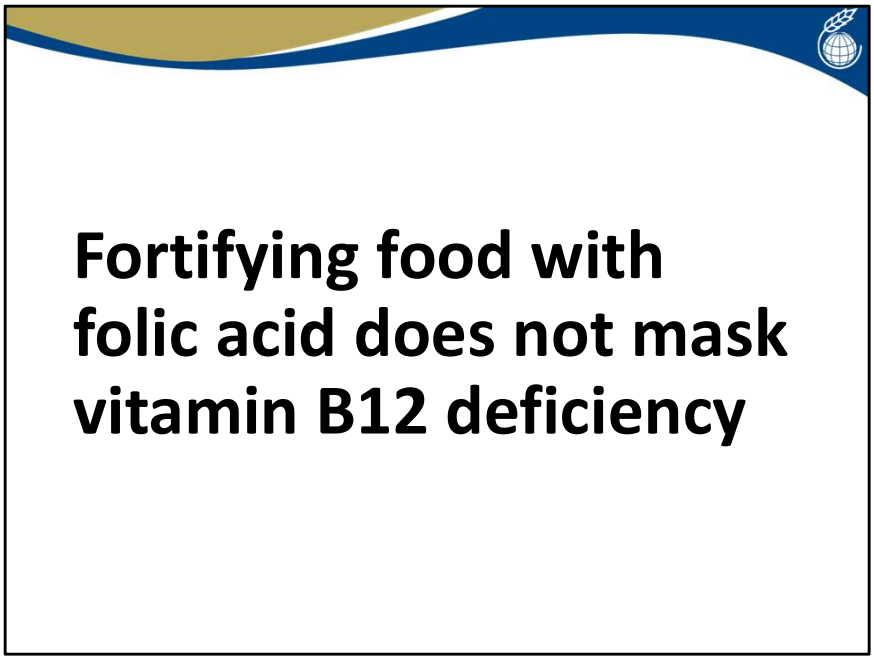
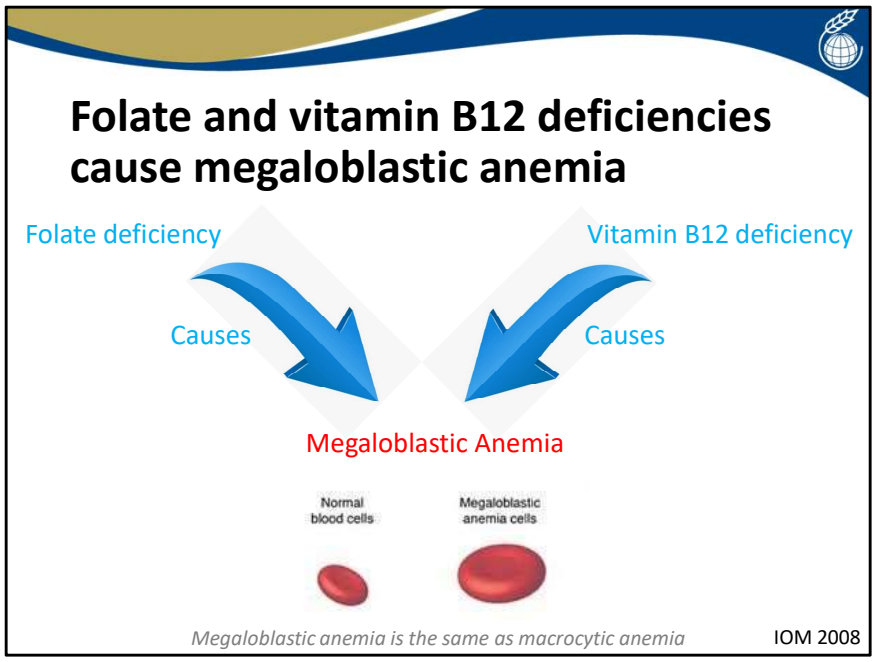
Source:
Global Fortification Data Exchange. Map: Number of Food Vehicles with Standards. Accessed 3 July 2019. [http://www.fortificationdata.org.]



Let’s start by reviewing evidence that fortifying food with folic acid does not mask vitamin B12 deficiency.



Folate deficiency independently causes megaloblastic anemia, that is anemia where the red blood cells are much larger than normal. Anemia is an important public health problem in many countries.

Vitamin B12 deficiency also independently causes megaloblastic anemia.

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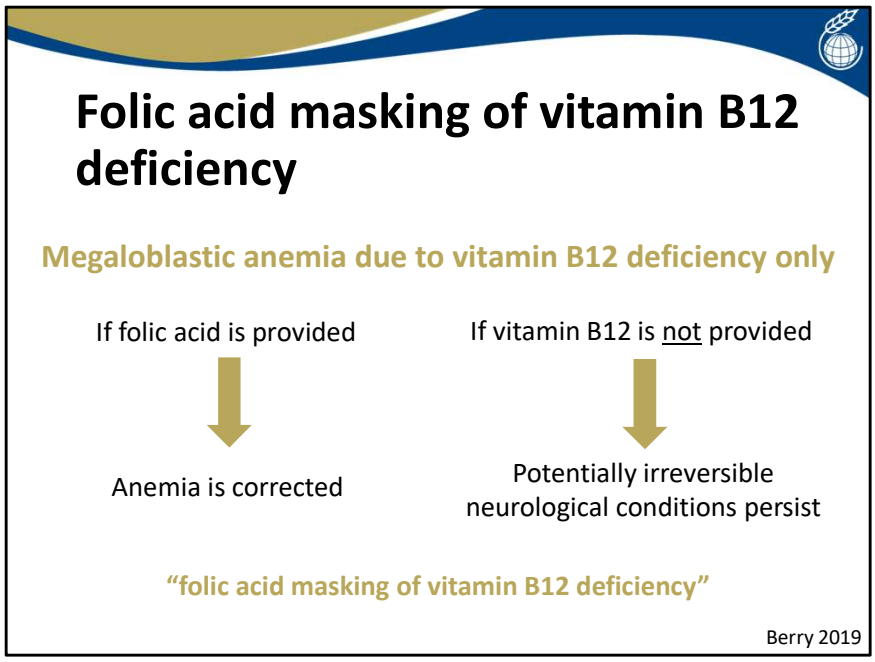
Source:

Institute of Medicine. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. 2000.

Megaloblastic anemia image: https://i.pinimg.com/236x/47/41/e6/4741e6ce99437a3260364ed6001b9ddf--macrocytic-anemia-b-deficiency.jpg

Blue arrow: https://www.seekpng.com/png/detail/12-122935_blue-arrow-transparent-background.png



Let's say a person has megaloblastic anemia due to vitamin B12 deficiency only. This is often observed in older adults because they no longer absorb vitamin B12 from the diet as well as they did when they were younger.

In these individuals, if folic acid is provided, the anemia is corrected.

However, if vitamin B12 is not provided to them, then their vitamin B12 deficiency can persist and with it, potentially irreversible neurological conditions such as memory loss, disorientation and frank dementia.

The fact that folic acid can correct megaloblastic anemia while not treating the underlying vitamin B12 deficiency is known as "folic acid masking of vitamin B12 deficiency."

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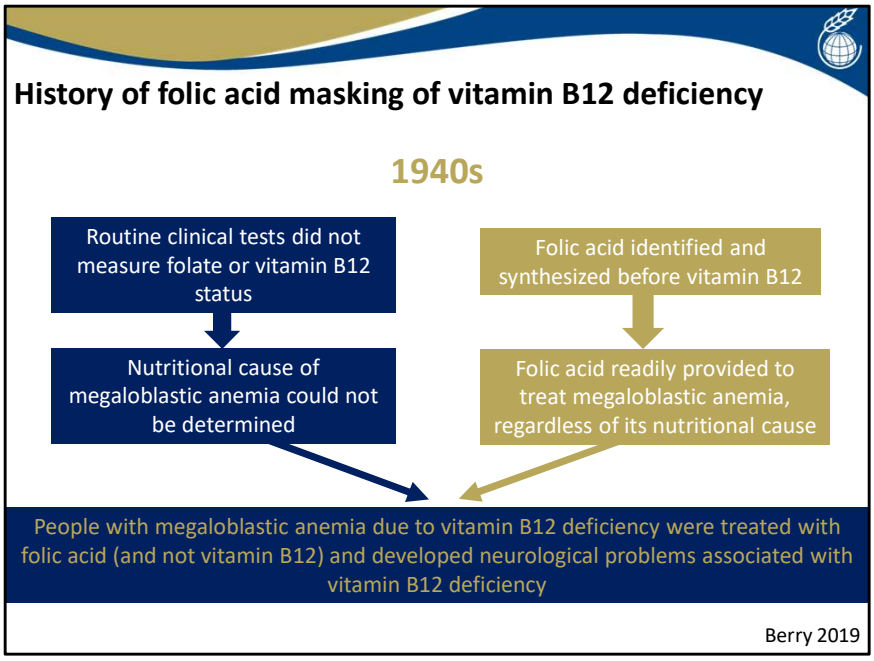
Source:

RJ Berry. Lack of historical evidence to support folic acid exacerbation of the neuropathy caused by vitamin B12 deficiency. American Journal of Clinical Nutrition 2019.



The history of folic acid masking of vitamin B12 deficiency goes back to the 1940s.

At that time, routine clinical tests did not measure folate or vitamin B12 status. Therefore, the nutritional cause of megaloblastic anemia could not be determined.

And, folic acid was identified and synthesized before vitamin B12, meaning that folic acid was readily provided to treat megaloblastic anemia, regardless of its nutritional cause.

So, putting these two situations together, people with megaloblastic anemia due to vitamin B12 deficiency were treated with folic acid instead of vitamin B12. Consequently, these people developed neurological problems associated with vitamin B12 deficiency.

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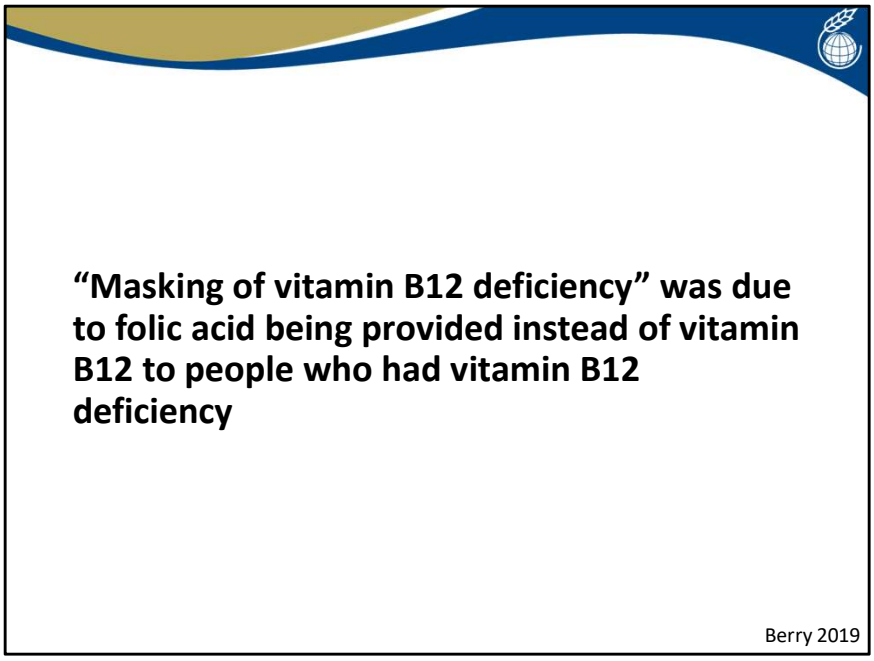
Source:
RJ Berry. Lack of historical evidence to support folic acid exacerbation of the neuropathy caused by vitamin B12 deficiency. American Journal of Clinical Nutrition 2019.



In synthesis, historical masking of vitamin B12 deficiency was due to folic acid being provided instead of vitamin B12 to people who had vitamin B12 deficiency.

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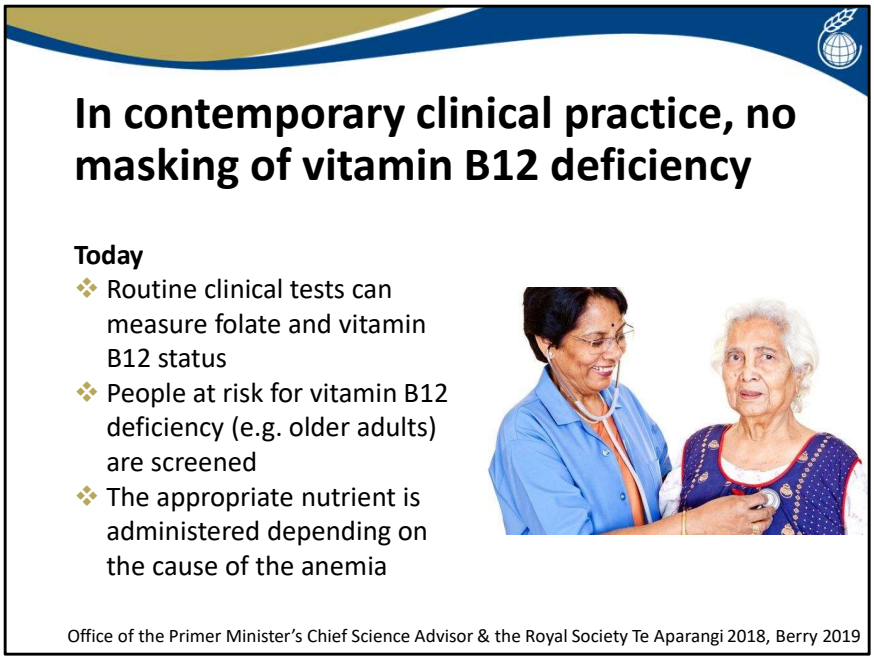
Source:

RJ Berry. Lack of historical evidence to support folic acid exacerbation of the neuropathy caused by vitamin B12 deficiency. American Journal of Clinical Nutrition 2019.



Today, however, the story is very different. Routine clinical tests can measure folate and vitamin B12 status. People at risk for vitamin B12 deficiency such as older adults are screened. And the appropriate nutrient is administered depending on the cause of the anemia.

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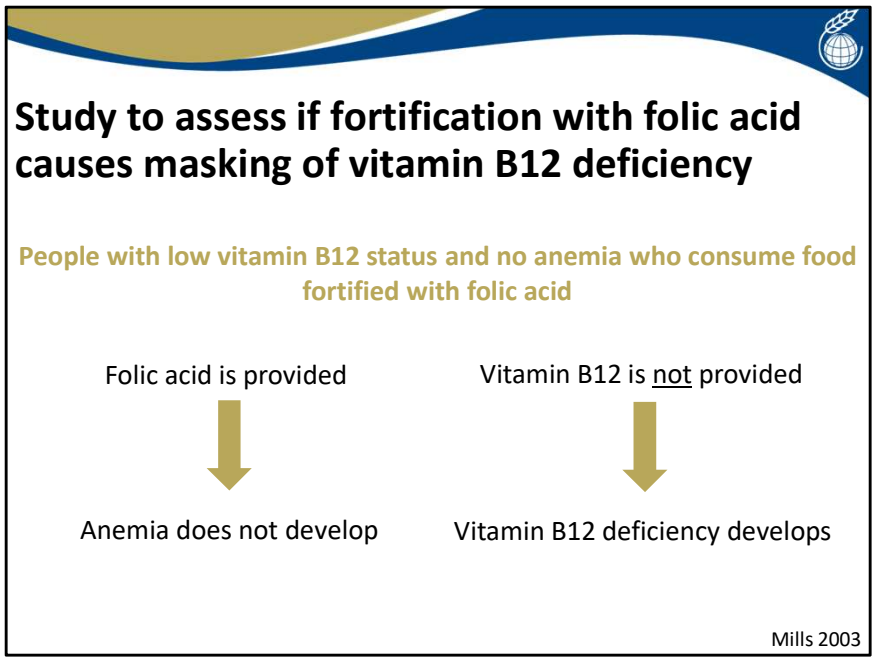
Source:

Office of the Primer Minister's Chief Science Advisor & the Royal Society Te Aparangi. The Health Benefits and Risks of Folic Acid Fortification of Food. New Zealand, 2018.

RJ Berry. Lack of historical evidence to support folic acid exacerbation of the neuropathy caused by vitamin B12 deficiency. American Journal of Clinical Nutrition 2019.

Photo:
https://www.sbs.com.au/yourlanguage/sites/sbs.com.au.yourlanguage/files/styles/body_image/public/1-gettyimages-155374522.jpg?itok=oLZyqWLs&mtime=1535095271



Is there any evidence that fortification with folic acid causes masking of vitamin B12 deficiency?

In one study conducted in the USA, researchers surmised that people with low vitamin B12 status and no anemia who consumed food fortified with folic acid could be at risk of developing vitamin B12 deficiency.

In other words, in these individuals, since folic acid is provided through fortification in the USA, they will not develop anemia.

However, since vitamin B12 is not provided through fortification in the USA, they may develop vitamin B12 deficiency.

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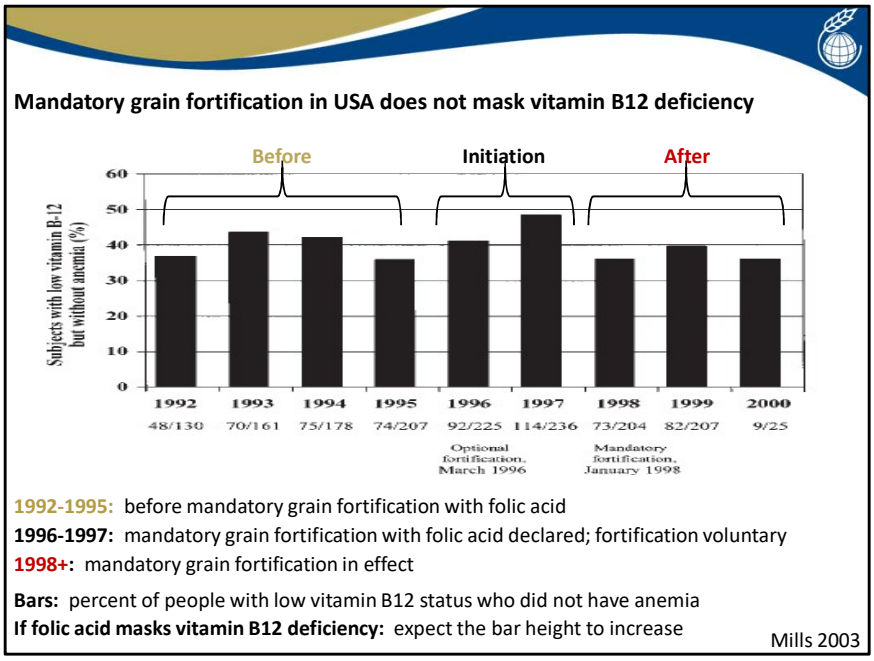
Source:
Mills JL et al. Low vitamin B-12 concentrations in patients without anemia: the effect of folic acid fortification of grain. *Am J Clin Nutr* 2003;77:1474–7.



This graph has data from 1992 to 2000 from the United States.

From 1992 to 1995, there was no mandatory grain fortification with folic acid in the USA; this is labeled as the "before fortification" period.

From 1996 to 1997, industry could voluntarily fortify grains but did not need to; this is labeled as the "initiation" period.

From 1998 forward is when mandatory grain fortification was in effect; this is labeled as the "after" period.

The bars represent the % of people with low vitamin B12 status who did not have anemia.

We would expect the prevalence to increase in the "after" period if folic acid from fortification was masking vitamin B12 deficiency.

What we can see from the graph is that the prevalence did not change across the three fortification periods. These data suggest that folic-acid fortification does not mask vitamin B12 deficiency.

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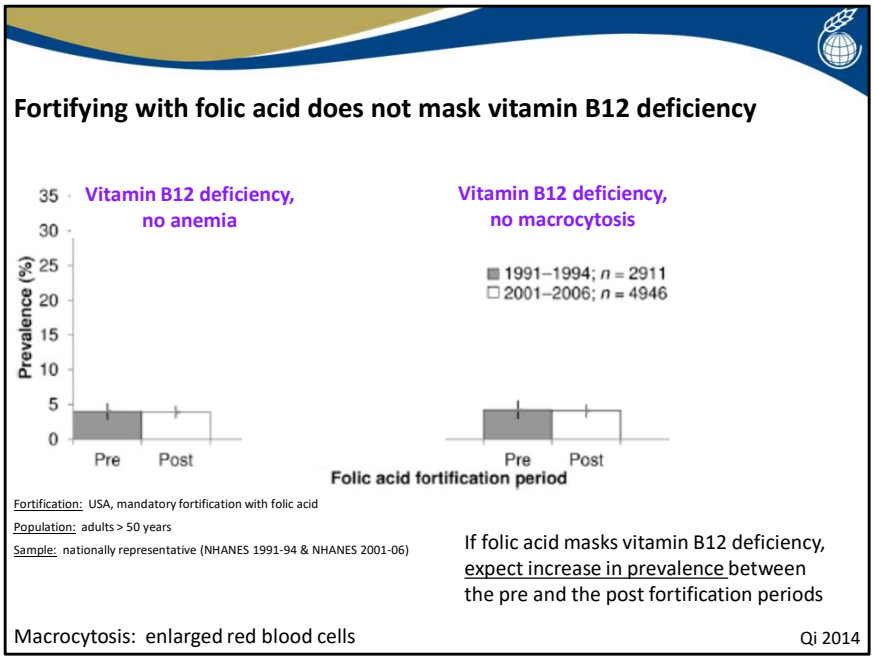
Source:
Mills JL et al. Low vitamin B-12 concentrations in patients without anemia: the effect of folic acid fortification of grain. *Am J Clin Nutr* 2003;77:1474–7.



Another study from the USA, published 11 years after the previous study, aimed to answer the same question.

On the left we have individuals with vitamin B12 deficiency and no anemia, and on the right those with vitamin B12 deficiency and no macrocytosis. Macrocytosis refers to enlarged red blood cells, like those we would observe in megaloblastic anemia.

The gray bars represent the period before mandatory fortification with folic acid in the USA and the white bars represent the period after mandatory fortification.

If folic acid was masking vitamin B12 deficiency, we would expect an increase in either of these groups during the post-fortification period.

We see that there was no change in the prevalence for these groups, suggesting there was no masking of vitamin B12 deficiency by fortification with folic acid.

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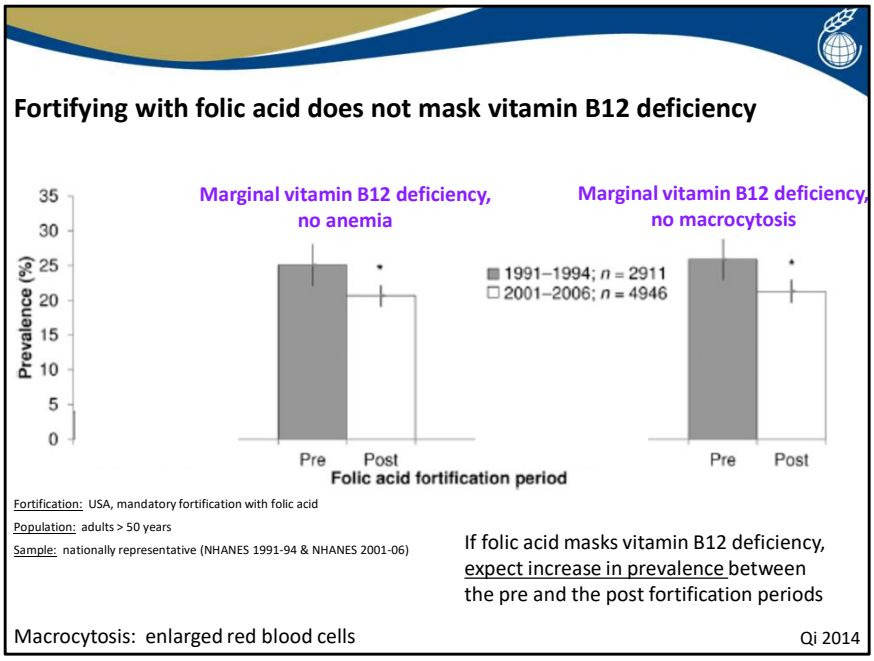
Source:
Yan Ping Qi, Ann N. Do, Heather C. Hamner, Christine M. Pfeiffer, and Robert J. Berry. The prevalence of low serum vitamin B-12 status in the absence of anemia or macrocytosis did not increase among older U.S. adults after mandatory folic acid fortification. J. Nutr. 144: 170–176, 2014.



These are the results for individuals who had marginal vitamin B12 deficiency. On the left, they were free of anemia. On the right, they were free of macrocytosis.

If folic acid was masking vitamin B12 deficiency, we would expect an increase in either of these groups during the post-fortification period.

However, there was a decrease in both groups, again suggesting that there was no masking of vitamin B12 deficiency by fortification with folic acid.

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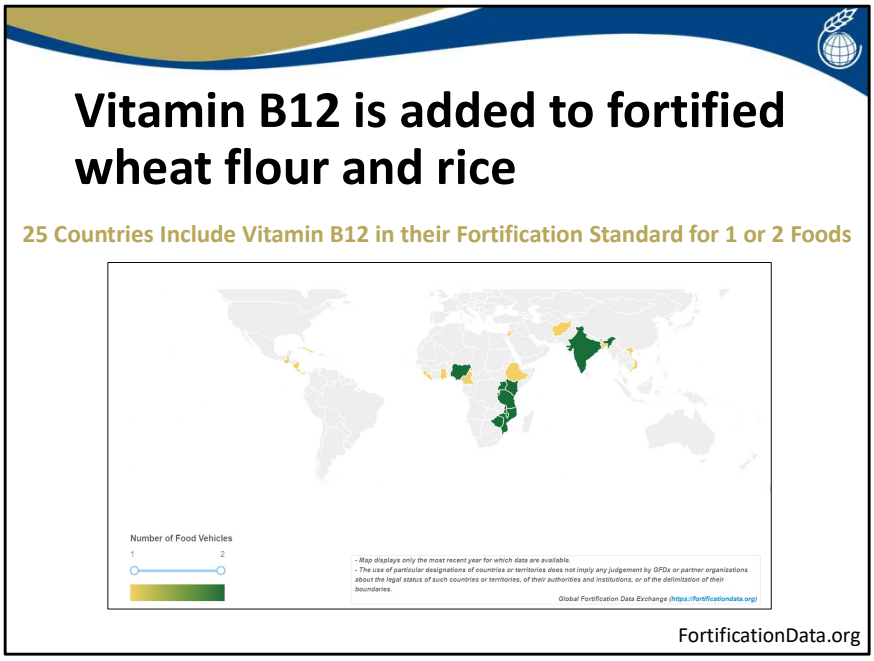
Source:

Yan Ping Qi, Ann N. Do, Heather C. Hamner, Christine M. Pfeiffer, and Robert J. Berry. The prevalence of low serum vitamin B-12 status in the absence of anemia or macrocytosis did not increase among older U.S. adults after mandatory folic acid fortification. J. Nutr. 144: 170–176, 2014.



In case you are wondering, yes it is possible to add vitamin B12 to fortified foods including wheat flour and rice.

Currently, 25 countries include vitamin B12 in their fortification standards for 1 or 2 foods.

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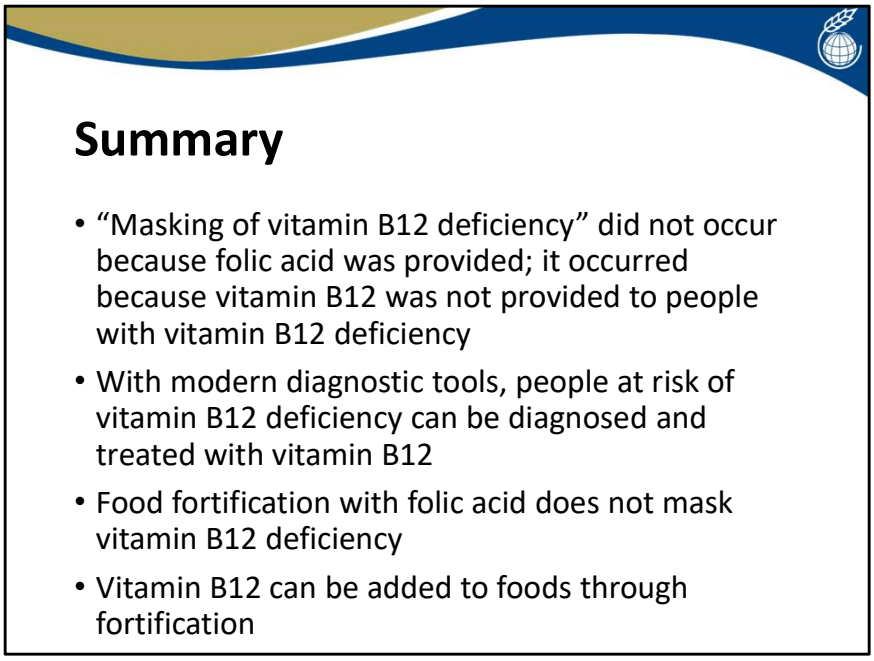
Source:
Global Fortification Data Exchange. Map: Number of Food Vehicles with Standards. Accessed 3 July 2019. [http://www.fortificationdata.org.]

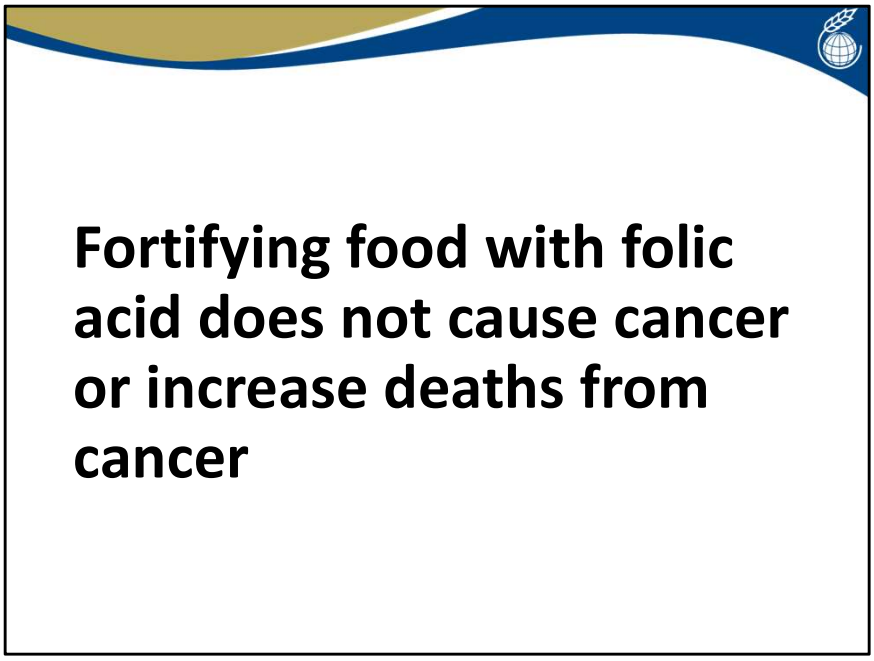


In summary, historical "masking of vitamin B12 deficiency" did not occur because folic acid was provided; it occurred because vitamin B12 was not provided to people with vitamin B12 deficiency.

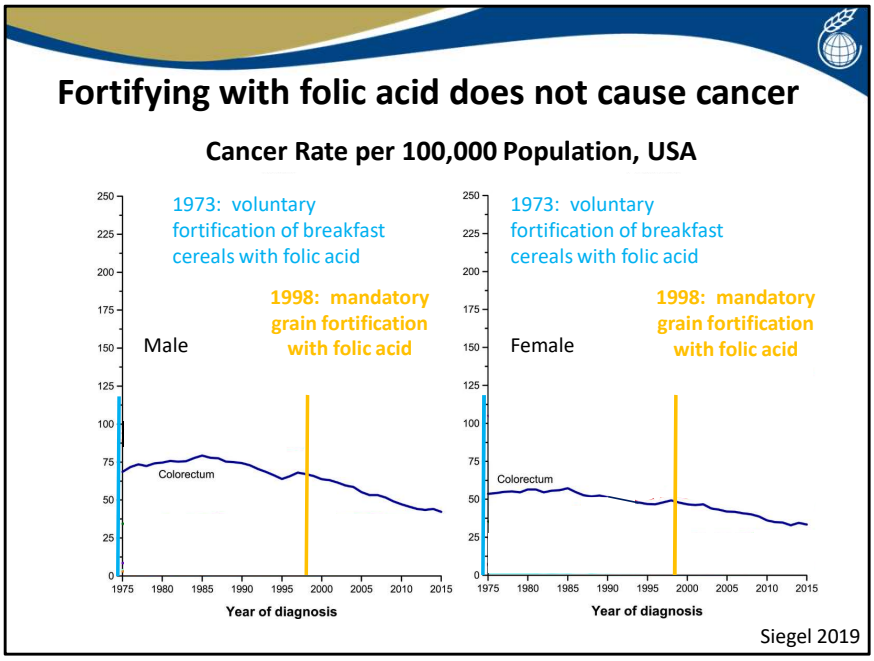
With modern diagnostic tools, people at risk of vitamin B12 deficiency can be diagnosed and treated with vitamin B12.

Evidence from the United States indicates that food fortification with folic acid does not mask vitamin B12 deficiency.

And, vitamin B12 can be added to foods through fortification



Now, let's review evidence that fortifying food with folic acid does not cause cancer or increase deaths from cancer.



Here we have two graphs with the rate of colorectal cancer per 100,000 population in the United States. As you can see in the horizontal axis, the year of cancer diagnosis ranges from 1975 to 2015.

The left-hand side has the data for males and the right-hand side has the data for females.

The dark blue line for men shows a reduction in the number diagnosed with colorectal cancer during this period. The dark blue line for women shows the same downward trend.

Voluntary fortification of breakfast cereals with folic acid began in 1973.

Mandatory fortification of grains with folic acid became effective in 1998.

These data suggest there is no increase in the number of people diagnosed with colorectal cancer beginning with the voluntary fortification period and extending into the mandatory fortification period.

In other words, there is no evidence that fortification with folic acid increases the number of people being diagnosed with colorectal cancer.

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Source:
Siegel R et al. Cancer statistics, 2019. CA: A Cancer Journal for Clinicians. 2019.

Fortifying with folic acid does not increase deaths from cancer

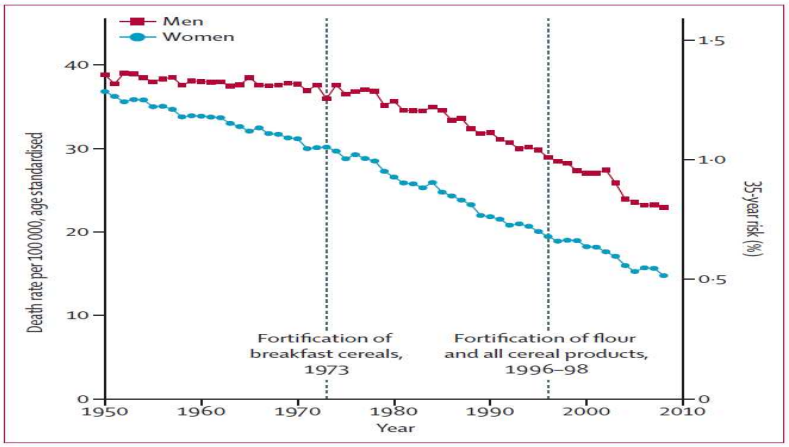

Figure 4: Annual mortality from colorectal cancer in the USA, 1950–2008, at ages 35–69 years

Vollset 2013

A related question is whether more people are dying from colorectal cancer due to fortification with folic acid.

Researchers reviewed data on the annual mortality in the United States from colorectal cancer from 1950 to 2010, which is the timeline that appears along the horizontal axis. They note in the dashed vertical lines that voluntary fortification of breakfast cereals began in 1973 and that mandatory flour fortification with folic acid became effective in 1998.

The data are presented for men in red and women in blue.

For both women and men, there was a decrease in annual deaths from colorectal cancer over this 60-year period.

It's clear from the graph that the downward trend in annual deaths from colorectal cancer has not changed since the introduction of voluntary and mandatory fortification with folic acid in the USA.

These data suggest that folic-acid fortification does not increase deaths from colorectal cancer.

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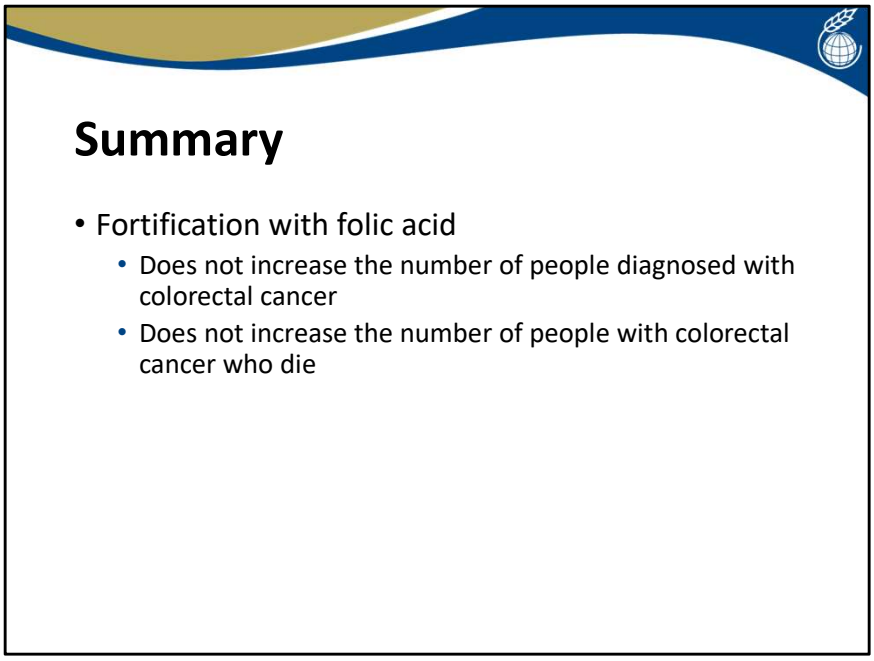
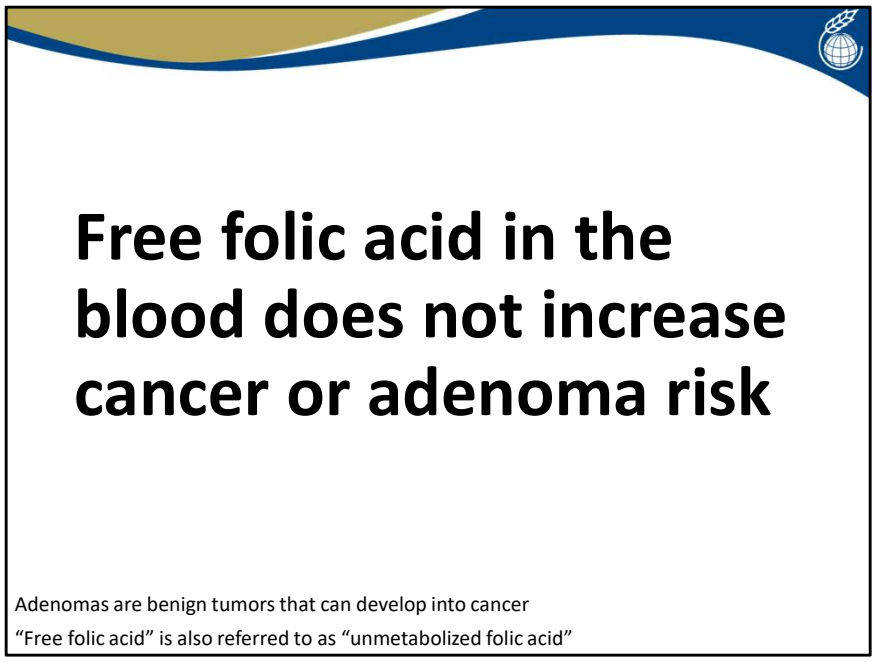
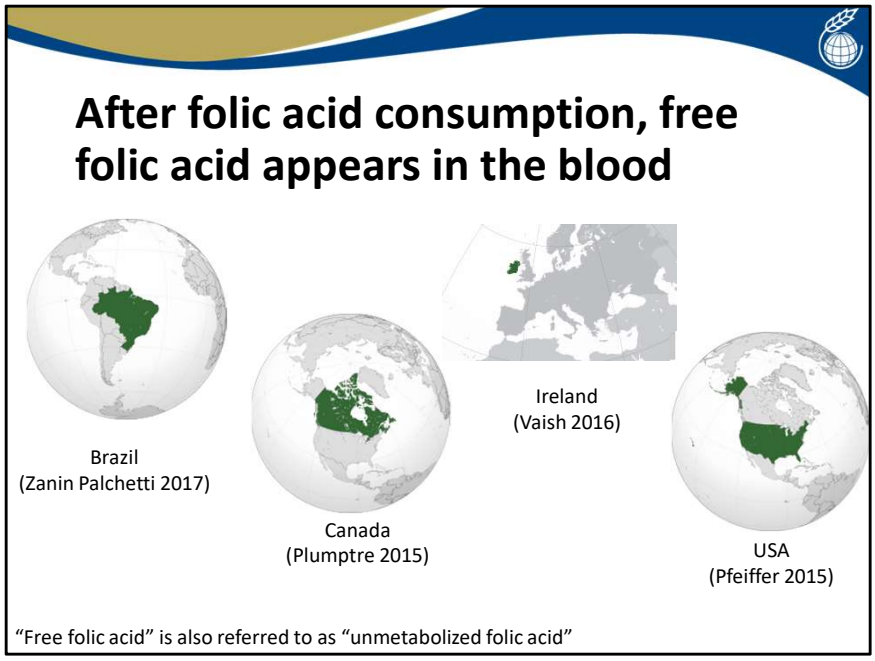
Source:
Vollset SE et al. Effects of folic acid supplementation on overall and site-specific cancer incidence during the randomised trials: meta-analyses of data on 50 000 individuals. Lancet January 25, 2012. http://dx.doi.org/10.1016/S0140-6736(12)62001-7.



In summary, evidence from the United States shows that fortification with folic acid does not increase the number of people diagnosed with colorectal cancer, or the number of people with colorectal cancer who die.



The final point we will review is that free folic acid in the blood does not increase the risk of cancer or adenomas.



Evidence from several countries with mandatory or voluntary food fortification with folic acid shows that free folic acid appears in the blood after folic acid consumption.

This has been observed, for example, in Brazil, Canada, Ireland and the USA.

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Source:
Bailey R et al. Unmetabolized serum folic acid and its relation to folic acid intake from diet and supplements in a nationally representative sample of adults aged ≥60 y in the **United States**. Am J Clin Nutr 2010;92:383–9.

Boilson A et al. Unmetabolized folic acid prevalence is widespread in the older **Irish** population despite the lack of a mandatory fortification program. Am J Clin Nutr 2012; doi: 10.3945/ajcn.111.026633

Pfeiffer CM et al. Unmetabolized Folic Acid Is Detected in Nearly All Serum Samples from **US** Children, Adolescents, and Adults. J Nutr 2015;145:520–31.

Plumptre L et al. High concentrations of folate and unmetabolized folic acid in a

cohort of pregnant **Canadian** women and umbilical cord blood. Am J Clin Nutr 2015;102:848–57.

Vaish 2016 et al. Synthetic folic acid intakes and status in children living in **Ireland** exposed to voluntary fortification. Am J Clin Nutr 2016;103:512–8.

Zanin Palchetti C et al. Association between Serum Unmetabolized Folic Acid Concentrations and Folic Acid from Fortified Foods. JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION 2017, VOL. 36, NO. 7, 572–578. [Study conducted in **Brazil**].

Source for maps: wikipedia

Free folic acid does not increase the risk of total & subtypes of colorectal cancer

Table 2. Association between unmetabolized folic acid level (nmol/L) and the risk of total and subtypes of colorectal cancer*

Endpoint	Unmetabolized folic acid, nmol/L			
	Undetectable	<0.5	≥0.5	P_{trend}
Median, nmol/L	0	0.10	0.53	
Colorectal cancer				
No. of case patients/control	254/437	233/507	131/263	
Crude OR† (95% CI)	1.00	0.94 (0.67 to 1.31)	1.01 (0.74 to 1.38)	.71
Multivariable† OR (95% CI)	1.00	1.03 (0.73 to 1.46)	1.12 (0.81 to 1.55)	.32
Colon cancer				
No. of case patients	152	147	78	
Crude OR (95% CI)	1.00	1.10 (0.75 to 1.59)	0.81 (0.55 to 1.19)	.25
Multivariable† OR (95% CI)	1.00	1.20 (0.82 to 1.77)	0.90 (0.61 to 1.34)	.75
Proximal colon cancer				
No. of case patients	96	83	55	
Crude OR (95% CI)	1.00	1.27 (0.82 to 1.96)	0.99(0.64 to 1.54)	.89
Multivariable† OR (95% CI)	1.00	1.39(0.89 to 2.19)	1.16 (0.73 to 1.85)	.39
Distal colon cancer				
No. of case patients	55	63	22	
Crude OR (95% CI)	1.00	0.79 (0.42 to 1.48)	0.55(0.28 to 1.08)	.08
Multivariable† OR (95% CI)	1.00	0.86 (0.45 to 1.62)	0.56 (0.28 to 1.11)	.11
Rectal cancer				
No. of case patients	45	46	21	
Crude OR (95% CI)	1.00	0.68 (0.32 to 1.45)	0.94 (0.51 to 1.72)	.08
Multivariable† OR (95% CI)	1.00	0.82 (0.38 to 1.77)	1.10 (0.58 to 2.08)	.63

Cho 2015

However, free folic acid in the blood is not harmful. This study looked at the risk of colorectal cancer (colored in blue) and four sub-types of colorectal cancer (colored in pink): colon cancer, proximal colon cancer, distal colon cancer, and rectal cancer.

In the very last column, all of the P-values are greater than 0.05 which suggest that having free folic acid in the blood does not increase the risk of total colorectal cancer, nor the risk of sub-types of colorectal cancer.

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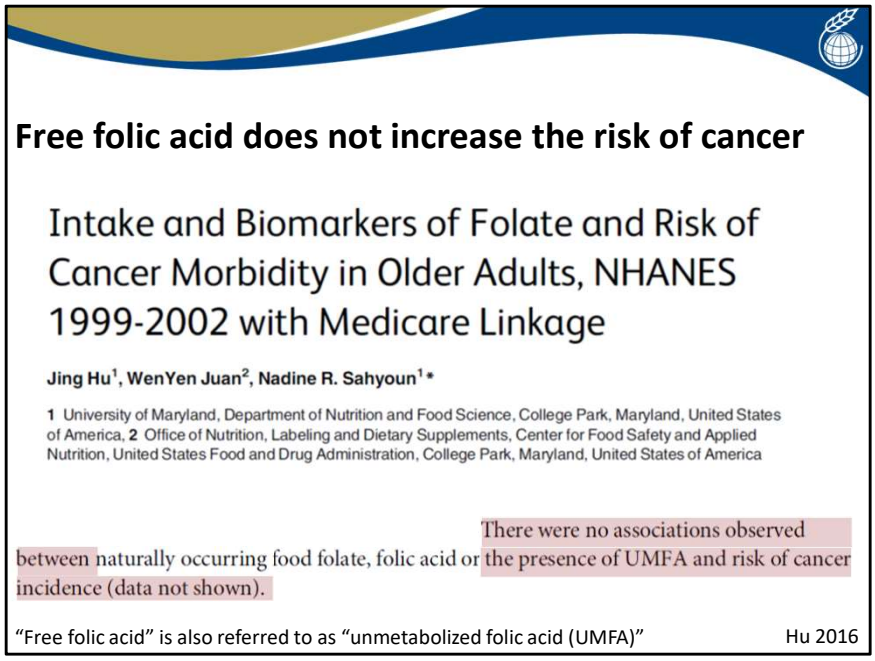
Source:

Cho E et al. Unmetabolized Folic Acid in Prediagnostic Plasma and the Risk for Colorectal Cancer. *JNCI J Natl Cancer Inst* (2015) 107(12): djv260.



This study was published one year later. It used nationally representative data from the USA to examine if there was a relationship between free folic acid in blood and the risk of getting any cancer.

The authors did not present the results in table or figure form. Instead they noted that "there were no associations observed between…the presence of UMFA (which refers to free folic acid) and risk of cancer incidence."

Like the previous study, this investigation showed that having free folic acid in the blood does not increase the risk of overall cancer.

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Source:

Hu J, Juan W, Sahyoun NR (2016) Intake and Biomarkers of Folate and Risk of Cancer Morbidity in Older Adults, NHANES 1999-2002 with Medicare Linkage. PLoS ONE 11(2): e0148697. doi:10.1371/journal.pone.0148697

Free folic acid does not increase the risk of adenomas

Table 2. Associations of plasma mF and UFA levels with risk of adenomas and serrated lesions

	Interval 1[a]		Interval 2[a]	
All adenomas[b]	***N* (events)**	**RR[c] (95% CI)**	***N* (events)**	**RR[c] (95% CI)**
UFA nmol/L				
0	475 (190)	1.00 (ref)	353 (130)	1.00 (ref)
>0–<3	163 (69)	1.04 (0.81–1.33)	111 (38)	0.88 (0.62–1.25)
3–<20	120 (51)	1.00 (0.74–1.35)	91 (45)	1.31 (0.95–1.82)
≥20	129 (45)	0.83 (0.58–1.18)	101 (36)	0.96 (0.64–1.43)
		$P_{heterogeneity} = 0.64$[d]		$P_{heterogeneity} = 0.14$[d]
		$P_{linear\ trend} = 0.13$		$P_{linear\ trend} = 0.81$

Interval 1: three years
Interval 2: an additional three years

RR, relative risk

Adenomas are benign tumors that can develop into cancer

"Free folic acid" is also referred to as "unmetabolized folic acid (UFA)" Rees 2017

This final study examined if there was a relationship between free folic acid in blood and the risk of getting colorectal adenomas, which are benign tumors that can develop into cancer.

Study participants were followed for two periods: interval one which was three years long and interval two which was an additional three years.

In the first column, they divided up the free folic acid levels in blood into four categories ranging from 0 nanomoles per liter to 20 nanomoles per liter or greater.

They then calculated the relative risk (or RR) to determine if there was any relationship between free folic acid levels in blood and the risk of developing adenomas.

It's hard to see, but in the pink values, all of the relative risks include 1. This means that free folic acid levels in blood do not increase the risk of adenomas.

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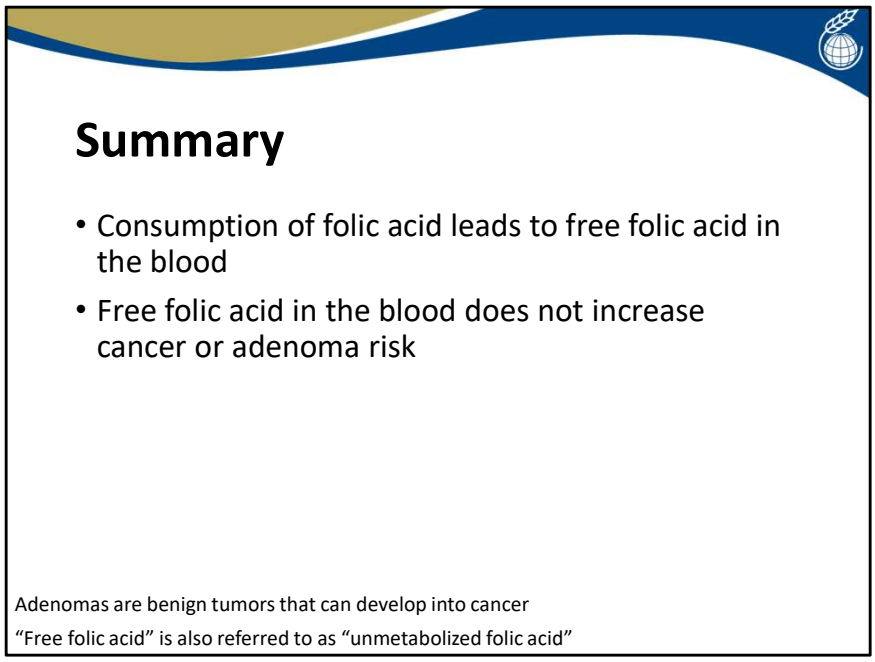
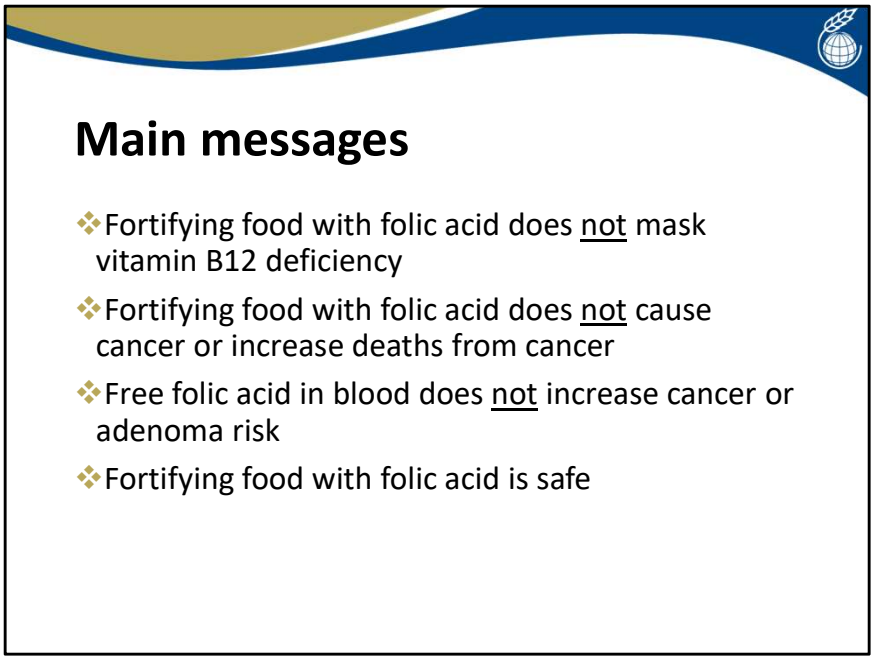
Source:

Rees JR et al. Unmetabolized Folic Acid, Tetrahydrofolate, and Colorectal Adenoma Risk. Cancer Prev Res; 10(8); 451–8. 2017.



In summary, consumption of folic acid leads to free folic acid in the blood.

However, free folic acid in the blood does not increase the risk of developing cancer or of adenomas.



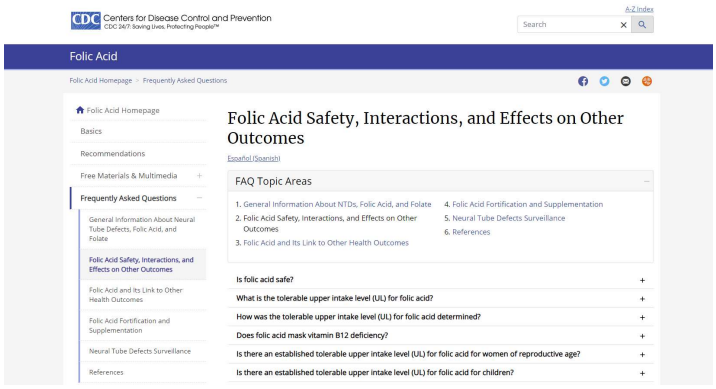
Fortifying food with folic acid does not mask vitamin B12 deficiency.

Fortifying food with folic acid does not cause cancer or increase deaths from cancer.

Free folic acid in blood does not increase the risk of developing cancer or adenomas.

And, fortifying food with folic acid is safe.

More information on the safety of folic acid



https://www.cdc.gov/ncbddd/folicacid/faqs/faqs-safety.html

For more information on the safety of folic acid, please visit this website from the US Centers for Disease Control and Prevention: https://www.cdc.gov/ncbddd/folicacid/faqs/faqs-safety.html

Also, you can contact the Food Fortification Initiative through these links. And, you can reach me via email.

Thank you.