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Nutrition Action HEALTH ETTER**

CENTER FOR SCIENCE IN THE PUBLIC INTEREST

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Nutrition Action's publisher, opened its doors. During that time, much has changed...in the supermarket, on food labels, in restaurants, and in our rapidly expanding waistlines. (See article on p. 10.)

Meanwhile, scientists have tossed out, overhauled, or generated brand new theories about food's impact on our health. (See article on p. 3.)



Unexpected Surprising Findings From the Last 40 Years

BY BONNIE LIEBMAN

oes coffee cause pancreatic cancer? Do B vitamins lower the risk of stroke? Do fruits and vegetables prevent colon cancer? Those are a few of the hunches about diet and disease from the last 40 years that haven't stood the test of time.

Other ideas weren't even on the radar screen in 1971, when the Center for Science in the Public Interest—*Nutrition Action*'s publisher—was founded. Few people suspected that excess pounds could boost the risk of cancer, that vitamin D might protect more than your bones, or that too little sleep could lead to obesity. Here are a handful of findings that few researchers expected 40 years ago.

Excess Pounds Boost Cancer Risk

"We've known since the 1960s about the very strong relationship between weight and endometrial cancer," says Alpa Patel, an epidemiologist who directs the Cancer Prevention Study-3 at the American Cancer Society. (The endometrium is the lining of the uterus.) "But the attention to weight and many other cancers has really been drawn in the last 15 years or so."

And the list of cancers linked to extra pounds keeps growing. In addition to endometrial, the evidence is strongest for postmenopausal breast cancer, as well as cancers of the colon, esophagus, kidney, and pancreas.¹

"And based on what we know so far," adds Patel, there is a "probable association for leukemia in adults, lymphoma, and ovarian, cervical, gallbladder, liver, and aggressive prostate cancer."²

It's not that researchers didn't think to look for a link between weight and cancer. They just got thrown off track.

"One reason was that more postmenopausal women were taking estrogen," explains Walter Willett, chair of the nutrition department at the Harvard School of Public Health. Higher estrogen levels—either from pills or from fat cells—raise the risk of breast cancer.

"If your estrogens are high because you're taking the hormone, it masks the effect of overweight," notes Willett. The estrogen from extra fat cells doesn't make much difference if your levels are already high.

A second reason was that being overweight lowers your risk of breast cancer

Extra pounds raise the risk of postmenopausal breast cancer, as well as colon, esophageal, kidney, pancreatic, uterine, and other cancers.

before menopause and raises your risk of breast cancer after menopause.

"The relationship flips after menopause," explains Willett. "That was definitely not anticipated by anyone." So studies looked at all women, and they saw no clear link. "That made the situation murkier."

Likewise, researchers missed the links between excess weight and prostate cancer because they didn't look separately at aggressive cancers.

"The evidence suggests no association with localized, non-aggressive disease—what you traditionally think of as prostate cancer," explains Patel. "But when you look specifically at high-grade or fatal prostate cancer, you see very consistent relationships with increasing weight."

How much extra weight matters? "For cancers like colon and postmenopausal breast, there's a linear relationship," says Patel. "With increasing weight, there is increasing risk. For other cancers, like pancreatic, you have to reach higher levels of obesity."

And for some cancers, the risk depends on where your body puts the extra fat. As with heart disease and diabetes, a wide waist is worse than wide hips. "For pancreatic and colon cancer, being overweight and apple-shaped may be more harmful than being overweight and pear-shaped," says Patel.

Exactly how obesity might increase the risk of cancer depends on the cancer. "For prostate, breast, ovarian, and endometrial cancer, sex hormones—estrogen and testosterone—seem to drive the increase," notes Patel.

Extra fat cells may mean that the body churns out more cancer-promoting growth factors. "For example, insulin may initiate and promote the progression of cancer growth," she explains. "And insulin-like growth factor 1 is associated with increased cell growth."



Photo: @SXPNZ/fotolia.com.

In other cases, nearby fat cells may be to blame. "For adenocarcinoma of the esophagus or cancer of the liver or gallbladder," Patel points out, "local fat deposits may be detrimental."

What's more, obesity may promote leukemia and lymphoma by boosting inflammation. "In obesity, you have a constant relatively mild inflammatory state," says Patel.

Whatever the mechanism, many people are still surprised to hear that staying lean may trim your odds of getting cancer.

"I don't think the message is out there yet the way it is for heart disease or diabetes, where people clearly know that if I'm heavier, I increase my risk for those chronic diseases," says Patel. "The cancer message is much newer."

And weight matters more than people realize. "Even 15 years ago, it wasn't really appreciated how much weight is related to so many cancers," says Willett. "The number of cancers is increasing."

For any one person, smoking boosts cancer risk more than being overweight, he notes. But for the nation as a whole, obesity matters as much.

"There are probably as many cancers caused by overweight and obesity in the United States as caused by cigarettes, because there are fewer smokers than overweight people."

Coffee Gets a Makeover

"Study Links Coffee Use to Pancreas Cancer," announced the headline in *The New York Times* in March 1981. Earlier studies had raised alarms that coffee might cause heart attacks.

These days, coffee is sounding more like a wonder drug...er, beverage.

"It's turned out to be remarkably safe," says Harvard's Walter Willett. "The evidence is very clear that coffee doesn't increase the risk of pancreatic cancer, and it probably reduces the risk of liver cancer."

In a 2007 meta-analysis, Swedish researchers estimated that people who drank two cups of coffee a day had about a 30 percent lower risk of liver cancer than those who drank none.³ (Researchers don't know whether people who drink decaf also have a lower risk.)

That's not all. "Coffee almost for sure reduces the risk of type 2 diabetes," adds



Regular or decaf coffee may lower your risk of diabetes and gout. Only regular coffee is linked to a lower risk of Parkinson's disease and gallstones.

Willett. When researchers combined nine studies on a total of nearly 200,000 people, they found that those who drank four to six cups of regular or decaffeinated coffee a day had about a 30 percent lower risk of diabetes than those who drank up to two cups a day.⁴

"It looks like coffee reduces insulin resistance," notes Willett. If your cells are insulin resistant, they don't respond well to the hormone, and you have a higher risk of diabetes, heart disease, and gout. That could also explain why people who drink either decaf or caffeinated coffee have a lower risk of gout.⁵

Only caffeinated coffee may lower the risk of Parkinson's disease and gallstones.^{6,7} "The mechanism is not clear, but the evidence is quite strong for Parkinson's," explains Willett.

His bottom line: "Coffee has turned out to be a health-promoting beverage rather than a carcinogen."

Vitamin D May (or May Not) Work Wonders

Forty years ago, vitamin D was just another ho-hum, run-of-the-mill nutrient. It was good for bones because it helps the body absorb calcium. Nothing special.

These days, you can scarcely pick up a nutrition journal or magazine without finding a study about the benefits of vitamin D. From cancer, heart attacks, and stroke to type 2 diabetes, depression, and autoimmune diseases, it seems as though vitamin D can prevent almost anything.

"It's unquestionable that vitamin D has far more extensive biological effects than just the relationship with fracture risk," says Harvard's Walter Willett.

"A study recently found over 2,700 places for vitamin D binding sites on the genome," he notes. "And there was a heavy concentration around genes related to autoimmune diseases like lupus, multiple sclerosis, and rheumatoid arthritis. That was pretty remarkable."

That's one reason why researchers at Harvard and elsewhere have launched the VITAL trial, which is giving either a placebo or 2,000 IU a day of vitamin D to 20,000 healthy older men and women.

"We're looking primarily at cancer and cardiovascular disease, but also at diabetes, depression, cognitive function, and autoimmune disease," says JoAnn Manson of the Harvard Medical School, who is leading the study. "Results are expected in 2016 at the earliest."

What to do in the meantime? In November, a panel of scientists at the National Academy of Sciences' Institute of Medicine announced that most people don't need to take vitamin D supplements.⁸

"There's concern that vitamin D deficiency and inadequacy have been overestimated in the United States and Canada," explains Manson, who served on the panel.

The problem: "People go to the doctor for a physical and for blood tests and are told that their vitamin D level is below 30 nanograms per milliliter, so they should take high doses," she notes. (It's difficult to get more than 200 or 300 IU of vitamin D from foods, even if they're fortified, so many people have to rely either on sun exposure, which can damage skin, or on a supplement.)

"Then they're told to come back for another test and to take higher doses of supplements until their vitamin D blood levels rise above 30 or 40 nanograms per milliliter. That is not a good idea."

Why? The panel was worried that taking high doses of vitamin D may be harmful. "There's increasing evidence that there may be risk at both low and high blood levels," says Manson.

For example, a 2006 study of Finnish male smokers found a higher risk of pancreatic cancer among those with higher

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New Advice on Vitamin D & Calcium

Vitamin D			
Age	RDA (IU)	Upper Level (IU)	
1 to 3 years	600	2,500	
4 to 8	600	3,000	
9 to 70	600	4,000	
71 and older	800	4,000	

Calcium

Age	RDA (mg)	Upper Level (mg)
1 to 3 years	700	2,500
4 to 8	1,000	2,500
9 to 18	1,300	3,000
19 to 50	1,000	2,500
51 to 70 (men)	1,000	2,000
51 to 70 (women)	1,200	2,000
71 and older	1,200	2,000

Source: Institute of Medicine.

What got lost in some headlines: The new Institute of Medicine report *raised* the Recommended Dietary Allowances and safe upper intakes for vitamin D and calcium.

blood levels of vitamin D.⁹ A 2009 study of (mostly non-smoking) U.S. men and women found a similar link, but curiously, it only showed up in people from states with low sun exposure.¹⁰

Harvard's Willett isn't concerned. "If you do enough studies, you'll always find some associations," he notes. The National Academy of Sciences' vitamin D report misinterpreted some evidence and raised alarms unnecessarily, he argues. "It was like they were dredging the whole data set to look for harm and to discount any benefit."

Randomized trials should answer the question, says Manson. "Until we have large-scale trials of high doses of vitamin D, we should be cautious. We shouldn't forget the lessons of other nutrients—like beta-carotene—where large doses showed no benefit and even caused harm in smokers."

But the controversy shouldn't matter to most people. What got lost in many headlines is that the panel actually *raised* the Recommended Dietary Allowance for vitamin D from 400 to 600 IU a day for adults up to age 70 and from 600 to 800 IU for people over 70 (see "New Advice on Vitamin D & Calcium").

Our advice: take a daily supplement

with the new RDAs. They should be safe. In fact, the report boosted the Tolerable Upper Intake Level (the highest safe daily dose) from 2,000 to 4,000 IU.

That way, if vitamin D turns out to prevent disease, you're covered.

What's more, taking a supplement is safer than getting more sun. "UV exposure is a carcinogen that's related to skin cancer and skin aging," warns Manson.

Too Little Sleep Can Lead to Too Much Fat

Thirty or 40 years ago, who would have sus-

pected that too little sleep could show up on your bathroom scale? Today, we sleep less and weigh more...and the two may be related.

The average American now sleeps one or two hours less per night than he or she did 40 or 50 years ago. In 1960, an estimated 16 percent of young adults slept fewer than seven hours a night. Today it's 37 percent.

"We now have lots of studies on sleep and obesity," explains Kristen Knutson, assistant professor of medicine at the University of Chicago. "And most find that short sleepers are more likely to be obese than longer sleepers."

A "short sleeper," she notes, is "someone who typically sleeps fewer than six hours a night." But the link is stronger if you look at just five-hour-a-nighters.

For example, in a study that tracked more than 68,000 women, those who slept fewer than five hours a night were 32 percent more likely to gain roughly 30 pounds over the next 16 years than those who slept for at least seven hours a night.¹¹

To find out how sleep deprivation might alter fat deposits, Knutson and her colleagues enrolled volunteers who slept overnight in a laboratory. When they were allowed to sleep for just four hours a night for one or two nights, the researchers saw more ghrelin (a hormone that increases appetite) and less leptin (a hormone that tamps down appetite) than when the volunteers were allowed to sleep for nine hours.¹²

"We also asked each person, 'Are you hungry?' during the day," notes Knutson. "After two days of short sleep, people were hungrier than after the long sleep."

And the more ghrelin and leptin changed, the more hunger changed. "That confirmed our suspicions that these hormones are having a strong effect on appetite," she adds.

In a month-long study, volunteers averaged 1,090 calories a day from snacks when they were allowed to sleep for 5½ hours a night, but only 870 calories a day from snacks when they could sleep for 8½ hours. (The participants, who couldn't leave the lab during the study, were allowed to eat as much as they wanted.)

They got their extra calories mostly from high-carb snacks like pretzels, chips, crackers, popcorn, snack bars, muffins, cookies, pudding, ice cream, and candy. And they snacked more after 7 p.m.

"The less people are allowed to sleep, the more they snack, and it's not just because they're awake for more hours," says Knutson.

Why would lack of sleep lead to less leptin and more ghrelin?

"Sleep restriction is associated with increased sympathetic nerve activity—the flight-or-fight response," explains



Getting only five or six hours of sleep a night may boost your appetite for high-carb snack foods.



Knutson. That stress response "could explain why sleep affects not just leptin secretion but glucose metabolism and insulin resistance."

And insulin resistance—which means that the body's insulin does a lousy job of lowering blood sugar levels—raises the risk of heart disease and diabetes.

Sure enough, "In a recent meta-analysis, short sleepers were more likely to develop diabetes than normal sleepers," says Knutson. Short sleepers are also more likely to end up with high blood pressure. 14,15

What's the next step? "To see if extending sleep will make good things happen," she says. "Does it benefit insulin resistance, blood pressure, inflammatory markers, and appetite hormones?"

Time will tell.

Sugary Beverages, Even Fruit Juices, Cause Trouble

"People have known for a long time that sugary beverages weren't necessarily good for you," acknowledges Harvard's Walter Willett. But 40 years ago, most experts were largely worried that sodas would rot your teeth.

Studies now link soft drinks and other sugar-sweetened beverages to a higher risk of weight gain, diabetes, the metabolic syndrome, heart disease, and gout.¹⁶⁻¹⁹

"Sugary beverages are much more of a problem than they were 30 years ago," adds Willett. "That's because we drink more, we've gained weight, and we're moving less.

"It's the amount of beverage consumed, and the interaction with underlying insulin resistance due to inactivity and overweight," he explains. "On top of that, we're consuming too many carbohydrate calories in general, and they're easier to overconsume in a beverage form."

Even fruit juice has lost its all-you-candrink, clean bill of health.

In a study of 51,000 women, those who increased their juice consumption over four years gained more weight (about nine pounds) than those who cut back on juice (about five pounds).²⁰ And women who drink more orange juice have a higher risk of gout.¹⁹

Juice is clearly more nutritious than soft drinks, but it's still liquid calories



Sugary beverages—even fruit juice—may boost your risk of weight gain and gout.

that don't curb your appetite as much as solid foods do.

"Juice is a little complicated because if someone is low in vitamin C and has a small glass of orange juice every day, that's a plus," says Willett. "The problem is that many people consume juices as their primary beverage." And they drink 8 to 16 ounces at a time, not the classic six-ounce juice glass.

"If you're highly lean and athletic, you can tolerate three or four glasses of juice a day," explains Willett. "But that doesn't describe much of the American public. For many people who drink multiple glasses a day, the harm starts to outweigh the benefits."

When a group of scientists issued advice on beverages in 2006, he notes, "we recommended not more than one small glass of juice a day."

Antioxidants (Mostly) Disappoint

Cancer, heart disease, memory loss, type 2 diabetes, cataracts, macular degeneration. Antioxidant vitamins (C, E, and beta-carotene) were supposed to help prevent all of them. So far, the three antioxidants (plus zinc) have succeeded with only one: slowing the pace of macular degeneration in older people who already have the eye disease.²¹

"The randomized trials for antioxidants have been very disappointing," says Harvard's JoAnn Manson, who led the Women's Antioxidant Cardiovas-

cular Study, the Women's Folic Acid Study, and other major trials.

What's more, "some risks have been identified that suggest that high-dose antioxidant supplements should be avoided."

For example, the Physicians' Health Study II gave roughly 14,600 men aged 50 or older either vitamin E (400 IU every other day), vitamin C (500 mg a day), and/or a placebo.²² The only significant difference after eight years: "Vitamin E increased the risk of hemorrhagic stroke," notes Manson.

In a recent meta-analysis of multiple trials, researchers estimated that high doses of vitamin E (200 to 800 IU a day in most studies) would prevent one ischemic stroke in every 476 people, but would cause one hemorrhagic stroke in every 1,250 people.²³

A hemorrhagic stroke (caused by a burst artery in the brain) is more devastating than an ischemic stroke (caused by a blocked artery in the brain). But even if the damage were equivalent, the odds wouldn't justify taking vitamin E.

And in 2005, the HOPE-TOO trial—which gave vitamin E (400 IU a day) or a placebo to roughly 10,000 people with diabetes or a history of heart attack, stroke, or peripheral artery disease—reported a 13 percent higher risk of heart failure in the vitamin E takers.²⁴

"Overall, most randomized trials have suggested either a neutral or adverse effect of high-dose vitamin E," says



Most studies that tested high doses of antioxidant vitamins (C, E, and betacarotene) on the risk of heart disease and cancer have come up empty.

Manson. "So from a public health standpoint, we can't recommend taking it at this point."

Vitamin C hasn't lived up to expectations either. The Women's Antioxidant Cardiovascular Study gave vitamin C (500 mg a day), vitamin E (600 IU every other day), and beta-carotene (83,000 IU every other day) to roughly 8,100 women with a history of heart disease. After nine vears, the risk of a heart attack, stroke, or other cardiovascular event was no lower in those who took vitamin C (or the other vitamins).25

"We have tested vitamin C rigorously," says Manson. "We've seen no benefit for cardiovascular disease or cancer."

(And, despite Linus Pauling's predictions from the 1970s, high doses of vitamin C don't seem to ward off colds. At best, they might shorten a cold by less than half a day.)

As for beta-carotene, high doses actually raised the risk of lung cancer and heart disease in Finnish smokers and American men who had been exposed to asbestos.^{26,27} The only ray of hope: in the Physicians' Health Study II, which included few smokers, men who got 83,000 IU of beta-carotene every other day for 18 years had better scores on tests of verbal memory (and no higher risk of lung cancer or heart disease).28

"Overall, we have not seen benefits for antioxidants and diabetes, heart disease, eve diseases, and cancer," concludes Manson.

Does that kill the hypothesis that antioxidants protect the body?

"It may still be reasonable," says Manson. "We don't know how much is being absorbed and whether it's actually being delivered to the critical tissues."

Perhaps the antioxidants never reached their targets. Or maybe the trials didn't last long enough. "Our trials have been too late and too short," says Harvard's Walter Willett.

"Also, if you're giving antioxidants to people who are eating very well to begin with, then you probably don't add too much. Trials need to start with people who have low intakes, because they're the people in whom the benefit is more likely to be seen," he notes.

"But we do know that these supplements as they've been tested—the supplements that people are buying overthe-counter," says Manson, "have not demonstrated benefits for cardiovascular disease or cancer."

Insulin Resistance Arrives

"In 1970 or the late 1960s, insulin resistance wasn't thought to exist," says Gerald Reaven, professor emeritus of medicine at Stanford University. Between a quarter and a third of Americans now have it. he adds.

"In the last 20 years, insulin resistance has become implicated in diabetes, heart disease, sleep apnea, various cancers, nonalcoholic fatty liver disease, and polycystic ovary disease," says Reaven.

If you're insulin resistant, your pancreas secretes plenty of the hormone. But the insulin doesn't do a good job of admitting blood sugar into your cells.

What makes muscle insulin resistant? "We tried to find the cause," says Reaven, whose team was the first to identify insulin resistance and show that it played

But after years of searching, he acknowledges, "my guess is that it's never going to be one thing. We've been looking for insulin resistance genes, but it's hard to find any one jumping out."

a role in diabetes.

Genes probably explain half of your

risk, he estimates. The other half is lifestyle. "If you gain 15 or 20 pounds, you

High triglycerides and low HDL ("good") cholesterol are signs of insulin resistance. Too many carbs may make triglycerides and HDL worse.

get worse. If you become sedentary, you become worse."

If you are insulin resistant, eating too much may matter more than what you

eat, adds Reaven. "If you lose weight, it doesn't matter a great deal which diet you lose weight on." But if you're not losing weight, too many carbs can cause trouble.29

"If you're eating more carbohydrates, one of two things is going to happen," says Reaven. "You can put out even more insulin to maintain blood sugar levels. Or, if you can't, blood sugar goes up." Both mean a greater risk of diabetes and heart disease.

How do you know if you're insulin resistant? High triglycerides (above 150) and low HDL (below 40 for men and below 50 for women) are the best clues.

"If I know that a patient has high triglycerides and low HDL, I tell them to eat less carbohydrate," explains Reaven. He suggests replacing carbs with unsaturated fats like oils, salad dressings, fatty fish, nuts, avocado, mayonnaise, etc.

"If you're not insulin resistant, then it doesn't make much difference," says Reaven. "You're so good at putting away blood sugar that increasing the load is going to have a trivial effect."

Fruits and Vegetables Switch

"Not so long ago many people believed that eating five servings of fruits and vegetables a day would cut the risk of cancer by as much as half," says Harvard's Walter Willett.

In particular, experts agreed that there was "convincing" evidence that vegetables could prevent colon cancer.

But by 2000, the National Cancer Institute's Polyp Prevention Trial reported no fewer pre-cancerous colon polyps in people who had upped their fruits and vegetables from four to six servings a day for four years.³⁰ (The participants also cut back on fat and boosted whole grains and beans.) Disappointing studies on other cancers followed.

"It's pretty clear now that the relationship between fruits and vegetables and overall cancer is pretty weak," acknowledges Willett. "The 50 percent reduction was way off target."

But that doesn't mean you can forget broccoli and cantaloupe. For starters, fruits and vegetables are remarkably low in calories. "And there is a clear benefit for heart disease and stroke," adds Willett.

He cites two kinds of evidence. The





Fruits and vegetables may help prevent heart disease and obesity, but are unlikely to lower your risk of most cancers.

Dietary Approaches to Stop Hypertension (DASH) study measured blood pressures on different diets.³¹ "The DASH study showed that fruits and vegetables reduce blood pressure," notes Willett.

"And in cohort studies, people who consume more fruits and vegetables have a lower risk of heart attack and stroke."

For example, in a study of 37,000 men and 72,000 women, those who ate at least five servings of fruits and vegetables a day had a 28 percent lower risk of heart attacks and strokes than those who averaged only 11/2 servings a day. 32

"When both kinds of evidence are reproducible and firm, that makes a very strong case," argues Willett.

B Vitamins Win Some, Lose Some

Each year, neural tube birth defects strike roughly one in 1,000 pregnancies. Those born with spina bifida (a hole in the spine) survive. Those with anencephaly (no brain) don't.

In randomized trials, the B vitamin folic acid prevents roughly half of neural tube defects. But there's a catch: the defects occur so early that women have to take the folic acid before they know that they're pregnant.

"Folic acid prevents neural tube defects," says Harvard's JoAnn Manson. "So it's very important that women of childbearing age—not just those who know that they're pregnant—take a

daily multivitamin to ensure that they have adequate folic acid in early stages of the pregnancy. I hope that point doesn't get lost."

But researchers had other hopes for B vitamins. They had clues that a mix of three B vitamins (folic acid, B-6, and B-12) could cut the risk of heart disease and stroke by lowering blood levels of a harmful amino acid called homocysteine. The vitamins struck out.33

"The randomized trials of B vitamins have been very disappointing," says Manson. "A recent meta-analysis looked at all trials to date for B vitamins and heart disease, stroke, and cancer and found no benefit across the board."34

Only two findings have given researchers hope.

When Manson and colleagues gave roughly 5,000 women at high risk for heart disease folic acid (2,500 mcg), vitamin B-6 (50 mg), and vitamin B-12 (1,000 mcg) every day for seven years, their risk of macular degeneration was 30 to 40 percent lower than the risk of placebo takers.35 Macular degeneration —a deterioration of the retina—is the leading cause of blindness in older people.

"That was a very exciting finding," recalls Manson. "This is only one trial, but I think there will be much more research in that area."

The other promising result came in a study that gave B vitamins to roughly 2,000 healthy women aged 65 or older for five years.36

As a group, the vitamin takers did no better on memory tests. "But in people who started out with low intakes of the B vitamins," notes Manson, "there was a suggestion of less decline in cognitive function than in those who got a placebo."

A suggestion is far from proof. But "a recent study suggested some benefit for high-dose B vitamins," adds Manson.

British researchers reported that among people over 70 with mild cognitive impairment—which often turns into Alzheimer's—those who took B vitamins for two years had less brain atrophy than those who took a placebo, but only among people who started out with high levels of the amino acid homocysteine.37

"The findings are promising enough that more research should be done," says Manson.

Why wait before rushing out to buy B vitamins? "Concerns have been raised that doses of folic acid over 400 mcg a day may increase tumor cell growth and proliferation once there's a pre-existing cancer," cautions Manson.

"So until more research is done, we can't assume that high doses of folic acid are harmless when it comes to cancer."

³⁶ Am. J. Clin. Nutr. 88: 1602, 2008. 37 PLoS One 5: e12244, 2010.



Folic acid can prevent birth defects, but it and other B vitamins won't lower your risk of heart attack or stroke.

¹ WCRF/AICR. Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective. Washington, DC: AICR, 2007.

² N. Eng. J. Med. 348: 1625, 2003.

³ Gastroenterol. 132: 1740, 2007.

⁴ JAMA 294: 97, 2005.

⁵ Arth. Rheum. 56: 2049, 2007.

⁶ Am. J. Epidemiol. 160: 977, 2004.

⁷ JAMA 281: 2106, 1999.

⁸ books.nap.edu/openbook.php?record_id=13050.

⁹ Cancer Res. 66: 10213, 2006.

¹⁰ Cancer Res. 69: 1439, 2009.

¹¹ Am. J. Epidemiol. 164: 947, 2006.

¹² Ann. Intern. Med. 141: 846, 2004.

¹³ Am. J. Clin. Nutr. 89: 126, 2009.

¹⁴ Diabetes Care 33: 414, 2010.

¹⁵ Arch. Intern. Med. 169: 1055, 2009. ¹⁶ Am. J. Clin. Nutr. 84: 274, 2006.

¹⁷ Diabetes Care 33: 2477, 2010.

¹⁸ Am. J. Clin. Nutr. 89: 1037, 2009.

¹⁹ JAMA 304: 2270, 2010.

²⁰ JAMA 292: 927, 2004.

²¹ Arch. Ophthalmol. 119: 1417, 2001.

²² JAMA 300: 2123, 2008.

²³ BMJ 341: c5702, 2010. doi: 10.1136/bmj.c5702.

²⁴ JAMA 293: 1338, 2005.

²⁵ Arch. Intern. Med. 167: 1610, 2007.

²⁶ N. Eng. J. Med. 330: 1029, 1994.

²⁷ N. Eng. J. Med. 334: 1150, 1996.

²⁸ Arch. Intern. Med. 167: 2184, 2007.

²⁹ Am. J. Clin. Nutr. 84: 813, 2006.

³⁰ N. Eng. J. Med. 342: 1149, 2000.

³¹ N. Eng. J. Med. 336: 1117, 1997.

³² J. Natl. Cancer Inst. 96: 1577, 2004.

³³ JAMA 299: 2027, 2008.

³⁴ Arch. Intern. Med. 170: 1622, 2010.

³⁵ Arch. Intern. Med. 169: 335, 2009.