4. Disappointing News Regarding the Role of Folic Acid Supplementation in the Reduction of Breast Cancer Risk

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Reference: Stolzenberg-Solomon RZ, Chang S-C, Leitzmann MF, et al. Folate intake, alcohol use, and postmenopausal breast cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Am J Clin Nutr* 2006;83:895904.

Design: Prospective observational study

Participants: 25,400 American women who were 5574 years old at baseline

Outcome Measures: Incident cases of breast cancer (CA) were studied in terms of baseline alcohol (etOH), dietary folate, and intake from folic acid supplementation, all determined from food frequency questionnaires. These findings were compared with similar data for women who remained breast CA-free.

Key Findings: 691 cases of breast CA developed during a 9.7-year follow-up. Overall, women taking at least 400 mcg/day of folic acid from supplements had a 19% *higher* risk of breast CA compared with women not taking such supplements (adjusted HR=1.19, 95% CI: 1.01, 1.41; P for trend=0.04). Women in the highest quintile of folate intake from food had essentially the same risk of breast CA as women in the lowest quintile (adjusted HR=1.04, 95% CI: 0.83, 1.31, NS). When supplemental folic acid was included, women in the highest quintile of intake had a 32% *higher* risk of breast CA compared with women in the lowest quintile (adjusted HR=1.32, 95% CI:1.04, 1.76; P for trend=0.03). A statistically significant 37% increase in breast CA risk appeared in women in the top quintile of etOH intake when compared with those in the bottom quintile. This increase in risk was more apparent in those consuming less dietary folate. (See below for more details).

Practice Implications: Most researchers now accept that etOH consumption in women increases the risk of breast CA, a finding independently confirmed by the current study. Though this effect may result in part from alterations in estrogen metabolism, some of the effect is hypothesized to be related to alterations in DNA methylation reactions. Folate from food and folic acid from supplements act as methyl donors and facilitate the normalization of these same reactions.

Thus, when researchers previously found that the increased risk of etOH-induced breast CA mostly disappeared in the presence of high dietary folate or by relatively high serum folate levels -- a situation now reported by several research teams and for several other cancers as well -- it seemed plausible that folic acid supplementation might reduce this risk.

In hindsight, this supposition may have been based on inadequate information. High dietary (and therefore high serum) folate correlates with many dietary and lifestyle factors and might simply be a marker for something as yet unknown that protects women on a high folate diet. Even now, no *intervention* trial has examined whether folic acid supplementation reduces the risk of breast CA in women who consume etOH.

The current observational study found no evidence that folic acid supplements protect against breast CA. These findings may have been affected by a variety of variables other than the supplements themselves. For example, since the FDA mandated folic acid fortification of foods (which occurred in the middle of the nearly 10-year follow-up), American women have collectively been consuming significantly more folic acid than they used to, regardless of whether they do or do not take additional folic acid supplements. This factor may have masked a protective effect resulting from the supplementation of folic acid in a more deficient population.

In this study, total folate intake correlated -- positively or inversely -- with literally *dozens* of factors that are linked with breast CA risk. For example, increasing folate intake -- apparently with or without supplements -- correlated positively with lower body mass index and more exercise, both of which are associated with a lower breast CA risk. On the other hand, increasing folate intake also correlated with younger age at menarche, older age at menopause and first delivery, a history of benign breast disease, HRT use, and several other factors known to be associated with an *increased* risk of breast CA. Almost all of these associations were highly statistically significant. When viewed collectively, these confounders tilt the scale toward identifying folic acid supplementation as being less protective than it otherwise would appear to be.

Seeing the obvious -- that these confounders would badly skew then data -- the researchers made a diligent effort to erase the effects of the confounding variables through multivariable adjustment. After ruling out nine major confounders, those who had been taking folic acid supplements at a potency <400 mcg/d had an 8% *increased* risk of breast CA compared with those taking no supplements. Those taking ≥400 mcg/d had a 16% *increased* risk. Neither of these associations was statistically significant, but surely there is nothing in these trends to suggest protection. Clearly, these trends run against our previous expectations.

As stated above, breast CA risk increased with increasing etOH consumption. When looking only at subjects with overall low folate intake (defined as ≤335.5 mcg/d), those in the highest quintile of etOH intake had over twice the risk of breast CA compared with those consuming essentially no etOH. For those consuming higher levels of folate however, *including both, food and supplemental sources,* the highest quintile of etOH intake was associated with a more modest 23% increased risk. Though hidden in a mountain of other data, these figures are arguably the most important. No one has suggested that folic acid would reduce breast CA in women who do not consume etOH, so the large portion of data in the current study dealing with nondrinkers or women drinking very little are at best irrelevant and at worst throwing us off the trail of what's really happening.

The fact that higher folate intake indeed appears to have shrunk some of the increased risk of breast CA observed in those women who consumed etOH but lower levels of folate may be important and tends to underscore rather than contradict findings from previous reports. Unfortunately, while *overall* folic acid supplement use correlated with an increased risk, the current study does not specifically look at such supplement use in terms of breast CA risk in drinkers.

Some of the numbers in this report appear odd indeed. The *highest* quintile of etOH intake was listed as only 7.62 g of etOH per day. That's less than one drink per day. A summary of previous studies would suggest that a full one drink per day might increase risk by only about 10%. Yet these researchers reported essentially a *doubling* of risk in those with low folate intake consuming less than one drink. This does not fit with most previous reports.

What are we to do with these complex data? Before seeing any results from a randomized trial (to date there are none), we have not yet proven that folic acid supplementation is useless in preventing breast CA in etOH-consuming women. However, the current observation of a trend showing that *increased* folic acid supplementation is associated with an increased risk, should keep practitioners from recommending folic acid as a way to reduce the risk induced by etOH -- at least until we have more information. Until then, the best way for women to avoid the increased risk of etOH-induced breast CA would appear to be avoidance of etOH.