

Jeffrey Bland Video Blog Transcript
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Well you know, there are always plenty of things to talk about in our field—it's amazing—the most recent one of which is this intervention trial that was recently published in *The New England Journal of Medicine* about folic acid intake and its relationship to colorectal polyps and prevention of adenomatous premalignancy and maybe even colon cancer. I'm sure you were as anxious to see that data as I was because this is a major intervention trial that is very well done, well constructed, multi-centered. It certainly is designed in such a way to be able to pick up certain things in this group population of people that have pre-existing polyps and then seeing if folic acid had anything to do with their recurrence and their transformation into malignancy.

The results, as you know, were really not very encouraging. They didn't show any positive benefit in chemoprotection (giving folic acid at a milligram a day), and there was even some statistical evidence that maybe people that had the most severe graded initial polyps then had, actually, a higher risk with folic acid supplements than those that did not take folic acid. Here is another one of those studies that we say, "Gee whiz, why?" And I think it is very complex. As you probably recognize from reading the studies that have been preceding this trial, there are many different bits of controversy related to the role folic acid has in neoplasia. There is some evidence to suggest (from animal studies) that it is chemopreventive, and there are some studies from animals and epidemiological work suggesting that it actually facilitates the growth of tumors once they are formed. The general thought that I think is emerging from this work is that folic acid in prevention (early stage), by proper formation of methylation of tumor suppressor and tumor activation and regulating gene expression through maybe the silencing of oncogenes, appears to be correct, but then later, if there is a carcinoma in situ, that maybe folic acid stimulates the growth of that tumor, just as you find with the converse being folate drugs like methotrexate that uses anti-cancer agents that try to arrest existing tumor growth. I think that what we can say is nothing is ever as simple as it seems.

Then we further put on top of this the recognition that—in studies that I have here that have been recently published in 2007, 2006—there is a cohort of individuals that may have the most sensitivity, which are those that carry the methylenetetrahydrofolate reductase polymorphism. In those cases, maybe MTHFR polymorphism is a multiplier or a sensitizing factor for this folate story that then colors the data, knowing that between 10% of the population has the homozygous TT MTHFR genotype and another 25% has the heterozygous CT form. So the way that penetrates in population is maybe 20-30% of the population carrying these various sensitivities to folic acid, and so that can alter, also, the outcome of a population-based study.

Let me, if I can, conclude by saying I think where we are going in all of this—taking all of the intervention trials that have been published to date with nutrients—this recognition that nutrition is for individuals, that statistical humans are of little interest (Roger Williams said this years ago), and that we need to start stratifying for genotypes. We need to look, actually, at who responds to what based upon these genotypic markers, and we need to recognize that these studies that come out ambiguous or kind of with mixed not-positive-not-negative results probably indicate that we haven't stratified our populations correctly to get the most sensitive individuals. By the way, this same model would hold true also for many pharmaceutical products as well—that when properly stratified for individuals at highest sensitivity, probably you get much better and more positive results.

So that's my story. I hope you are following it with me.