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Vitamin D and cancer: Can we believe the evidence from observational studies?

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Guest:
Dr. Nancy Cook is a Biostatistician at the Brigham and Women's Hospital and Professor at Harvard Medical School and a Professor of Epidemiology at the Harvard Medical School of Public Health.

Bob Barrett: This is the podcast from *Clinical Chemistry*. I am Bob Barrett.

Chemicals in tobacco smoke may influence vitamin D metabolism and function, and vitamin D itself may modify the carcinogenity of tobacco smoke. In the May 2013 issue of *Clinical Chemistry*, a study from the University of Copenhagen in Denmark examined this relationship, and the lead author of that paper, Dr. Børge Nordestgaard, joined us for a separate podcast.

In the same issue of *Clinical Chemistry*, Dr. Nancy Cook published an editorial questioning the use of observational data such as those to draw conclusions regarding clinical recommendations for use in cancer prevention. Dr. Cook is a Biostatistician at the Brigham and Women's Hospital, and a Professor at Harvard Medical School, and a Professor of Epidemiology at the Harvard School of Public Health. She joins us in this podcast.

Dr. Cook, the study from the Copenhagen Group in *Clinical Chemistry* showed an increase in tobacco related cancers among those with low levels of vitamin D. What sort of problems are there with observational data such as those?

Dr. Nancy Cook: Well, observational data can suffer from a number of biases, including confounding biases, especially for exposures that involve individual choice or individual behaviors. For example, those who take a particular drug might be different than those who don't; they might be of an either better health or worse health. So you need statistical methods to account for such things; that's called confounding by indication.

And, it's also true for studies of diet, or other lifestyle behaviors. Those who adhere to a particular aspect of diet who eat say fruits and vegetables, or other lifestyles such as physical activity, they may do other healthy behaviors too. People with a healthy diet maybe more active; they might

exercise more, they may not be smokers for example. So, it's very important to control for these other factors, in analysis of observational data.

That's why evidence from randomized trials can be a lot stronger, because people don't choose their treatment group. So, there is less likely to be confounding in general from these other sources.

Bob Barrett: Is this a particular problem for micronutrients like vitamins and trace elements or is it more widespread?

Dr. Nancy Cook: Well, it is widespread, but it's particularly true for micronutrients. And the problem there is that it's very difficult to separate these out.

There are many different micronutrients, and they tend to be correlated in a healthy diet. So, it's hard to tease out what the individual beneficial components are.

There have been a lot of studies now looking at healthy diets, fruits and vegetables, etc. And in the 1980s, it was thought that perhaps this was due to beta-carotene. There were some studies in pharmacodynamics which supported this, there are studies of blood levels of beta-carotene, and also dietary intake. So, there is a lot of observational data which suggested that maybe taking beta-carotene might be helpful.

So, there were some studies done including the Physicians Health Study which was done here at the Brigham and Women's Hospital, as well as some others, that ended up showing no effect. In fact, some studies suggested an increase in risk among smokers, or asbestos workers. So, that was pretty disappointing.

And then later on in the 1990s or so, it was thought that vitamin A was the new wonder drug. It was thought to be protective against cardiovascular disease. Now, this is an antioxidant, and a lot of basic research had shown that antioxidants tend to reduce atherosclerosis. It was a lot of observational data related to plasma levels, and also to diet, that showed that there was a reduction in cardiovascular disease in those with high levels of vitamin E. And in fact, by 2000, about 13% of US adults were taking vitamin E. So, it's very popular thought to be well supported.

However, when trials were done, they showed no effect. The Women's Health Study which was done again here, and the Physicians' Health Study II showed no overall effect of vitamin E on cardiovascular disease. In fact, some meta-analyses even suggested some increase, slight increase in mortality, although others have not, that really hasn't held

up. But, it did not show the protective effect that everyone expected.

Now, people have argued that it wasn't the right form of vitamin E that was tested. Trials used alpha-tocopherol, some said it was gamma-tocopherol or mixed tocopherols that might actually help. But, in general, the enthusiasm for vitamin E certainly has been diminished. The same has been true for the B vitamins and for vitamin C; the promising hypotheses that were seen with observational data just didn't hold up in trials. I will say though that there still is a consistent effect for fruits and vegetables, and most of that has been based on observational studies.

But, there are now some trials that have shown protective effects too. For example, the DASH studies looking at diet and blood pressure have shown there is an effect of a healthy diet, the DASH diet, on blood pressure reduction. So, that's pretty strong evidence that there is some dietary effect.

There was also just recently the PREDIMED study which was published in the *New England Journal [of Medicine],* which showed a reduction in cardiovascular disease among those on a Mediterranean diet. So now there are clearly some benefits of healthy diets, but we just don't know the individual components, and we don't know whether giving individual supplements will help.

Bob Barrett: Well, it seems the new wonder drug is vitamin D, and we hear a lot about vitamin D and many seemingly unrelated illnesses. What's the current evidence regarding vitamin D and cancer?

Dr. Nancy Cook: Well, there have been a lot of animal studies, and studies in cells, looking at effects on carcinogenesis and suggesting that it might have an effect. There have also been a lot of observational studies looking at serum hydroxyvitamin D and they suggest a reduction in cancer. So people are very excited about this.

However, trial data is limited. There was one study that come out that was done in Nebraska, which showed a reduction of a combination of vitamin D and calcium. There was a combination which showed a significant reduction. However, when that combination was compared to calcium alone, there was still about a 24% reduction that was not statistically significant.

So, we don't know if it was the vitamin D or the calcium or the combination of those. There have been a couple of other studies which have been null though; one in Oxford and the Women's Health Initiative which again was a combination.

But, there is very, very limited trial data at this point to suggest an effect on cancer and to support the observational studies.

There are now some trials going on that are starting up that are going to specifically look at this; one is the VITAL study which is going to study 20,000 men and women across the US, giving 2,000 IUs a day. It's going to look at both cancer and cardiovascular disease.

There are also some studies in other countries in Finland, New Zealand, in Europe etc. that are also going to look at this. So, when we have the results of these studies, then we'll know for sure whether there's an effect of vitamin D on cancer as well as other outcomes.

Bob Barrett: Randomized trials usually provide more definitive answers to question like these. But, are they always preferred?

Dr. Nancy Cook: Well, randomized trials can answer specific questions, and they are very good at answering specific questions. However, they usually give only a single dose and they are used in a specific population. They can't really study a wide range of doses or they don't necessarily apply to all subsets of the population.

There was a study done that got a lot of prominence on looking at hormone therapy in post-postmenopausal women, a lot of data showed that hormone therapy would lead to cardiovascular risk reduction. In trials, it showed that there was a reduction in LDL cholesterol and observational studies suggested a large reduction.

But, when the Women's Health Initiative was done, in fact they found no effect on cardiovascular disease. So, there was a disconnect between the trials and the observational data.

Now, since then, there have been thoughts that it might be due to the timing of the effect. The hormone therapy, and the trial, was given to women who could have been many years post-menopause. And it's possible that giving it right at the time of menopause when it's usually given to women in practice would have a greater impact.

So, instead of having those hormone levels go down and then go back up, if they were sustained over time perhaps that would lead to reduction in cardiovascular disease. It's still being examined. I think there is less enthusiasm for hormone therapy hypotheses. But, studies like KEEPS are still looking at this in women who are just becoming post-menopausal and looking at giving hormone therapy then.

Bob Barrett: Can observational data add anything else?

Dr. Nancy Cook: Well, observational data is still necessary. As I said, the trials can't do everything. And observational data is very important for rare outcomes for example, such as in the study on tobacco related cancers and vitamin D. It's very difficult to look at rare cancers and trials because there are so few of them, there is not enough power to really look at effects for these. And also, observational studies can look at a range of doses or range of levels of vitamin D and the effects across a wide range which is important.

The other thing that observational studies can add is the long follow up. It's hard to continue a trial past five years or perhaps ten years, but observational studies can follow people for much longer, or do retrospective analyses over longer periods of time. They also can help develop hypotheses, some of which can be later tested in trials.

So, observational studies are still very important, and they help to fill out and address many questions that randomized trials just can't do.

Bob Barrett: The original article also raises the question of whether vitamin D is a mediator of the effect of tobacco smoke. Now, can you explain how this can be?

Dr. Nancy Cook: Well, they thought that vitamin D might reduce some harmful effects of tobacco smoke. And they thought this is true because they found an effect only on tobacco related cancers, and not on some of the others. They also found a stronger effect among smokers.

Now, this is just a hypothesis. It may not hold out. The Vitamin D Pooling Project of Rarer Cancers didn't find a protective association with some of these cancer outcomes. So, it may or may not hold up under further investigation. This kind of theory though with mediation is very tricky and it really needs sophisticated causal analyses in order to answer it.

Trials will be able to help because we can look at what changes in vitamin D will do: are there differential effects in smokers and non-smokers; does that translate into differences in those two groups? And so, you'd still need sophisticated analyses, but having the actual changes in the variables will help try to elucidate some of these causal or mediation effects.

Bob Barrett: Well, let's get to the bottom line. What's the next step for vitamin D? Should we take it, should we avoid it?

Dr. Nancy Cook: Well, the jury is still out. We still need to wait. There have been a couple of big panels that have looked at the incidence. The Institute of Medicine did a review that came out November of 2010, and they found that there was an effect on bone health. So, they thought vitamin D might be helpful for things like osteoporosis, perhaps fractures. But, they didn't find any evidence really supporting other outcomes.

US Preventive Services Task Force actually came out with a report saying that they didn't find evidence for an effect on fractures either. So, it's still unclear whether or not there is an effect even there. But, the effect seem to be if anything stronger for bone related outcomes.

For cancers and even for cardiovascular disease, we just don't know, we don't have the data from the trials. The observational data are suggestive, but they are by no means definitive. For some of these rare cancers, we may even need to wait longer for meta-analyses of trial data because the individual cancers, if it is only tobacco related cancers for example, we may not have enough of those, even in these large trials that are underway now.

So, we may have to wait longer if the effect is restricted to those. But, the trials will at least maybe give us some evidence as to whether it's important for subgroups, for example for people with low levels of vitamin D, or for smokers versus non-smokers. So, we will get some information from these, but we really can't recommend that people take this, at this point except perhaps for people with osteoporosis, or other bone related diseases for which it may still prove promising.

Bob Barrett: How about you? Do you take them?

Dr. Nancy Cook: I don't, I am waiting, and healthy.

Bob Barrett: Dr. Nancy Cook is a Biostatistician at the Brigham and Women's Hospital and Professor at Harvard Medical School and a Professor of Epidemiology at the Harvard Medical School of Public Health. She has been our guest in this podcast from *Clinical Chemistry*. I am Bob Barrett. Thanks for listening!