Milk, Hormones & Human Health: State of the Evidence

Walter Willett, MD, DrPH
Harvard School of Public Health

I thought it would be useful to go over those issues -- what I think we know with reasonable certainty, absolute certainty is very, very hard to come by -- where we have a pretty high level of confidence. Michael (Pollak) talked about some of these issues a bit. I think there are a few things that we can say, given what we knew before and what we've learned since we've come here. So I will go over those and then come back to the specifics about what is desirable milk intake. And I should say that this whole area I find about the most interesting area in nutrition because it is so complex. People used to think of milk as a calcium solution, and it is clearly much more than that.

What do we know? Number one, I would say that it is clear that milk contains a wide variety of hormones, including steroids and peptide hormones. The determinants are not yet clear and there is a lot to be learned about the details of their levels in different types of milk. A very fundamental question is -- does milk have a physiological role that is related to these hormones? We can't be totally clear about which of the hormones are the active components. But I think we do see quite clear effects of milk on birth weight, probably independent of the protein content, given the particularly detailed and large Danish Birth Cohort study. There is also suggestive evidence on acne, which is a hormonally responsive outcome, and also on twinning. A physiological effect also has been seen in the animal studies that have looked at milk consumption and mammary carcinogenesis. So I think, in general, there's fairly strong evidence -- though every study needs to be replicated and we need more work in this area -- that the collection of hormones in milk is physiologically relevant. However, we can't be totally clear whether some of these effects are separable from the mix of amino acids or fatty acids. Second, I think there's quite clear evidence that milk does modestly increase IGF-1 levels in the blood. And as Michael said, we're not totally clear about the physiological relevance of this increase.

In moving to the epidemiologic studies, though complex, I think there are some things we can see based on multiple studies with a very large amount of data. First, dairy consumption after menopause is not related to any substantial increase in risk of breast cancer. You can never prove the negative in science, but given the size of the studies and the level of validity that we have measured for the dietary assessment methods, we can be pretty confident that we are not missing a large or even a moderate relationship between milk intake after menopause and breast cancer risk within the range of intake that's been studied -- up to three or so servings of dairy a day, which is the recommended level. I also think we can be pretty confident that intake of low-fat milk during the pre-menopausal years is not related to increased risk of breast cancer during those years. With high fat milk, there does seem to be a relationship, and I think that is worthy of much additional investigation, first of all, replication and an additional look at what that high fat milk might be doing during the pre-menopausal years.

Second, I think we can also be fairly confident that there is a modest inverse relationship between milk intake and colorectal cancer risk. One of the reasons why I emphasized the prospective data is that when you look at those, like in the pooling project where they are all analyzed in the same way, there is no heterogeneity there. Those studies are really very consistent with each other, and there is a moderately lower risk of colorectal cancer. I think John Baron's study that shows the effect on reduction of polyps with calcium supplements adds a lot to the plausibility of that finding.

Probably, for many of these big issues we are never going to have randomized trials where cancer is the end point. From the Women's Health Initiative study, we've come to understand that there are huge practical problems in doing that. It is hard to imagine randomizing 90,000 women to 3 glasses of milk or placebo for several decades and keeping them on those diets. It's just not going to happen, and that is what you really need to do to test the hypothesis with a randomized trial. So probably this combination of prospective epidemiologic studies and intermediate end points, supplemented with animal studies and other kinds of evidence is about the best we are going to be able to do in coming to certainty. And I think we are at the level of high probability for colon cancer. But does that mean you should drink milk to reduce colon cancer risk? Not necessarily, John's study was done with a calcium supplement. And Vitamin D is probably best increased with a supplement as well, it's calorie-free, inexpensive, and you can get better levels.

Third, in terms of human data, I think the evidence that milk consumption is related to prostate cancer risk is actually very strong, specifically for aggressive and fatal prostate cancers. It is there in many studies and it is really quite robust. This is, of course, of great concern.

For ovarian cancer risk, I think the evidence is not as firm or as robust as it is for prostate cancer risk. But there is a 20 to 30 percent increase that is marginally significant at the very level that is the Dietary Guidelines Committee recommendation. And as Stephanie showed, ovarian cancer is number 6 in incidence, but is right at the top along with lung cancer and breast cancer in terms of mortality. It is a lethal disease. And we do know that we underestimate relative risk somewhat. So if this is real, there may well be a 40 or 50 percent increased risk for ovarian cancer, and that would be a very serious problem. We can't be 100 percent sure that it's there and that it's causal, but it has to make one worried about recommending three servings of milk a day, given that finding in women.

And as Carlos pointed out, there are lots of other end points we didn't talk about here. The fracture data, though, is very consistent epidemiologically. Every large study that has looked at this issue has found that there is no reduction in fracture risk with higher dairy consumption, very consistent findings, all the way up to over 4 glasses of milk a day. I didn't show that data, but we have done a meta-analysis that is in the publication pipeline. So the main justification for high dairy consumption, fracture reduction, is really not supported. In fact, the whole area of what is the real requirement for calcium intake is very much up in the air. Our DRI's (daily recommended intake) say 1,200 milligrams of calcium for everyone over age 50. The UK reviewed this and they said 700 milligrams. The WHO reviewed it and they said 500 milligrams is adequate intake. So different people looking at the same data are coming to very different conclusions. It would take another two or three days just to talk about that. I won't go into it. But I think from everything I can see, 1,200 milligrams of calcium is really not necessary for bone health.

So how do we put all of this together in terms of what intake levels of milk to recommend, particularly given the evidence for prostate cancer and for ovarian cancer. Certainly there is a lot more research to be done, but, you really want to be on strong ground that something is safe if you are recommending it for the population as a whole. So for adults, I think it is not wise to be recommending three servings a day.

Now, Carlos alluded that I might say something about where the Dietary Guidelines recommendation came from. Basically, the rules were set even before the Guidelines Committee met. It was inevitable it was going to come to three servings a day of dairy because the rules are that you have to meet the DRIs with diet alone. You can't do it with supplements. I went back and forth, talking to Carlos and to Janet King, who chaired the committee, and one critical factor was getting enough potassium. They got up to over 10 fruit and vegetables servings a day and still were not up to the DRI for potassium. I was out on a bike ride on an annual trip to the Cape a couple years ago drinking my orange juice for hydration and potassium, when I noticed on the nutrition facts label that I would have to drink all of my calories in orange juice to just barely make my potassium requirement. That struck me as pretty strange because we're all taught that orange juice is an excellent source of potassium and to advise people to take potassium if they are using diuretics. How can we need that much potassium and barely reach it with a 100 percent orange juice diet?

I dug back into the DRI book to find out how they got the potassium requirement, which is 4.7 grams per day. If you go back and look it up, basically, the number came from one study where they salt loaded fewer than ten black men with a huge amount of salt and it took 4.7 grams of a potassium supplement to return their blood pressure to where it was before they salt loaded them. It took 2.5 grams in white men, which was the next lowest dose below 4.7 grams and we don't know anything about levels in between. So that is where the DRI for potassium comes from. It is interesting and a bit ironic that this small study, using a potassium supplement, has been translated into 3 servings of dairy a day including for the population in the original study that is lactose intolerant and probably can't even drink those three glasses of milk a day, at least not many of them. And, of course salt-loading people is not a good idea to begin with. One would hope that the Guidelines recommendation would be based on evidence of clear benefit and very strong evidence of no harm. And I think that is not the case, not the state of the evidence in this area.

So what is the right recommendation for milk and dairy? It is very hard to come up with a single number. First, thinking about adults, probably one serving a day is the level where we don't really see much evidence of harm. I don't see really much of any reason not to consume one serving, given what we have seen. But given that we know there are never step-wise gradients in biology, we start to get concerned about two or three servings a day because it looks like there is some strong potential for harm, particularly for men and maybe for women.

For children, of course, everything is much more complicated, and we also have much less data. We'd really like to know how milk consumption at age 5 and 10 relates to long-term risk of these various outcomes that we've talked about. We are really very much beginning that era of epidemiology, and are probably going to have to start some new studies as well as follow people up in the studies that we already have. So I think, again, where you don't know, it pays to be a little bit cautious when we are dealing with something with real biological activity and where there is a lot of uncertainty. Again, whether high dairy consumption prevents fractures is not at all clear in children. Children do need more nutrition, more calcium, but the studies on calcium supplementation that have been done in adolescents do not show a long-term permanent increment in bone mineral density. You get a one-time, small increment that is not sustained a few years later if you stop the calcium supplement. The DRIs are based on very short-term studies that, I think, are likely to be completely misleading. It is clear that high dairy consumption is not essential. We do know that people around the world grow up without milk consumption; yet they would probably be a little bit taller with milk during that period. But this is, I think, an area where we do not have firm answers yet. Hopefully we will have more data in the future.

DISCUSSION:

DR. GUNNELL: I think that's a really nice summary. As a generic epidemiologist and public health physician, my concern is that a lot of the focus here has been on specific cancers, and a big part of the composite picture that we are missing are the associations with other major causes of mortality in populations, for example, coronary heart disease (CHD) and stroke. I think it would have been nice if we could have had a discussion around those issues. The one meta-analysis, or the one review of the issue of the association of milk with CHD mortality, suggests a potential beneficial effect with a hazard ratio around .85. In terms of dairy advice, I think that one needs to weigh out not only specific cancers, but other causes of mortality as well. And I guess the other note of caution concerns using observational research. I agree we are not going to get randomized trial evidence in this area, but there are limitations in the observational research as we all know relating to confounding, and these may in part relate to potentially beneficial effects of milk on CHD in a number of studies. I think there is a slightly bigger picture than the one we focused on here that future studies should address, as well as looking at the cancer issues.

DR. BAUMRUCKER: One of the things that I think I have learned from the conference is the unique growth factor effect of milk on the increase in birth weight that Dr. Olsen remarked about. And it was pointed out that this was in comparison to meat or other protein sources from animals. So I think milk is unique. But I come back to the same question again, that we know that nutrition is linked to the IGF axis. Maybe this whole conference is proving that better nutrition does a number of things: you get greater growth, and if you have a cancer, you get greater growth of that cancer. That is the message that is coming to me. Getting back to the imprinting concepts and the aspect of vulnerability in young children, females or males, I would say that is related to some of the work that has been done with mice and rats; that there is some evidence of these things. I am not sure a lot of people have looked at the development of somatotrophs, lactotrophs, the pituitary axis that is driving this, so that is a very interesting area that I think has great potential.

DR COLLIER: I wanted to correct one major misperception. Today we have a population of 300 million people consuming the same amount of milk that 100 million people consumed in 1950. Our total production of milk in this country has not changed. What has changed is average milk consumption per capita has gone down, and because our average production per cow has increased, our cow population has gone from 22 million down to 9 million. So we are not trying to force people to drink the milk that's being produced, rather it is the market that's determining the size of our national herd. We have not changed our total milk production in this country since 1950. If you want to talk about a major change that has occurred in our nutrition, it has been the rise in nondairy beverages because dairy consumption has gone steadily down. I guess the issue here is relative to the fact that we are drinking one-third the amount of milk that we did in 1950. This doesn't really support the contentions about cancer incidence and other disease. It goes counter to that.

DR. POLLAK: The point that I was trying to make was that among the different methods for choosing the optimum amount of milk to consume for optimum health, it would be simplistic to use

our capacity to produce milk as the way of assessing how much we should drink.

DR. COLLIER: I don't think we are. I think that's the point I was trying to make.

DR. POLLAK: But, for example, I also learned at this meeting that there is actually a systematic and major effort on the behalf of the government of China to boost milk production, start a dairy industry, and have Chinese raise their milk consumption from historic levels to levels closer to North Americans. I am not sure about whether there is a sound basis for that, but I am sure that malnutrition is a bad thing for health. It comes back to the difficulty in establishing the optimum amount of milk intake for health. I don't think anyone has voiced an opinion that the best amount of milk is no milk. I think that we just don't know precisely how optimally to use this important part of our diet.

DR. COLLIER: I am just trying to clarify the misperception here that we are increasing our milk consumption. We have not been.

DR. HOLLY: Just a comment that for the cancers we are talking about, it may be that the exposures early in life and around puberty are causing the effects. So maybe, if we have reduced the consumption of milk, we will see the benefit of that in the next 50 years or so in studies. Another point, relates to John Bunting's impressive talk in the beginning of the meeting. We've had experience in the UK with mad cow disease and people became really stressed about consuming any cow protein and tried hard to avoid it. But avoiding it is incredibly difficult now because we eat so much processed food. When we are considering how much milk we consume, we have to consider that a lot of it is not in the cartons we drink, but increasingly in numerous processed foods. In the UK where people tried to avoid cow protein they couldn't entirely because it's in beer, it's in dry biscuits, it's everywhere, because processed food manufacturing has changed so much.

DR. NEVILLE: There are two points I would like to emphasize, and Jeff just touched on one, but early life needs to extend to fetal life. We need to be looking at these maternal-fetal interactions in milk consumption. I think that is very important because we are beginning to understand that is a period when a lot of these things are programmed. The other point is that differences in growth due to milk, exemplified by IGF-1, are not duplicated, it doesn't appear to me, by meat proteins. So it is not just the protein content of the diet. And I think that an area of emphasis might be -- what is it about milk that makes it different from other high protein foods? One might also look at the difference between cow milk and breast milk because breast milk does not promote growth nearly to the same extent that cow milk does. What's the mechanism there?

DR. BARON: To the extent that we can see milk as a neutral or protective exposure, it means that we can ethically do clinical trials, an advantage we have in some other research that we might want to apply here. We have seen, particularly in nutritional epidemiology, where early epidemiology suggests something, clinical trials are done and suggest something else, and then after the fact the epidemiology is able to perceive what the clinical trials have suggested. And so my personal viewpoint is to try to design a judicious mix of observational studies and randomized trials when possible. It is really helpful, furthermore, you can often embed in the randomized studies further observational research.

DR. MA: I presented IGF and insulin data for prostate cancer. For colon cancer, I also think we have strong data showing consistently in men in the Physicians' Health Study, and also in women in the Nurses' Health Study, that IGF-1 is positively associated with colon cancer risk as is C-peptide and also obesity is a big risk factor. So just add on one more cancer there.