

Host: This is the podcast from *Clinical Chemistry*. I am Bob Barrett. Obesity is a major public health problem and is associated with several diseases, including cancer. The relationship between obesity and prostate cancer, however, is complex and several studies appeared to be in conflict, though there is increasingly clear data that obesity is linked with lethal prostate cancer.

Some studies have suggested this link may be mediated by adipocytokines, hormones produced by fat cells. We have two guests today to talk about this topic. In the January issue of *Clinical Chemistry*, Dr. Jing Ma and her colleagues evaluated whether concentrations of leptin or adiponectin correlated with subsequent prostate cancer incidence or aggressiveness in mortality. Dr. Ma is an Associate Professor of Medicine at Harvard Medical School and an Associate Epidemiologist in the Department of Medicine at Brigham and Women's Hospital. Dr. Ma, tell us what was the purpose of your study.

Dr. Jing Ma: The purpose of the study is really looking at the two major public health concerns for middle-aged men in the affluent countries: that is prostate cancer and obesity. More than a dozen prospective studies have been suggested a higher prostate cancer mortality rate in men with excess bodyweight, as measured by body mass index, as compared with men of normal weight. However, it is remained unclear, why excess bodyweight is associated with higher mortality rate of prostate cancer. So, to answer this question, we come back to this study to investigate two major molecules that is biomarkers that are mainly produced by the fat tissue; one of those two is leptin, which is possibly correlated with obesity, and the other one is adiponectin which is inversely correlated with obesity.

We measure these two biomarkers prospectively in blood collected among cancer-free US male physicians, who are participants of the Physicians' Health Study, a randomized trial of aspirin and β -carotene in prevention of cancer and cardiovascular diseases. So, our question is, whether men with higher levels of leptin, a marker of obesity, had higher risk of developing prostate cancer, whereas men with higher level of adiponectin, a negative biomarker of obesity, had a lower risk. So, among those who were diagnosed with cancer, we also assessed whether men with different levels of the two biomarkers are more or less likely to die of the cancer.

Host: Very interesting. So, what were the most important findings?

Dr. Jing Ma: Actually, we found that comparing to men with prostate cancer, they were trend for higher concentrations of adiponectin, but not of leptin to be associated with a 75% lower risk of developing high-grade and lethal prostate cancer. In addition, among men with prostate cancer, those who had higher adiponectin levels had a 60% higher chance of survival from the cancer. In other words, these men were less likely to die of the cancer, even after taking into account of age at diagnosis, clinical stage, and tumor grade. More importantly, the benefit was observed mainly in men of overweight or obese but not in men of normal bodyweight.

Host: Impressive findings. So what are the public health and clinical implications of the study?

Dr. Jing Ma: There are several thoughts of implications. First, our findings suggest that not all markers of adiposity are created equal. In contrast to adiponectin, circulating concentrations of leptin were unrelated to risk of developing lethal prostate cancer or prostate cancer-specific mortality. As I said, in fact, leptin is much more strongly correlated with BMI than adiponectin in this study population. So, our findings provide for the first time, the evidence linking adiponectin to risk of developing fatal prostate cancer, which is supported by experimental data showing a biological role of adiponectin in regulating energy balance, suppressing inflammation, inhibiting angiogenesis, and a tumor metastasis, thus may slow down prostate cancer progression.

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Secondly, the significant inverse trend between prediagnostic adiponectin concentrations and a prostate cancer-specific mortality with apparent, mainly among men with high BMI, BMI above 25. This observation is quite consistent with our previous findings of a stronger positive association of plasma C-peptide that's another marker, a marker of insulin protection with prostate cancer mortality, primarily in men with higher BMI, over 25. So that means the obesity-linked up-regulation of insulin production and down-regulation of adiponectin and as a consequence, up or down-regulation of several downstream biological pathways is a possible mechanism, whereby obesity directly or indirectly influences prostate cancer progression.

Third, these observations support a hypothesis that certain obesity-related metabolic factors, such as hyperinsulinemia favor aggressive neoplastic behavior,

whereas adiponectin concentrations come to act these obesity-related adverse effects. Our prospective data further support the notion that tumors can start developing metastasis very early, that is before they may even become clinically detectable and that aggressive neoplastic behavior could be manipulated by systemic metabolic factors.

These concepts may aid in refinement of prostate cancer risk protection, especially for lethal outcomes by including BMI and related biomarkers, in clinical outcome prediction. The concepts may also help to identify normal cancer that are critical and prevention strategies. Finally, circulating an adipose tissue, adiponectin concentrations can be increased whereas insulin or its biomarker, C-peptide concentrations can be reduced by weight loss, dietary modifications, caloric restriction, physical exercise or anti-diabetic therapy, such as metformin, a commonly used anti-diabetic drug that recently showed a potential anti-cancer effect. In other words, adiponectin could act as an endogenous metformin, packeting on the same AMP kinase pathway. These observations further indicate the importance of maintaining a healthy bodyweight and lifestyle to reduce risk of developing a clinically significant high-grade tumor or lethal prostate cancer.

Host: So, what is the bottom line here? Should all men have blood adiponectin evaluated at the same time they get PSA checked, and if so, is age a factor?

Dr. Jing Ma: The bottom line is that after a previous finding, linking hyperinsulinemia and the fatal prostate cancer outcome, the study provides another piece of evidence linking biomarkers of adiposity with fatal prostate cancer outcome. Although, we have taken into account many potential factors that might influence these associations, such as aging, and clinical stage, and the tumor grade, we consider these findings as very preliminary. So, these findings need to be further confirmed by larger studies and in different populations before we consider them as a clinical use for risk prediction. So, the bottom line is we need more evidence to confirm or refute our findings.

Host: Well finally, could you give us a glimpse as to where your research in this field is going. Is there anything beyond adiponectin that our listener should know about?

Dr. Jing Ma: We had previously found in the same Physicians' Health Study that men with elevated insulin protection had a higher risk of progression to fatal prostate cancer. So,

given the limited influence of PSA as a screening to prostate cancer mortality as shown by two recent reports of clinical trial data, there is an urgent need to identify markers that could predict which prostate cancer patients would progress to fatal outcome from those patients whose cancer will stay within their prostate for the rest of their life. So all research efforts are focusing, identifying such biomarkers and at the same time, trying to understand the underlined biological mechanisms that help to develop targeted drug development and cancer prevention.

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Host:

And again, that is Dr. Jing Ma, talking about the results of her study on prostate cancer that was published in the January issue of *Clinical Chemistry*. In the same issue of *Clinical Chemistry*, there was an editorial on the topic by Dr. Stephen Freedland, an Urologist in the Duke Prostate Center in Department of Surgery at Duke University. Dr. Freedland is also our guest today.

Tell us Doctor, you say, one out of three men in the United States today are obese. In your opinion, what's the reason for this dramatic and rapid increase in obesity and what about the roles of genetics compared to just a bad diet.

Dr. Stephen Freedland:

I think it's a complex question. I think that's really one of the challenges we have, is what is driving this. And if you look, it's essentially the same people today in the United States by and large is what we had 20 to 30 years ago. So, the genetics really haven't changed a whole lot. So, I don't think we can blame it on a change in genetics. So, I think we really do have to ascribe a lot of it to bad diets and lack of physical activity. The question is what component of the bad diet is driving this and we kind of come collectively with what we call a Western diet, which is characterized by many things, probably the number one thing is just caloric excess: too many calories.

But within that diet, we tend to find a lot of refined carbohydrates, very simple sugars, it's really probably the biggest dietary change that's occurred in last 20 to 30 years, and I think it's unfortunate that dietary fat gets a lot of the blame. We have actually looked in the last 20 years or so, as the US government has been telling us, eat less fat; you need to eat less fat. The American people have actually responded. We actually have less fat as a percent of calories today than we did 20 years ago. And yet 20 years ago, we had half the obesity rate we do today. And the problem is we have

replaced fat, especially animal fat may not be the greatest thing for you, but we have replaced it with simple sugars. So we have gone from something that was kind of neutral, to something that's clearly bad.

So I think we need to kind of rethink what is a healthy diet, but I think a lot of it probably is more dietary than genetic.

Host: The Physicians' Health Study is a longitudinal study of physicians followed for many years. Why was this group of men the best choice for this study? Are there other perspective cohorts used today for prostate cancer that could have been used?

Dr. Stephen Freedland: Yeah, I mean that's an important question because whenever you get a very nice study like this, it's obviously done in one group of people. So, the question is, well, is that the best group to look at, or is that just easy to do, and what would happen if we look in other groups. Now, obviously, the authors had access to this data, but actually it is a very useful group to study and these are a group of physicians that have been followed for a long, long time, and they had blood prior to the men getting prostate cancer.

So, you can actually look at the levels of these various hormones before the men ever knew they have prostate cancer. One of the questions we always come up with is, is this something a hormone or a marker that leads to the cancer, or is this something made by the cancer, and you get kind of these chicken-and-egg arguments. So, by having these very valuable blood samples, before the men have prostate cancer, we really can't say this is probably influencing the likelihood of developing prostate cancer.

That being said, there are other groups where we could look at this question, and that's actually I think one of the important things that now that we have this very exciting observation, is to see how well and strong this is in other groups. There is the Health Professionals Follow-Up Study, which is a group of health professionals, mostly dentists, the optometrists. There are a lot of other groups, American Cancer Society as a group, there is the Multiethnic Cohort. So, there are a number of groups where this can now be tested. Now, once we actually have an idea, we think adiponectin is important, now let's go out and test that. So, this is a great start, but hopefully we will see more studies like this going forward.

Host: Adiponectin and leptin are often thought to work as opposites of one another: adiponectin affecting the anticancer pathways, while leptin affects pro-cancer pathways. How do you explain the association between prostate cancer and adiponectin, but not leptin?

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Dr. Stephen Freedland: I think, obviously the normal function of leptin and adiponectin is not to inhibit or promote cancer. They are normally functioned in appetite regulation, insulin control. They just kind of happen to have these effects on promoting and inhibiting cancer. So, from that aspect, I'm not sure we necessarily expected to see anything, and it's quite exciting that we did see something.

There has been a link between leptin and perhaps more hormone refractory prostate cancer. Hormones are, there's kind of standard treatment for prostate cancer, and once they stop working, there is some data at least in vitro in a petri dish. We take those really aggressive cancer cells, and we add leptin to them, they do tend to grow a little bit faster.

So, I wouldn't, necessarily from this study, say that leptin is not important at all. I think, this is mostly men with earlier stage prostate cancer, and they did have some men who had more aggressive disease but not a huge number. So I don't think we can say that leptin is not important, but I think it is pointing us to the idea that adiponectin is more important, and I think adiponectin helps to regulate angiogenesis with the new blood vessel formation of the tumor. Leptin tends to be more of a direct tumor stimulant, and it's very likely that early on, tumors need both: they need to be stimulated, but they also need to get new blood vessels. So that's why I think adiponectin in particular is an exciting molecule to be looking at.

Host: Adiponectin seems to be protective against things such as insulin resistance, an inflammation. How important are these in prostate cancer progression, and are there any known links between prostate cancer and diabetes?

Dr. Stephen Freedland: Absolutely, I mean, I think insulin resistance leads to high insulin levels and inflammation is interestingly related to obesity as well as insulin resistance. So, there is actually a reasonable amount of data, including data from the same authors, actually, the high insulin levels actually are correlated with prostate cancer mortality; specifically with that aggressive lethal phenotype that insulin really seems to play an

important role. We know from animal studies, if you feed animals a particular diet that lowers their insulin levels, you actually slow the growth of the cancer, and that's work that we've been doing in our laboratory with one of our post-docs, Dr. Elizabeth Mascal that we've been able to show, if you cut out the carbohydrates from the diet, lower insulin levels, you actually slow the growth of the cancer.

Inflammation is probably pretty important as well. It's a little bit harder to tease out because it may be possible that a little bit of inflammation may be a good thing, whereas too much inflammation is a bad thing. It's not as clear cut as that's a yes-no. But there is some epidemiological data certainly to link inflammation and prostate cancer.

Regarding the second question, it's actually very interesting. If you look at diabetes itself and you look at what makes someone diabetic and usually mostly it's non-insulin dependent adults onsets, kind of, what we call it type 2 diabetes and classically, those are people whose pancreas has been working overtime, trying to provide enough insulin to their body. And because they are obese, they are not on the right diet, they have bad genes, whatever it may be and eventually, the pancreas just can't keep up and starts to fail.

So typically, diabetes develops actually once the insulin level start to fall, and so given low insulin levels in diabetics, if insulin were important, you would expect diabetics to be less likely, actually, to have prostate cancer. That's absolutely what we see. Actually, very large meta-analysis, diabetics tend to be about 10 to 20% less likely to be diagnosed with prostate cancer, again suggesting that insulin probably is an important player in prostate cancer.

Host: What do you think is the overall significance of this study? Is adiponectin going to be a reverse biomarker, where if it's found to be under a certain concentration and further testing should be done to rule out prostate cancer?

Dr. Stephen Freedland: I think that's an interesting idea but I don't think the data at this point would support the idea that say, a reverse biomarker. I think it's fascinating biology, and really it says, what are the root causes of prostate cancer, what role does obesity and excess fat, what are the hormones that mediate it, I think it's really, really interesting.

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But if you look at it as a biomarker and say, can we use this to start screening for prostate cancer. Well, first off, adiponectin didn't predict who had cancer at all. So in that sense, it actually failed the test.

Now, we could say, well, we're really more interested in the high-grade, aggressive prostate cancer, and there it seem to perform a little bit better, but still, it was kind of borderline significant for that. I think where it really had the most use is among men who were diagnosed with prostate cancer. So, I think that's where it's potentially intriguing to say, we're going to screen for it the way we usually do, but if you are diagnosed and the adiponectin is low, then that's particularly aggressive. We may need to be more aggressive in our management. But I think also it suggests that there are some biological clues to again what causing this prostate cancer. To me, that's the significance of the study. Not so much that is to give you this great biomarker book, but what is the biology, we have identified adiponectin.

Adiponectin, as we've talked about, it regulates insulin levels, it affects angiogenesis, may play a role in inflammation, I mean many, many different pathways that adiponectin regulates. So, the question is, which one of those are the most important. Then ultimately, how can we target that. If it's inflammation, should we be putting everyone on anti-inflammatory to prevent prostate cancer? It's actually some data that's showing that they may have lower risk of prostate cancer. Do we need anti-adiponectin drugs? I would say, to get people to lose weight would be the best thing, but easier said than done. So, this to me is really a biology study, very interesting and important biology study.

Host: Well finally, if you were the author, what next step would you take to further investigate the relationship between increased adiponectin levels in prostate cancer aggressiveness or mortality?

Dr. Stephen Freedland: As I said, I mean we talked about that this was one study, using the Physicians' Health Study, which is a really important cohort group of men, but there are other groups of men that this could be tested in. So, I think one thing is to say, are these data replicable in other data sets. Are we able to verify and validate that this is a true association verses just some random noise? I think to me that would be step one.

Step two is then saying again, so adiponectin is correlated with bad cancer. What is it about

adiponectin, which of its functions is correlated with bad cancer, and there is ways. We talked about kind of insulin resistance, well they controlled actually for C-peptide, which is a marker of insulin secretion, and the results by and large weren't really changed that much, which says, it's probably not the insulin resistance pathway perhaps. So let's look at inflammation. Are there markers of inflammation we could use? Yes, there is; there is C-reactive proteins, there is now a highly sensitive way to measure that.

So, let's look at that because that explain why adiponectin. Let's look at angiogenesis. Let's start to look at the tumors and cells, you can stain the tumors to the level of their amount of blood vessels within the tumor, because that explains why adiponectin. I'm really teasing out, which specific components of adiponectin, which again, I think we've a very interesting observation, we haven't quite teased it out to the exact pathophysiology and that's ultimately where we need to go. So, once we understand that, we know where to go in terms of preventing or ultimately treating prostate cancer better.

Host:

Dr. Stephen Freedland is an Urologist in the Duke Prostate Center at the Department of Surgery at Duke University. Dr. Jing Ma is an Associate Professor of Medicine at Harvard Medical School and an Associate Epidemiologist in the Department of Medicine at Brigham and Women's Hospital. They have been our guest in this podcast from *Clinical Chemistry*. I am Bob Barrett. Thanks for listening.

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