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Insulin Resistance & Colorectal Cancer

RESISTANCE AND ASSOCIATION WITH COLORECTAL CANCER

Insulin resistance in colorectal cancer, is there a connection? You are listening to ReachMD, The Channel for Medical Professionals. I am your host Dr. Gary Kohn and joining me is Dr. Andrew Flood, who is the Assistant Professor in the Division of Epidemiology at the University of Minnesota School of Public Health in Minneapolis, Minnesota. Dr. Flood is a PhD epidemiologist and in addition to his academic appointments is an adjunct investigator at the National Institute of Health Division of Cancer, Epidemiology, and Genetics.

DR. GARY KOHN:

Today, we are going to be talking about insulin resistance and colorectal cancer. Dr. Flood, thanks for being with us today, we appreciate that.

DR. ANDREW FLOOD:

It's my pleasure.

DR. GARY KOHN:

Maybe before we get into the topic about insulin resistance in colon cancer, perhaps you could tell us a little bit about your background and how you got into this area of investigation.

DR. ANDREW FLOOD:

Sure, I mean it's kind of a long story like just about everyone I know who works in Public Health. I didn't come in here by some direct mechanism, no one grows up as a little kid thinking of 'boy, I really like to be an epidemiologist some day.' You know it's not a doctor or lawyer or one of the traditional things. I was planning to go to law school of all things, and I needed some work and I just got placed at a place called the American Institute of Cancer Research, and I started working for them and I had an undergraduate degree in biology so it wasn't like this was unfamiliar territory to me, but they do diet and cancer research. In fact, they published a bunch of huge landmark reports on diet and cancer, and I was involved in the initial one and one thing led to another and I decided I actually wanted to pursue this as a career and that's how it worked out.

DR. GARY KOHN:

When you ended up looking at this issue, insulin resistance in cancer, had there been other work, had other people looked into this, was that association postulated before?

DR. ANDREW FLOOD:

Oh sure, yeah. The initial hypothesis was floated really in the mid 90s by < ____ > Harvard < ____ >. They independently had identified insulin resistance or hyperinsulinemia at least as something that was potentially very important in determining colorectal cancer risk. They noticed that a lot of the risk factors for both diabetes and colorectal cancer tended to be similar, if not the same. There were a number of studies through the years that began at that point to start looking at this in some detail and in 1997 at the time of the initial AICR report that I mentioned, they classified all the different diet and cancer relationships according to the strength of evidence supporting them and diabetes was one that they thought for a colorectal cancer; there was not sufficient evidence at that point to make a conclusion, but since that time, there have been a number of cohort studies, epidemiologic studies that have looked at diabetes as a risk factor for colorectal cancer and pretty much consistently we find about a 30-50% increased risk among people, who have diabetes and subsequent risk of colorectal cancer, perhaps a little stronger association for the colon cancer and for rectal cancer. I think it's fairly well established now that that's the case. The question is exactly what the mechanism driving the diabetes and colorectal cancer association.

DR. GARY KOHN:

And are there some potential physiological explanations that are plausible to you at this point?

DR. ANDREW FLOOD:

Sure. The primary one that has driven this work is the role of insulin. People who are diabetic, obviously, are going to be hyperinsulinemic at least at the initial stages of that disease and the few studies that have looked at times since diagnosis, which you find is that people's risk increases for a period of time after their diagnosis and then sort of declines so that the maximum period of increased risk might be between 5 and 10 years and 10 and 15 years, so right around that period you are at the maximum point of increased risk and after that it tails off and perhaps consistent with the idea that as the pancreas begins to give out and the insulin levels begin to decline that the insulin is no longer there to be causing its mischief and the risk of cancer is going down. That's one possibility. There are other ways of looking at that too. So it's a little complicated, but that's the primary thing that people are concerned about.

DR. GARY KOHN:

Last year you published on the topic and as you and your team were looking at this issue, could you show us how you thought about the study design and what methods you wanted to use to get at this question some more?

DR. ANDREW FLOOD:

Well, I had done it in a number of different ways and one of the primary tools of the cancer epidemiologist is the cohort study, I mean, that's a very nice design because many of the things that we like to do are not really suitable for experimental designs and a cohort study is a good design. Among the observational designs, it's probably the most effective one in trying to assess risk and so we had a

group of about 45,000 women that we had recruited into a cohort back in the 80s actually. We had a bunch of questionnaire based information on them related to diet, lifestyle factors and we had asked them to report, if they had never been diagnosed with diabetes. Among the women who did, they had about a 50% increased risk of colorectal cancer in the 8 years of followup.

DR. GARY KOHN:

That was 50?

DR. ANDREW FLOOD:

Yeah, about 50%, so that was a pretty nice result. One of the interesting things about those we thought that, well, if we are really thinking that it's the insulin that's driving this association, then people, who are not yet diagnosed as having had diabetes are probably if they are about to become diagnosed as diabetic, are probably hyperinsulinemic so if we just restrict ourselves to people, who have reported the case of diabetes that we may be misclassifying a bunch of people as unexposed to hyperinsulinemia when in fact they are not and so what we did as we included people in our exposed group, people who subsequently became diagnosed with diabetic during the followup period, the idea being that if it's truly hyperinsulinemia that matters, then these people perhaps should show an increased risk. We should strengthen the association by including these people in our exposed group and what we found was exactly the opposite and actually the risk estimate went down by including these people and the question is why is that and there are a bunch of potential explanations.

DR. GARY KOHN:

So in this most recent observational study that you talked about, you said there were a number of possible explanations for the results, what if you settled on in your own mind as to the best explanation.

DR. ANDREW FLOOD:

Well, I haven't settled on one. We still have to figure this out still, but potentially it could be that the people, who were prediabetic at baseline who became diabetic within the few years of baseline, may be that our classification was correct initially that these people really weren't hyperinsulinemic enough to increase their risk and so including them in the exposed group was incorrect or that may be the degree of hyperinsulinemia wasn't high enough or the duration of hyperinsulinemia was not long enough, so they hadn't been truly exposed in a way that would increase their risk. Now that's consistent with the state that I described before where we saw a peak of risk for diabetics and colorectal cancer for people who had been diagnosed with diabetes may be 10 years prior to the onset, so those two things may be consistent. It's also possible that there is something else about diabetes aside from hyperinsulinemia that is driving this association. What that might be is something we have to try to figure out.

DR. GARY KOHN:

With the original cohort and then with the addition of the prediabetic patients, were the results surprising to you?

DR. ANDREW FLOOD:

Not the main analysis where we just looked at diabetics and colorectal cancer, that's what we expected and that makes it consistent with a growing body of observational studies of that type showing very similar result, actually amazingly consistent 30-50% increased risk of colorectal cancer for diabetic patients. I was surprised by the lower risk when they included the people who became diabetic. Maybe I shouldn't have been surprised, but I was thinking maybe it would go the other way.

DR. GARY KOHN:

So, Andrew, once you shared this work both with the original cohort and then the added prediabetic patients, you shared the results, what kind of reaction that you had from your peers with respect to critical comments or agreement, anything you can share with us.

DR. ANDREW FLOOD:

Well, I haven't had too much either way, really. I think I was a bit surprised that the amount of press interest in this story. It made a lot of news. I think that the main result, it was, like I said, not terribly surprising. The one was the including the people who were prediabetic, was a bit surprising, so we will see what happens with that. I think that does raise some questions and I think there are some questions in general, similar types of questions that have been raised by other studies of this type, so I think it's a field that, you know, it's going to require a little additional work.

DR. GARY KOHN:

What's untapped for a your group and following up with this particular study?

DR. ANDREW FLOOD:

Well, we have done some other work in this area that's somewhat related and looking at things like impaired fasting glucose among people who have had an adenoma removed and seeing that those people are at pretty highly increased risk of having a second adenoma within four years, in fact it's even more so for people, who have advanced adenomas within four years, very strong increased risk, so which we were beginning to think that maybe we should try to consider doing a study where we actually try to address hyperinsulinemia or impaired fasting glucose among people who have had an adenoma removed to see if we change that, does that actually then benefit those people in terms of reducing rates with recurrent adenomas.

DR. GARY KOHN:

Right. Well, that will be interesting, I am looking forward to seeing that, but do you think that this association is commonly or well appreciated amongst the medical community. Do we need to get this message out to medical students and residents and fellows?

DR. ANDREW FLOOD:

I think it is not that well appreciated to be honest. My wife is a physician and when this paper came out, I forwarded; it actually was the presentation, I had a conference in the fall; I forwarded the press release to her, just sort of as a joke, and she forwarded to her professional colleagues and they were, many of them, quite surprised and they think that this actually changes the way I am going to practice and I was surprised of that because I didn't think that this was that controversial, but apparently it's not reached the practicing

clinician

DR. GARY KOHN:

I don't think so

DR. ANDREW FLOOD:

As well as I would have thought.

DR. GARY KOHN:

Do you feel comfortable that the evidence supports clinical applications that this ought to change the way we interview, examine, and treat our patients?

DR. ANDREW FLOOD:

You know, I am not a clinician, I don't want to go too far down the road, but I think that the evidence that diabetics are at increased risk of colorectal cancer is pretty solid and if you have a patient who is diabetic that's just one more thing you need to consider in your management of that patient and that management of their glucose could be strongly related to whether or not they are going to get cancer, have adenomas, and so on, and I do think it does have some clinical implications as we understand the data right now.

DR. GARY KOHN:

In your analysis of the data, I know you also asked about family history of colorectal cancer, could you explain to us a little bit about that relationship, does that change the association?

DR. ANDREW FLOOD:

In the one analysis I did was the people, who had had an adenoma and we measured their fasting insulin and fasting glucose, we found that the people, who had no family history of adenoma actually had a much stronger association between the impaired fasting glucose and the subsequent risk of a second adenoma. I don't know whether or not that is sort of a chance result or if it's some sort due to pathological relationship here, and it may be that the relationship for the people who had a family history, that their risk of adenoma may be dominated by their family history, so that the impaired fasting glucose makes only a minor contribution to the indication of risk they might have and that the people, who have no family history, the action is really at the impaired fasting glucose, but you know I can't say that with any certainty at this point.

DR. GARY KOHN:

Sure, that is a fascinating area for further exploration and I think your wife is right, I think it's not well appreciated amongst our

community, but hopefully after this broadcast it will be. I want to express my thanks to Dr. Andrew Flood for being our guest. We've been talking about insulin resistance and association with colorectal cancer.

I am Dr. Gary Kohn and you've been listening to the Clinician's Roundtable on ReachMD, The Channel for Medical Professionals.

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