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Rise in Early-Onset Colon Cancer Being Studied Through Single-Cell Sequencing

ReachMD Announcer:
Welcome to ReachMD. This medical industry feature is titled “Rise in Early-Onset Colon Cancer Being Studied Through Single-Cell Sequencing” featuring Dr. Joel Gabre, a gastroenterologist at NewYork-Presbyterian and Columbia. This audio is a production of NewYork-Presbyterian with world-class doctors from Columbia & Weill Cornell Medicine.

Erin Welsh:
Colon cancer rates for young Americans are on the rise. According to the American Cancer Society, more than twice as many people under 55 are being diagnosed with colon cancer today as compared with a decade ago. But the reasons for these increases are not yet well understood by the scientific community.

So what do doctors need to know about these rising rates, and how is science working to address this public health problem?

This week, Dr. Joel Gabre, a gastroenterologist and physician scientist at NewYork-Presbyterian and Columbia, joins me to discuss what could be driving these rising colon cancer rates. He and his team are searching for answers at the cellular level with cutting edge technologies. And today we dig into the groundbreaking findings from his team's recent study comparing the biology of early onset and late onset colorectal cancer.

Dr. Gabre, thank you so much for joining me today.

Dr. Gabre:
Pleasure to be here. Thank you.

Erin Welsh:
What does it mean that we are seeing younger people being diagnosed at a higher rate with colon cancer than we have in the past? When did this first come to light?

Dr. Gabre:
Yes. So, I would say, in the literature, these reports have been out for about 10 years or so. But those reports have noted that there's been an increase in incidents of colorectal cancer.

Traditionally, colorectal cancer has been thought of, and the literature supported this initially, of a disease of people who were older than age 50, commonly really 60s. And unfortunately, what we're seeing now is it's being diagnosed in people who are in their 30s and 40s, and even rarely in the 20s. And what's even more concerning is this seems to be accelerating. It seems like people who were born more recently as the 90s are even more likely to get colorectal cancer at an earlier age than people who were born before then, so there's this birth cohort effect that we're seeing.

Erin Welsh:
Wow. Okay. And how variable is colon cancer? You know, how do these cases that we're seeing in younger adults differ from those that we're seeing in older adults in terms of the progression or the location of onset or the cancer biology of it all.

Dr. Gabre:
Yeah, great question. So, we are noticing some differences in the younger population, in particular in location. So the colon is a large tube, and it has different segments. And what we've noticed is that the younger patients are getting colon cancer at the very end of the colon traditionally.

While, if you look at older patients, it's pretty much equally distributed along the different parts or segments of the colon. And that's an interesting presentation because the question is why? Kind of the big thing that stands out is that these colon cancers in younger adults tend to be the distal colon.

Erin Welsh:
Fascinating. So the precise location of these early onset cancers is distinct compared to late onset cancers. And I'm wondering, what are some of the known modifiable risk factors or drivers of colon cancer?

Dr. Gabre:
Obesity is known to be a risk factor for colorectal cancer. A Western diet is known to be, to increase the incidence of colorectal cancer, and specifically within that, red meat. Sedentary lifestyle. There's some evidence for diabetes and hyperglycemia being linked to colorectal cancer.

So, broadly, those are the major lifestyle factors that are associated with colon cancer, modifiable risks. Those same risk factors are also associated with early onset colorectal cancer, and there's literature to show this. However, there's a lot of anecdotal evidence of young, healthy people also getting colon cancer. So, the question is, are we missing something here beyond the standard risk factors, modifiable risk factors that we know are associated with colorectal cancer?

Erin Welsh:
Right. And is this something that you have seen in your clinic? Like, I'm wondering if there's a particular patient story that comes to mind that, kind of, demonstrates how this rise in colon cancer rates is affecting otherwise healthy young people?

Dr. Gabre:
Yeah, Absolutely. So this was, I would say this is the case that really moved me emotionally and made me want to really study young onset colorectal cancer. So about four years ago, a young patient came into my clinic with abdominal pain, referred by a primary care doctor.

I wanted to do an ultrasound, but saw that the primary care doctor already ordered a CT scan for that day. And so I just waited for the CT scan and then was going to order an ultrasound. And then to my surprise, the primary care doctor messaged me and said, they have metastatic colorectal cancer. And so the primary care doctor said, can you tell the patient? And that phone call, I will not forget, because there was just silence on the other end of it because I had just completely changed their life.

I brought them in quickly and I will never forget the look on their face. The feeling in the room was quite sad and palpable because we all knew why we were there. I did the colonoscopy and it was, there was a big mass there and it was colon cancer. And that was, you know, it was kind of earlier in my career and that was shocking, scary. And as a physician, the first thing as a scientist, more importantly, I said, why? Like, why is this young, healthy patient getting metastatic colorectal cancer? And so that's why I started studying it.

Erin Welsh:
Yeah. Yeah, that is such a powerful story. And when you are face to face with someone and this is what is happening in their life, I can imagine that that's a really important motivator for the next steps. What do you do? Like, why is this happening, as you said? And so I'm wondering, where did this "why" lead you? What is some of the research that you're working on now?

Dr. Gabre:
So that "why" led me to look at the literature and realize there are gaps in our knowledge just basically about the disease. Are there differences between early and late onset colorectal cancer? And so I felt that was a gap that needed to be addressed. And so I just completed a study, where we profiled the young onset colorectal cancer tumors to late onset using new molecular biology techniques where we can really profile each individual cell.

Erin Welsh:
That's really incredible and it sounds like it could provide some important insight into the cellular differences and what might be driving the development or progression of early onset and late onset colorectal cancers. Can you tell me more about the broad aims of this study and what you were hoping to learn?

Dr. Gabre:
Studies up to this point have used approaches that look at the DNA primarily. Some studies look at the RNA of early onset and late, but by using aggregate data, not looking at single cell differences between early and late.

So that was the gap in the field that we wanted to look at to hopefully generate new hypotheses in terms of the reason why we're seeing

tumors develop in younger patients. And so, what we did is we used patient samples. Here at Columbia and NewYork-Presbyterian, from patients that were young and old, and then combine that with publicly available data of young and old patients that had not been stratified based on age.

And so we aggregated that data from Columbia and that public available data to get a large data set and look at the differences at the cellular level between early and late onset colorectal cancer.

Erin Welsh:
And so to get at this question, you used single cell RNA sequencing. Why did you choose this approach? What does single cell sequencing give you that, you know, tissue level sequencing cannot?

Dr. Gabre:
So what it gives you is a single cell resolution of the types of cells that are in different cohorts. Single cell RNA sequencing as a tool has been around for a little more than five years. Our study is unique because we're amongst the first to leverage the tool to look at early onset tumors, specifically in a Western cohort. So we're amongst the first to give people a map of what might be different between early and late onset.

Erin Welsh:
Okay, so it gives you sort of a peek behind the curtain in terms of, like, what these cells are doing and when, and what role they might be playing in Tumorgenesis, for example.

Dr. Gabre:
Exactly. It gives you a very powerful tool to granularly look at differences between cohorts, in our case, early onset tumors versus late onset. And one of the other unique things that we leverage in this study is not just single cell RNA-Seq, but we're very fortunate here to have one of the best systems biology programs in the country, basically computational biologists.

And they've developed a really novel tool where you can infer protein expression from RNA data. And, this came out of here at Columbia. Our colleagues in this department, I'm very proud to be able to work with them. They're really pioneers in using this inferred protein expression algorithm, and were able to take RNA data and inferred protein expression to give us, you know, even more information about the cell types and their composition, which was I think quite another quite unique thing about this study.

Erin Welsh:
Right. And so I understand VIPER is the name of the tool. What does that stand for?

Dr. Gabre:
VIPER stands for Visualization Pipeline for RNA-Seq.

Erin Welsh:
Okay. And so when you, when you get this protein expression data, what can that tell you?

Dr. Gabre:
So you can infer more information from the cells, basically, because the single cell RNA-Seq approach is very novel. But there's what we call RNA dropout, so you can lose some RNA in the preparation process. And so being able to use this VIPER tool, inferred protein expression, allows us to find proteins that we wouldn't necessarily be able to know were there based on RNA data because of the high dropout rate.

We used the single cell RNA-Seq data as is and looked at the cell clustering that we had, and then we did the VIPER program and for protein expression, we're able to, I think, make some of these critical findings because of it.

Erin Welsh:
And so now that we've got this picture of this incredible new technology that you used for this study, I'd love to get into some of your findings. What expression differences did you see in the tumor cells of early onset and late onset colorectal cancers?

Dr. Gabre:
First I wanna start off with what we expected. Our hypothesis was that these tumors were gonna be immune cold. Basically tumors that wouldn't have a lot of immune cells present. And therefore, maybe that's the background in which these tumors arose from.

We did not find that. We found that the immune composition overall was quite similar. But what we did find that was different was the early onset tumors looked like they had more fibroblasts, cancer associated with fibroblasts. Fibroblasts are very important in the process of tumorgenesis.

They secrete a lot of different cytokines, interact with other different cell types to promote tumors. And the other thing that we found is, when we looked at the epithelial cluster, the tumor cells themselves, we found that there was an increase in a subset of epithelial cells in the early onset tumors with higher expression of inflammatory markers.

In particular one called TLR four. And this was very interesting because TLR four and that mechanism is known to be associated with colitis-associated cancers, and particularly in the context of IBD. Something is engaging, we think, these cells in creating an inflammatory signaling pathway within the epithelial cells, likely promoting tumor development.

Erin Welsh:
Right. Okay. So this expression signature where you have this, like, greater inflammatory pathway in early onset cancers, is that pathway cause or consequence of this cancer type?

Dr. Gabre:
We think it's cause and the reason I bring up like IBD is beause it links it more to an inflammatory phenotype and the question is what's engaging with this receptor? And there've been a lot of studies that have shown that this receptor can be activated by bacteria.

And so this TLR four receptor might be, we think, kind of the integrator of that, you know, engagement. This bacteria might be acting on this receptor. Additionally this receptor can be activated by high fat diets. Saturated fats can engage TLR four and activate signal pathways. It's lighting up the bulb in our minds. Like, maybe bacteria now, having easier time engaging with our colonic epithelium. And maybe it's bacteria that can cause DNA damage. And so TLR four is kind of a marker of that, of that going on.

Erin Welsh:
So this TLR four is acting kind of like the initiator button, like something elevates this or somehow triggers this receptor and whether it's high fat diet, whether it's these different types of bacteria, and then that sort of is what sets off this potential cascade of essentially tumorgenesis or at least a higher likelihood of developing a tumor.

Dr. Gabre:
Exactly. That's our new hypothesis.

Erin Welsh:
And so, finding these expression differences, can that help develop biomarkers to either determine different tumor types, or can it also even lead to targeted therapies? Like, could you downregulate the recruitment of fibroblasts to your tumor or something using that specific receptor?

Dr. Gabre:
Potentially, but we're really interested in biomarker development because if we can somehow leverage this knowledge in subsequent studies to look at things in people's blood plasma in their stool, inflammatory markers in the stool, will that increase the pretest probability to know that these patients are higher risk for adenoma development younger and therefore they get a colonoscopy younger?

You know, you wanna start off with something non-invasive, potentially, so you can really risk stratify and know who to test. That's how you will improve the yield, so to speak, of a colonoscopy, you know, doing it on a 35-year-old right now, highly unlikely still to find colon cancer. But if that 35-year-old has particular markers in their stool and their blood, it may mean that we should, you know, do a colonoscopy on them.

That's where I hopefully see this going.

Erin Welsh:
And so with this study, I mean, you have demonstrated the tremendous potential of new sequencing technology, analysis techniques and really the power of collaboration to shed light on this really concerning issue. And it must be thrilling to conduct such cutting edge research.

And I'm curious, what do you think has been a main driver of your team's success in studying early onset colorectal cancer at NewYork-Presbyterian and Columbia?

Dr. Gabre:
This doesn't happen in a silo. You know, I'm very lucky to work with world class oncologists, world class surgeons… and I think that's what's gonna lead this field forward is a team science approach. We hope to get this paper out so that people can hopefully learn something and then collaborate to move this further, to learn more.

Erin Welsh:

It really does demonstrate the importance of, like, all of these different backgrounds of expertise and how we can use them together to kind of say, let's innovate and also learn more than we could have if we were just working independently in our own silos.

Dr. Gabre:
Exactly. Team science.

Erin Welsh:
Yeah. Team science. Love that. That was such a fascinating and a really impactful and emotional conversation and I really appreciate you taking the time to chat with me today.

Dr. Gabre:
Absolutely. Thank you so much for bringing attention to this issue. It's very important.

Erin Welsh:
Huge thanks to Dr. Joel Gabre for taking the time to speak with me about his team's recently published and groundbreaking study on the mechanisms behind the increase in colon cancer among young people.

I'm Erin Welsh.

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