Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital.
Welcome to Yale Cancer Answers with Doctor Anees Chagpar.
Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week it’s a conversation about new research into the early detection of ovarian cancer with Doctor Stacy Malaker. Dr. Malaker is an assistant professor in the Department of Chemistry at Yale University, and Dr.
Chagpar is a professor of Surgical Oncology at the Yale School of Medicine.

So, Stacy, maybe we can start off by you telling us a little bit more about yourself and what it is you do.

I got my PhD at the University of Virginia where I was in the lab of Professor Donald Hunt and he is one of the founding fathers of biological mass spectrometry and mass spec is kind of what I do or what I'm known for.

And then I did my postdoc in the lab of Carolyn Bertozzi, who just recently won the Nobel Prize in Chemistry.

And there I got really interested in a class of proteins called mucins.
which have tons and tons of sugar.
And so I spent five years there researching those.
And so now in my own laboratory, I combine the expertise of the instrumentation or the mass spec and the sugars or glycobiology and we do something that’s called glycoproteomics, which is studying sugars that modify proteins.
So now everybody wants to know, what does any of this have to do with cancer? Sure. So sugars are altered in
pretty much every disease that’s ever been studied and primarily in cancer, but also other diseases like inflammatory bowel disease or cystic fibrosis or even heart disease. And so we try to monopolize on those changes in the sugar structures to identify new biomarkers or potential therapeutics.

Tell us more about your research in particular, what are you looking at and how might this make a difference to people with cancer?
particular regarding ovarian cancer, right now more than 70% of women are diagnosed with ovarian cancer in the late stages, so stage 3 or stage 4 and the five year survival rate for women diagnosed in those stages is really poor. It’s less than 20%. Now if ovarian cancer is caught in early stages like stage 1 or two, that five year survival rate goes up to 95%. But the problem is that we don’t have a really good biomarker for ovarian cancer right now. Right now what is currently used
something that’s called CA-125
and CA-125 happens to be one of
those mucin type proteins that
I was talking about earlier.
And so it’s this really,
really huge protein that’s decorated
by tons and tons and tons of sugars.
And so 80% of its mass is actually sugar
units as opposed to the protein backbone.
Again, the sugar units
are perpetually disordered in cancer
yet when doctors are detecting the CA-125,
ye’re usually only detecting the
unmodified regions of the protein.
And so we want to identify altered
sugar units on this huge protein
to ideally detect cancer earlier. So that if we can do that and identify something that’s changed early on in the progression of cancer, then we could ostensibly develop a better biomarker and early stage detection.

Yeah, I think the problem though is that for ovarian cancer, it’s not incredibly common. You’re quite right, when it is diagnosed, it’s diagnosed late because we don’t have a screening test. But one of the questions always is, you know, are there blood
00:04:18.380 --> 00:04:20.560 tests for detection of cancer?
NOTE Confidence: 0.9350412
00:04:20.560 --> 00:04:22.756 Are there blood tests for screening?
NOTE Confidence: 0.9350412
00:04:22.760 --> 00:04:25.476 And while CA-125 is a biomarker that
NOTE Confidence: 0.9350412
00:04:25.476 --> 00:04:29.128 might be used to help doctors in terms
NOTE Confidence: 0.9350412
00:04:29.128 --> 00:04:31.533 of monitoring progression of disease,
NOTE Confidence: 0.9350412
00:04:31.540 --> 00:04:34.340 it’s really not a widespread
NOTE Confidence: 0.9350412
00:04:34.340 --> 00:04:37.140 screening tool like for example,
NOTE Confidence: 0.9350412
00:04:37.140 --> 00:04:39.036 a colaguard would be or
NOTE Confidence: 0.9350412
00:04:39.036 --> 00:04:40.300 a mammogram would be.
NOTE Confidence: 0.9350412
00:04:40.300 --> 00:04:42.939 So is your research trying to look
NOTE Confidence: 0.9350412
00:04:42.939 --> 00:04:45.260 at these altered sugar moieties,
NOTE Confidence: 0.9350412
00:04:45.260 --> 00:04:47.780 really trying to find a screening modality?
NOTE Confidence: 0.9350412
00:04:47.780 --> 00:04:48.896 And if so,
NOTE Confidence: 0.9350412
00:04:48.896 --> 00:04:50.756 would that be administered on
NOTE Confidence: 0.9350412
00:04:50.756 --> 00:04:52.760 a population basis like to all
NOTE Confidence: 0.9350412
00:04:52.760 --> 00:04:55.007 women or would it be for women
who are particularly at high risk?

So that’s a great question and I think that as a basic scientist, I can only say that I’m hopeful that we’ll be able to identify something that has changed early on in cancer. So we’re using serum from high risk patients, some of whom developed ovarian cancer. And so the idea would be that we do identify something that could be used as a screening modality, but I don’t want to make any early promises since we haven’t actually identified anything quite yet.
Tell us a little bit more about your project. I mean, when you say you're looking at high risk women, you tell us more about who those women are. And the concept that you kind of laid out, if I've understood it correctly, is that you're looking at these high-risk women. You're taking blood samples from them and comparing those of them who went on to truly develop ovarian cancer to those who didn’t? Is that right? That's basically correct. So we have access to approximately 4000
serum samples from high-risk women. These are women that have been diagnosed with the BRCA, one or two mutations. So from the point of genetic diagnosis, you know throughout the years many, many samples have been collected from these various women. And so to kind of develop our technology we’re using women that have not actually been diagnosed just to be able to identify the CA-125 modifications or sugar units and then we’d basically be given a blinded sample and hopefully.
identify those biomarkers or what have you that could indicate cancer versus non-cancerous samples.

And so that sounds really interesting when we think about BRC A1 and two often times we think not only of ovarian cancer but also of breast cancer and one of the questions that is often asked is, is there a blood test for breast cancer as well. You mentioned earlier that the sugar moieties tend to be, you know, involved or disrupted or altered in a variety of processes. Do you think that your technology might have a role to play in breast
cancer as well as ovarian cancer?

Or is it really something specific about ovarian cancer that you’re looking at?

It’s pretty much any epithelial cancer, you know, has these altered mucin structures and so

CA-125 is known as Mucin 16 or Mach 16. CA-125 is known as Mucin 16 or Mach 16.

Mucin one or Mach one is dysregulated or upregulated in over 90% of breast carcinomas.

Pancreatic cancer is another one that would be really interesting to look at.

Pretty much any epithelial cancer is associated with dysregulated mucins.
And so presumably in this population of BRCA one and two gene mutation carriers, you'd be able to see not only the comparison between those who developed ovarian cancer and those who did not, but also those who developed breast cancer or in fact pancreatic cancer because that's another cancer that tends to be associated with those mutations, right?

Yeah, absolutely. I would have to talk to my collaborators to see how many of these women actually did develop breast and or pancreatic cancer. But that could be done.
one would think that time has something to do with it, right that it takes time to develop these alterations in the protein structure or in the sugar structure and it takes time to develop cancer. So have you found any correlation between the timing of things, I mean presumably if somebody just gets a blood sample today and you know and isn’t followed for very long, you may not find an association. Yeah, that’s a really great point. And you know this is we’re very, very early on in this project.
It was just awarded a few months ago. And so I anticipate we will actually see changes over time. But because again we haven’t actually done much of the research quite yet, I can’t give you a straight answer to that. But of these 4000 women, are you kind of looking at these women going forward as well or is this kind of a deidentified mass sample that you’ve got where you’ve got some clinical correlation data and would have to use covariates to see whether a relationship existed. For example, looking at age as a surrogate.
OK. So just to clarify, it’s not 4000 women, it’s 4000 samples that have been collected from I think 50 to 100 women over the course of their life. I see, so then you’re comparing samples as you go along in time. So there might be out of the 4000, say 100 people, then that would be like 40 time points per person on average. So then that’s very cool, right, because then you could see whether these people are...
acquiring these mutations.

Exactly, exactly.

So now that makes a lot more sense because now you can actually see, you know, how long does it take for people to develop these alterations and do these alterations once they do occur, how quickly or not do people develop cancer?

Y es, precisely.

Tell us about some of the research.
that kind of led up to this award. What have you found in your more earlier studies?

When I was a post doc, when we do mass spectrometry we usually take a protein and we digest it using enzymes into short peptides and then you know we basically blast those apart by bombarding them with gas molecules and/or radical anions and by the way that they fall apart we can kind of piece back what was present there previously.

But one of the problems with these really, really densely like oscillated proteins
or you know sugar modified proteins

And so when I was in my postdoc I characterized a series of enzymes that we call mucineases that are actually able to create short segments of the protein that are amenable to mass spec analysis.

So before we couldn’t look at these at all by my instrumentation method, but now we can actually get pieces and see them in the mass spectrometer.

So why is that important? Why is looking at these with mass spec so important as opposed to looking at them with other techniques?
Or are there no other techniques to look at them? I mean, you could potentially use staining techniques, or certain other techniques. I’m not saying that mass spec is the only technique. However, in my opinion, and of course I’m biased, it’s the best way of actually digging into what sugar structures are modifying what amino acids in what patterns. And you’re not going to get that molecular level of detail using other methods.
that you did before embarking on this was to figure out how you could actually use mass spec to look at these sugar moieties in these proteins going forward. Precisely, yes. And so my lab, you know, I have kind of two arms in my laboratory, one being, you know, instrumentation development and method development so that we can better see these altered sugar structures and various diseases. And then another arm where we study the biological role of the altered, glycosylation patterns in cellular systems.
Fantastic. Well, we’re going to take a short break for a medical minute, but please stay tuned to learn more about the early detection of ovarian cancer with my guest, Doctor Stacy Malaker.

Funding for Yale Cancer Answers comes from Smilow Cancer Hospital, where their Oncodermatology program treats dermatologic concerns, including very dry skin, itching, and skin changes that arise as side effects from chemotherapy.

Smilowcancerhospital.org. The American Cancer Society
estimates that over 200,000 cases of Melanoma will be diagnosed in the United States this year, with over 1000 patients in Connecticut alone. While Melanoma accounts for only about 1% of skin cancer cases, it causes the most skin cancer deaths, but when detected early, it is easily treated and highly curable. Clinical trials are currently underway at federally designated comprehensive Cancer centers such as Yale Cancer Center and Smilow Cancer Hospital to test innovative new treatments for Melanoma. The goal of the Specialized Programs
Research Excellence in Skin Cancer

Grant is to better understand the biology of skin cancer with a focus on discovering targets that will lead to improve diagnosis and treatment.

More information is available at yalecancercenter.org.

You're listening to Connecticut Public Radio.

Welcome back to Yale Cancer Answers.

This is Dr. Anees Chagpar, and I'm joined tonight by my guest doctor Stacy Malaker.

We're talking about the early detection of ovarian cancer.

As all of you know,
this has been widely talked about as the silent cancer and the cancer that whispers.

And Stacy in her lab is trying to figure out whether we can actually, well, make ovarian cancer speak a little bit more loudly by looking at sugar molecules and how they’re disrupted or altered.

Right before the break, one of the things that you were talking about is that in the work up to your current project which is looking at how these alterations over time are changing and how that might affect people with a BRCA 1 or 2.
NOTE Confidence: 0.93090713
00:15:51.352 --> 00:15:54.390 mutation both in the
development of ovarian cancer
NOTE Confidence: 0.93090713
00:15:54.390 --> 00:15:55.710 your primary of interest,
NOTE Confidence: 0.93090713
00:15:55.710 --> 00:15:57.280 but also other cancers.
NOTE Confidence: 0.93090713
00:15:57.280 --> 00:16:01.861 One of the things that your lab
NOTE Confidence: 0.93090713
00:16:01.861 --> 00:16:04.470 did was to really look at how
NOTE Confidence: 0.93090713
00:16:04.470 --> 00:16:07.370 you can use mass spectrometry
NOTE Confidence: 0.93090713
00:16:07.370 --> 00:16:10.690 to look at these alterations,
NOTE Confidence: 0.93090713
00:16:10.690 --> 00:16:13.810 which is something that you really
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00:16:13.810 --> 00:16:17.538 couldn’t do otherwise and you couldn’t
NOTE Confidence: 0.93090713
00:16:17.538 --> 00:16:20.610 do and look at at the molecular
NOTE Confidence: 0.93090713
00:16:20.610 --> 00:16:22.210 level with mass spectrometry.
NOTE Confidence: 0.93090713
00:16:22.210 --> 00:16:25.730 So I guess the other question that I have is,
00:16:26.002 --> 00:16:27.906 can you tell us a little bit
NOTE Confidence: 0.93090713
00:16:27.906 --> 00:16:29.529 more about this technology?
NOTE Confidence: 0.93090713
00:16:29.530 --> 00:16:32.029 I mean presumably if you can now
look at the sugar moieties and as you said before the break that these alterations are seen in not just cancer but a variety of other diseases. How is this being utilized now in terms of looking at other cancers and other diseases? I mean, how do you see this moving forward? Yeah, I mean, the world is our oyster really. We have this is 1 project of many in my lab right now. We’re looking at cardiovascular disease. We’re looking at breast cancer.
but in a different fashion.

And we also look at changes in intestinal linings and stress and depression and so on and so forth. And so we’re really trying to monopolize on these developments that we’ve made in order to study altered sugar structures in a whole host of different diseases. And so tell us a little bit more about, you know, these sugar moieties. I mean, I know that you became very interested in these during your postdoc working with a Nobel Prize winner whose lab really looked at these, these molecules. But you know,
these days I think a lot of people think
about cancer from the perspective of
genetics and they think about it from the
perspective of environmental factors.
But we really don’t think about how
these two things affect sugars.
So can you tell us a little bit more about those interactions
and how prevalent they are?
I mean, do you really think that
by looking at these sugar muleides
that we might actually, you know,
to unlock a portion of cancer
biology that had heretofore been
largely well overlooked to some degree?
Yeah, absolutely.

I think that sugar structures, sugar structures, excuse me, are extremely difficult to study. One of the issues is that you just mentioned genetics, glycobiology or the sugar structures are not templated, meaning that there are 200 different enzymes that build these sugar structures on the surface of our cells. And so you can’t necessarily look at changes in those enzyme levels via genetics in order to build back up what’s possibly going to be on the cell surface.
And so because of that it’s much more difficult to study and so it’s lagged behind in you know, in comparison to more general fields like genomics or transcriptomics or proteomics. And so we really want to monopolize on these changes in order to break open a whole new area of cancer biology. I mean, do you think that there’s an interplay between genomics and these sugar structures? Or do you think that these are two separate issues that they cause or are affected by cancer independently? In other words, I mean,
do you think that these two play together or not really?

Oh, they definitely do.

It’s just that you can’t look at enzyme changes and then immediately know how that’s going to change the sugar

So if for instance, there’s a capping structure called sialic acid and you can look at the sial transferases and if those are up or down you could then gather that your structures will have more or less of a
certain type of that sugar structure, but it won’t tell you exactly what it’s modifying. So what protein it’s on or it won’t tell you exactly what type of sugar structure it’s on and so on and so forth. And so going back to the project for which you were just awarded a grant where you’re looking at these BRCA mutation carriers, is it possible that BRCA in and of itself, I mean we know BRCA as being a gene which is largely responsible for DNA repair.
00:20:50.275 --> 00:20:52.702 mistakes that your DNA may have and

00:20:52.702 --> 00:20:54.940 the thinking is that

00:20:54.940 --> 00:20:57.187 really leads to the higher risk of

00:20:57.260 --> 00:20:59.690 developing a variety of malignancies.

00:20:59.690 --> 00:21:03.452 So if genetics and these altered

00:21:03.452 --> 00:21:05.960 sugar structures are related,

00:21:05.960 --> 00:21:08.046 do you think that

00:21:08.046 --> 00:21:10.790 BRCA might be doing something to the sugar

00:21:10.863 --> 00:21:13.439 structures and are you looking at that?

00:21:13.440 --> 00:21:14.416 For example,

00:21:14.416 --> 00:21:17.506 are you comparing BRCA carriers to

00:21:17.506 --> 00:21:20.396 people who are not BRCA carriers

00:21:20.396 --> 00:21:22.186 and seeing whether there’s a

00:21:22.186 --> 00:21:23.870 difference in terms of

00:21:23.870 --> 00:21:25.590 these sugar structures between

NOTE Confidence: 0.92736816
these two populations?
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That’s not something that we’re currently
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looking at simply because we
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only have access to these BRCA1 and 2 samples.
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healthy, you know, healthy samples or healthy
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patient serum in order to compare them.
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So definitely something we could do,
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but not something that’s
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currently on our docket.
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And then the other thing that I
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kind of wonder about is one of the
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questions I always get asked is,
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well, why did I get cancer?
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Can you tell us a little bit more
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about whether you think that
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having these altered sugar moieties might have something to do with people's risk of developing cancer? And secondary to that, why do people have these alterations in these sugar moieties anyways? I mean what causes that? Again, that's a very, very loaded question. So what was the first part of the question? Could these altered sugar moieties be part of the explanation of why some people develop cancer even though they did everything right? Sure. So I mean there are many,
many possible answers to that question, but I’ll probably lean into the one that I’m most familiar with. So you know, cancer immunotherapies are the new pillar of treatment as I’m sure you’re aware. And so altered sugar structures are a way that cancer cells can actually avoid the immune system and the immune system is really key in getting rid of cells that have become transformed or cancerous. And so there’s this really fine-tuned balance where you want your immune system to be active and
killing off these cancer cells.

Now the sugar moieties can actually act as a mechanism to shield the cancer cell from immune cells that would normally kill it off.

For instance, my lab studies what’s called a checkpoint inhibitor where when that checkpoint inhibitor is bound to one of its ligands through sugar structures, it shuts down T cell function.

And it’s so important that antibodies that block that interaction are currently being investigated in the clinic.

And so we’re trying to again monopolize on the altered sugar structures.
in order to potentially develop a better cancer immunotherapy. But basically kind of summarizing that is that these sugar moieties can serve to shut down various types of immune cells which then allow the tumor cells to proliferate and become a solid tumor or various cancers. So why do some people get these altered sugar moieties that can essentially shut down your immune system or at least its ability to detect cancer and other people don’t? I mean, are there factors that drive that? You know, some people might be wondering,
is it the sugar that I’m eating
or is it how I metabolize it?
Or is it, you know, diabetes?
Or is it something to do with my genetics?
Yeah. So I mean that’s a great question
that I don’t have the answer for.
I will specify that the sugars that you’re eating are very,
very different than the sugars I’m talking about.
These are very different structures.
very, very different than the sugars I’m talking about.
sugars I’m talking about.
I mean, essentially they can get metabolized and turned into the sugar structures that are on the cell surface.
But I’m not looking at glucose or sucrose or anything like that.
These are very different structures.
And so, you know, I think a lot of people may be asking, especially now that the WHO is coming out with their statement against some artificial sweeteners of thinking that they may be carcinogenic. Do do those have anything to do with the altered sugar moieties that you’re talking about? I don’t know, my understanding for those altered sugar moieties that are in, you know artificial sweeteners and so on is that they can’t be broken down or metabolized in the same way that normal sugars would be.
But that is just what I understand.

I have not studied up on that too much.

So for the alterations

of sugar moieties, I mean the

the truth of the matter is,

that at least the research

that you've done so far,

your hypothesis is that these alterations

have a role to play in cancer,

whether it’s the immune system

evading cancers or you know,

increasing risk or whatever.

Do we know of any risk factors

that make people more susceptible

to having altered sugar moieties,

the ones that you’re studying?
I mean not that I'm aware of. I think that if you did genetic studies again, you could probably create hypothesis and individuals regarding different enzymes that are up or down regulated. But as far as I'm aware, there's not anything like a BRCA1 that would definitely indicate that you're going to have these altered sugar structures. And my perception is from your description of your earlier study, it's not like you're born with these altered sugar moieties.
it’s that they develop over time.

Is that right?

I mean it would be kind of similar to,

you know, genetic mutations that accumulate over time in cancer cells.

And again,

you were asking if genetics and altered sugar structures are related.

If you acquire many,

many genetic mutations over time,

you tend to develop cancer.

Similarly, you would also mutate these various glycan structures on the surface of cells.

And so it sounds like there’s a lot going on in your laboratory both
NOTE Confidence: 0.9316189
00:27:20.757 --> 00:27:23.886 on the kind of developing the
NOTE Confidence: 0.9316189
00:27:23.886 --> 00:27:26.402 methodologies as well as in terms of
NOTE Confidence: 0.9316189
00:27:26.402 --> 00:27:28.346 looking at the actual clinical impact
NOTE Confidence: 0.9316189
00:27:28.346 --> 00:27:30.547 of these altered sugar moieties.
NOTE Confidence: 0.9316189
00:27:30.550 --> 00:27:33.022 Looking forward, what projects are you
NOTE Confidence: 0.9316189
00:27:33.022 --> 00:27:35.658 most excited about and what do you
NOTE Confidence: 0.9316189
00:27:35.658 --> 00:27:38.115 think we can expect to hear about in
NOTE Confidence: 0.9316189
00:27:38.115 --> 00:27:40.428 the next year or two or five or 10?
NOTE Confidence: 0.93945575
00:27:42.030 --> 00:27:45.140 Oh gosh, my students listen to this and
NOTE Confidence: 0.93945575
00:27:45.140 --> 00:27:46.989 I won’t say their individual projects.
NOTE Confidence: 0.93945575
00:27:46.990 --> 00:27:48.826 I don’t want to pick favorites.
NOTE Confidence: 0.93945575
00:27:48.830 --> 00:27:50.710 Obviously I’m very excited about
NOTE Confidence: 0.93945575
00:27:50.710 --> 00:27:52.590 this ovarian cancer project simply
NOTE Confidence: 0.93945575
00:27:52.650 --> 00:27:54.460 because I think that, you know,
NOTE Confidence: 0.93945575
00:27:54.460 --> 00:27:56.980 CA-125 is really a black box of information
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that I think we can monopolize on to develop an improved diagnostic tool. And it's a somewhat selfish project because I am a BRCA 2 carrier. So I would like to identify ovarian cancer earlier for my own self and family in addition to all of the women that are at risk. But I also, you know, I love all of my projects equally in my lab, and I'm really excited about the instrumentation developments that we have, as well as really cracking open all of the biological underlying of altered glycosylation.

Doctor Stacy Malaker is an assistant
professor in the Department of Chemistry at Yale University.

If you have questions, the address is Cancer Answers at Yale dot Edu.

And past editions of the program are available in audio and written form at yalecancercenter.org.

We hope you'll join us next week to learn more about the fight against cancer here on Connecticut Public Radio.

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