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Welcome to Yale Cancer Answers with your host 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 is a conversation about the role of obesity and insulin in cancer with doctor Rachel Perry. Doctor Perry is an assistant professor in Medicine and Endocrinology and cellular and Molecular Physiology at the Yale School of Medicine, where doctor Chagpar is a professor of surgical oncology.

Rachel, maybe we can start by talking a little bit about obesity. They talk about it being like the other pandemic. It’s really something that’s prevalent across the world.
Yes, that is absolutely true.
So at this point we’re coming up on close
50% of Americans who are obese and
large numbers really worldwide as well.
And with that obesity is a problem
And with that obesity is a problem
and of itself, it increases
the risk of cardiovascular disease,
stroke and cancer which we will discuss
today and other conditions,
but it also brings with it an
increased risk of type 2 diabetes
which can be caused by obesity and
is expected to effect 100% of
Americans, or would affect 100%
of Americans if current trends
continue by the year 2050.
That really is mazing.
So that tells us we need to do
something to intervene here.
Two statistics that
you put out in a single sentence
that just completely blew me away.
The first is that almost half of all
Americans are obese and all of us are
going to end up with Type 2 diabetes
in 30 short years,
that’s incredible.
I just have to correct myself.
Overweight or obese, almost 50%.
I was gonna ask about that.
So what really is the definition of obesity?
I mean are we talking about that last five or 10 pounds that everyone has to lose? Or are we talking about people who are seriously several pounds or several 100 pounds overweight? Somewhere in between the two. Technically, obesity is defined as a body mass index over 30, and that really corresponds to being about 30 to 50 pounds, closer to 50 pounds over our ideal body weight, and so we’re not talking about, you know the last five or 10 pounds from high school. That may put us into the overweight category, but we don’t need to be hundreds of pounds overweight to be in that obese category. That can really increase our risk of a number of health conditions, and so one of those conditions is cancer. Can you give us a metric? How much does obesity really increase your risk? I know a lot of people worry about cancer, I mean certainly they worry about diabetes and heart disease, all of those are some of the key killers of Americans these days. But how much does obesity
0:03:32.175 - 0:03:33.258 really impact cancer?
0:03:33.26 - 0:03:35.773 And does it affect all kinds of
cancer or just a select few?
0:03:37.95 - 0:03:39.039 Well, those are
0:03:39.04 - 0:03:41.044 both great questions and in the
0:03:41.044 - 0:03:43.044 answer to the first question,
0:03:43.04 - 0:03:45.476 how much does obesity affect cancer risk,
0:03:45.48 - 0:03:47.7 it’s difficult to answer because it
0:03:47.7 - 0:03:49.912 really depends on the tumor type
0:03:49.912 - 0:03:52.222 and so I’m going to answer your
0:03:52.222 - 0:03:54.6 second question first and that is
0:03:56.976 - 0:03:59.451 at this point there are 13 tumor types
0:03:59.451 - 0:04:02.335 that the Centers for Disease Control have
0:04:02.335 - 0:04:04.616 associated with obesity and that means,
0:04:04.62 - 0:04:06.738 with obesity increasing the risk and
0:04:06.738 - 0:04:09.215 causing a worse prognosis of those tumor
types and those include breast cancer,
0:04:11.23 - 0:04:12.274 ovarian, uterine, renal,
0:04:12.274 - 0:04:13.408 pancreatic, thyroid, colorectal,
0:04:13.408 - 0:04:15.598 as well as several others.
0:04:15.6 - 0:04:18.113 And but there are few tumor types
0:04:18.113 - 0:04:20.41 where there’s no risk of obesity,
0:04:20.41 - 0:04:23.105 and we really don’t understand what causes
0:04:23.105 - 0:04:25.958 some tumor types to be worse with obesity,
0:04:25.96 - 0:04:28.179 and other tumor types not to be
0:04:28.179 - 0:04:30.508 worse within the tumor types that
0:04:30.508 - 0:04:32.244 are associated with obesity,
0:04:32.25 - 0:04:34.882 there are some where obesity brings with it
0:04:34.882 - 0:04:37.429 a relatively lower risk in breast cancer.
0:04:37.43 - 0:04:39.65 I believe the increase is about
0:04:39.65 - 0:04:42.2 20 to 30% of an increased risk
0:04:42.2 –> 0:04:44 with obesity, still very significant
0:04:44 –> 0:04:45.609 but smaller than others.
0:04:45.61 –> 0:04:47.102 Whereas with pancreatic cancer,
0:04:47.102 –> 0:04:50.329 risk is a couple fold, ovarian cancer as well,
0:04:50.33 –> 0:04:52.864 a couple fold greater risk with obesity.
0:04:52.87 –> 0:04:54.69 So as I said
0:04:54.69 –> 0:04:57.224 it really depends on the tumor type.
0:04:57.23 –> 0:04:59.701 But because these 13 cancer types that
0:04:59.701 –> 0:05:01.927 are associated with obesity are among
0:05:01.927 –> 0:05:04.489 the most prevalent cancer types out there,
0:05:04.49 –> 0:05:06.3 it really translates to a
0:05:06.3 –> 0:05:07.386 significant excess risk.
0:05:07.39 –> 0:05:08.842 From an epidemiological standpoint
0:05:08.842 –> 0:05:09.568 that comes
0:05:09.57 –> 0:05:10.659 with obesity.
0:05:10.659 –> 0:05:13.562 And we really don’t know why.
0:05:13.562 –> 0:05:16.578 Even 20 to 30% increased risk of breast
0:05:16.578 –> 0:05:18.93 cancer seems pretty significant to me.
0:05:18.93 –> 0:05:21.716 But why is that 20 to 30%
0:05:21.72 –> 0:05:23.715 but in ovarian cancer we’re
0:05:23.715 –> 0:05:25.71 talking about more like 200%?
0:05:25.71 –> 0:05:28.91 Do we know why that is?
0:05:28.91 –> 0:05:31.458 Why it is that obesity effects more
0:05:31.458 –> 0:05:34.49 cancers in some situations than in others?
0:05:34.49 –> 0:05:35.687 We really don’t,
0:05:35.687 –> 0:05:38.48 and that is a tremendous open question
0:05:38.48 –> 0:05:40.88 that we need to figure out.
0:05:40.88 –> 0:05:43.19 Because if we could figure out
0:05:43.19 –> 0:05:44.73 why obesity worsens certain
0:05:44.8 –> 0:05:46.86 cancer risks worse than others,
0:05:46.86 –> 0:05:49.604 then perhaps we would have a better handle
0:05:49.604 -> 0:05:52.46 on why obesity increases cancer risk
0:05:52.46 -> 0:05:54.791 at all, and that would be the
0:05:54.791 -> 0:05:56.984 target that would be where we
0:05:56.984 -> 0:05:58.844 can intervene in this process.
0:05:58.85 -> 0:06:02.4 A lot of labs, mine included as well as
0:06:02.4 -> 0:06:04.38 many others are working on this
0:06:04.38 -> 0:06:07.02 question to try to uncover number one,
0:06:07.02 -> 0:06:09.216 why are certain tumor types affected
0:06:09.216 -> 0:06:11.279 and not others and #2 why are
0:06:11.28 -> 0:06:13.596 certain tumor types affected worse than
0:06:13.596 -> 0:06:15.512 others because there’s really going
0:06:15.512 -> 0:06:17.668 to be a major epidemiological role for
0:06:17.67 -> 0:06:19.09 uncovering that information.
0:06:20.51 -> 0:06:23.598 Do we know what exactly or how exactly
0:06:23.598 -> 0:06:25.817 obesity increases your risk of cancer?
0:06:26.84 -> 0:06:30.761 We’re still working on that and there
0:06:30.761 -> 0:06:33.32 have been a number of potential mediators
0:06:33.32 -> 0:06:35.696 that people have thrown out there.
0:06:35.7 -> 0:06:37.776 One that my lab studies is
0:06:37.776 -> 0:06:39.59 insulin and related to that,
0:06:39.59 -> 0:06:41.35 insulin-like growth factor one.
0:06:41.35 -> 0:06:43.185 The concentrations of these molecules
0:06:43.185 -> 0:06:45.695 increase with obesity and we and others
0:06:45.695 -> 0:06:47.837 have shown that in vitro those molecules
0:06:47.837 -> 0:06:49.82 can increase tumor cell division.
0:06:49.82 -> 0:06:52.644 We can talk a little bit later about
0:06:52.644 -> 0:06:55.119 the mechanism by which that may occur,
0:06:55.12 -> 0:06:56.071 if you’d like.
0:06:56.071 -> 0:06:58.779 But there have been a number of other
0:06:58.779 -> 0:07:01.677 factors that people have proposed as well,
0:07:01.68 -> 0:07:02.805 including inflammatory cytokines.
Obesity is a pro-inflammatory state and so inflammatory cytokines are up in obese individuals. There’s leptin, a protein that is secreted by the fat and has been shown in certain models to accelerate tumor growth. There are other hormones that may be involved, we mentioned insulin, but also potentially Glucagon, Adiponectin. And any and all of these have been shown in vitro, so in cell culture studies, to accelerate tumor growth, and there’s been increasing work in mice and humans, it’s a little bit more difficult to tell the answer because you know a patient comes in with cancer. you can’t do all these types of interventions that we’re able to do in the lab to really be able to pick out certain positive factors, but all of these hormones and cytokines that I just listed correlate with tumor appearance and progression. And a point I wanted to make related to the role of obesity, we talked about how obesity may increase
the risk of certain types of cancers, but it also worsens the progression and increases the rate of recurrence of the cancer.

So when we say that obesity may increase the risk of breast cancer by 20%, it also worsens the prognosis of someone who’s already diagnosed with breast cancer as well as increasing her risk of recurrence, so that 20% increased risk is really not just 20%. Because the increased risk continues down the line and we really need to figure out what the reason for that weight gain or that obesity increases their risk of recurrence. So have people looked at that? Some of the therapies that we use actually make you gain weight, so many breast cancer survivors actually gain weight during therapy and then on top of that weight gain or that obesity increases their risk of recurrence. So have people looked at that?
being overweight to begin with? Does that make a difference to your recurrence? If you were normal weight, for example, when you were diagnosed and then you gained weight with your treatment, does that increase your risk of recurrence because that weight gain was related to your treatment versus if you were overweight to begin with? In fact it does. So people have looked at this specifically, the change of weight during the course of treatment and those who gain weight during treatment. Actually specifically for breast cancer as you mentioned, are in fact at a higher risk of recurrence of their cancer, and so that’s something that absolutely needs to be kept in mind during therapy. Now that said, it’s not as simple as it may appear, because those who lose weight during treatment also have a poorer prognosis. This gets into the issue of cancer cachexia. So when patients are being treated for cancer, have cancer and they lose a significant amount of weight,
a very large amount of weight so that they lose a lot of fat and start to lose muscle as well, those patients are also at higher risk for poorer outcomes, and so we can’t simply tell people, just go and lose weight, and that’s really why we need to understand mechanistically what this link is between obesity and cancer, so that instead of telling people, oh, just go and lose weight, we can give them a mechanistically driven intervention that may help mitigate that risk of obesity, while not predisposing them to cancer cachexia. So let’s unpack that a little bit more. What do you mean by a mechanistically driven intervention? We want to understand what the molecule is or molecules are that are responsible for this link between obesity and cancer. For instance, if the link is at least in part insulin, one of my favorite hypothesis, there are ways that we can lower insulin while not forcing a patient to lose weight. There are different drugs that work in different ways that would all lower circulating insulin and that would
not require the patient to go on a restrictive diet or put themselves at risk for cancer cachexia syndrome. Similarly, if the link were certain inflammatory cytokine, there are various antibodies that are being developed to block certain inflammatory cytokine action, and so we could potentially give folks an antibody to that particular cytokine that might lower their risk, while again, not requiring them to lose weight. So it would just allow us to more safely intervene in this link between obesity and cancer if we could understand exactly what mediates it. Except that they’d still be at increased risk of heart disease and diabetes if they were overweight, right? Yes, certainly weight loss within a healthy range, so not becoming underweight but weight loss within a healthy range is probably going to be the best way to mitigate this risk. Overall though it may be very difficult during cancer treatment, as you mentioned.
Cancer treatment tends to cause people to gain weight, and so during that short period of time it may be better to focus on what we can do from a cancer standpoint, rather than focusing on weight loss. But long term from a population standpoint, absolutely we should all be encouraging our patients and ourselves to maintain a healthy weight.

Rachel, I want to dig a little bit deeper into what your lab is doing in terms of insulin and its link to obesity. One of the statistics that you gave us at the top of the show, which was the link between obesity and diabetes, was just mind blowing to me. So talk a little bit about that and how insulin plays into that.

Yeah, so my training was in straight metabolism. I studied diabetes and substrate metabolism during my graduate work and we developed methods to be able to assess whole concept of obesity.
metabolism in different tissues and different settings and so one of the hormones that we focus on in the metabolism world is insulin. Insulin is secreted by the endocrine pancreas when we eat a meal. When blood sugar levels go up, insulin helps ourselves to take up glucose or sugar so that the sugar is taken out of the bloodstream and into the tissues. And when we do that, the tissues or even tumors in certain cases can use that sugar as fuel for themselves while lowering blood glucose concentrations. So in diabetes, that process doesn’t happen efficiently. People tend to become insulin resistant, so their bodies don’t respond as well as they need to insulin and so it either needs to be given by injection, or certain interventions need to take place to allow the body to respond better to insulin and the work that we’ve been doing in my lab in the last several years has been specifically looking at this link between insulin, obesity and cancer.
I think there’s a lot more we need to learn about obesity, insulin, and cancer, and how all of that plays together. But first we need to take a short break for a medical minute.

Please stay tuned to learn more about obesity, insulin, and cancer with my guest doctor Rachel Perry.

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This is a medical minute about genetic testing which can be useful for people with certain types of cancer that seem to run in their families. Patients that are considered at risk receive genetic counseling and testing so informed medical decisions can be based on their own personal risk assessment. Resources for genetic counseling and testing are available at federally designated comprehensive cancer centers. Interdisciplinary teams include geneticists, genetic counselors, physicians, and nurses who work together to provide risk assessment and steps to
0:15:40.36 → 0:15:42.345 prevent the development of cancer.
0:15:42.35 → 0:15:44.11 More information is available
0:15:44.11 → 0:15:44.99 at yalecancercenter.org.
0:15:44.99 → 0:15:47.63 You’re listening to Connecticut public radio.
0:15:48.84 → 0:15:50.74 This is doctor Anees Chagpar
0:15:50.74 → 0:15:52.831 and I’m joined tonight by
0:15:52.831 → 0:15:54.716 my guest doctor Rachel Perry.
0:15:54.72 → 0:15:56.796 We’re talking about the role of
0:15:56.796 → 0:15:58.986 obesity and insulin in cancer and
0:15:58.986 → 0:16:01.212 right before the break Rachel, you
0:16:01.212 → 0:16:03.559 were starting to tell us a little
0:16:03.559 → 0:16:05.742 bit about how insulin really works in
0:16:05.742 → 0:16:07.989 terms of causing obesity and how that
0:16:07.989 → 0:16:10.29 plays into the development of cancer.
0:16:10.29 → 0:16:12.972 Can you take us back a couple of
0:16:12.972 → 0:16:15.83 steps and talk about insulin and obesity?
0:16:15.83 → 0:16:17.738 I know insulin is a hormone
0:16:17.738 → 0:16:20.029 it’s made by the pancreas,
0:16:20.03 → 0:16:23.648 but how does that cause us to be obese?
0:16:23.65 → 0:16:26.457 And if all of us make insulin,
0:16:26.46 → 0:16:27.669 how come not
0:16:27.67 → 0:16:29.68 all of us are obese?
0:16:29.68 → 0:16:32.086 Those are both important questions,
0:16:32.09 → 0:16:34.834 and honestly, we’re still not certain the
0:16:34.834 → 0:16:37.213 metabolic community is still not certain
0:16:37.213 → 0:16:39.493 to what extent insulin causes obesity
0:16:39.493 → 0:16:42.139 versus obesity causing high insulin levels.
0:16:42.14 → 0:16:44.42 We know that obesity causes high
0:16:44.42 → 0:16:46.437 insulin levels because as individuals
0:16:46.437 → 0:16:48.567 become more and more obese,
0:16:48.57 → 0:16:50.65 they become more and more
insulin resistant and that’s due to increased levels of lipid or fat in various tissues. When we become insulin resistant, that means we don’t respond, our bodies don’t respond very well to insulin and so our body has to secrete more insulin to counteract that effect. Now the question of whether insulin causes obesity is very interesting in sort of a chicken and egg type of question, and there are a number of studies that do suggest that insulin may itself independently cause obesity and that’s at least in large part because insulin causes fat deposition. It causes those small molecules of carbohydrate and fat that are floating by in our bloodstream to actually be deposited in tissues in subcutaneous fat depots and form larger pieces of fat, and so in that regard, it is likely that insulin causes obesity, at least to some extent. But as I said, it’s more certain that obesity causes hyperinsulinemia or high insulin levels because of that insulin resistance phenomenon. As you said, we all need to have insulin.
The body knows if it doesn’t have enough functioning insulin, because when we don’t have enough insulin, our blood glucose levels get high without insulin action on various tissues, we’re not able to take up enough glucose or sugar from our bloodstream into those tissues, and when that happens, the body senses the high blood sugar level and secretes more insulin to try to counteract the effects of insulin resistance. So let me get this straight, obesity causes you to be insulin resistant, so your body needs to make more insulin. But that insulin takes sugar from your bloodstream and deposits it as fat, which then causes you to be more obese. So isn’t this a vicious cycle? It absolutely is a vicious cycle and we and others have shown that if you intervene in any step of this cycle, so if you intervene in the step of eating too many calories, if you intervene in secreting too much insulin, if you intervene in depositing that sugar in tissues as fat if you intervene in any of these steps, you can intervene in the cycle of the development of obesity. But yes, absolutely,
it’s a vicious cycle and this absolutely contributes to this pandemic of obesity that we have in our country and worldwide. We’re going to get back to exactly how we can intervene, but let’s talk a little bit about the cancer part. So we talked a little bit at the beginning of the show about the fact that obesity really does drive, I think it was what 13 different types of cancer, but not all cancers are affected by obesity, but certainly a large number of cancers are. So how does that happen? And what does insulin have to do with it anyways?

Individuals with obesity frequently have high circulating insulin levels because they tend to be insulin resistant. We found in a few studies, both in vitro
so in a dish and in vivo, in mice, insulin can drive tumor glucose uptake and metabolism, that initially because conventional wisdom has said that tumor glucose or sugar metabolism is constitutively high, so it would always be high and not regulated by any hormones, but the surprising finding that we and others have also shown is that in fact, tumor glucose or sugar metabolism is insulin dependent, and so in mice that are obese, they have high circulating insulin levels and this causes glucose uptake into their tumor cells. After the tumor cells take up glucose, it can be used in two different ways. It can be used for metabolism, so simply to provide the fuel that allows the cells to keep going, and it can also be used to make building blocks for cells. So a unique feature about tumor cells is that in order to be a tumor, these cells need to be growing and dividing all the time. They grow and divide very rapidly and they need building blocks to be able to do that,
and glucose is a key fuel to be able to provide those building blocks for these tumor cells, and so in that way glucose and insulin which drives glucose uptake, and insulin which drives glucose uptake, is a key pathogenic factor in tumors. So let me ask you this, we know a lot of diabetics who are type one diabetics who take insulin. Does that mean that the insulin can actually be driving tumor growth in these people? Putting them at increased risk since their injecting themselves with insulin? You know that’s a key question. A very important question, and frankly a personally relevant question, as I am a person with type one diabetes and so this is something that I am very curious about. The epidemiological evidence doesn’t seem to support a strong role for exogeneous insulin, that is injected, in type one diabetic individuals in driving tumor growth, and there could be a few different reasons for that. It is a little bit surprising, but what we currently believe is that you may need two hits. That is, high glucose and high insulin levels,
so type one diabetic individuals who take as much insulin as they need tend not to have chronically high glucose levels all the time, and so it may be that keeping blood sugar normal is also very important in these individuals who need to inject insulin exogeneously to stay alive. But that’s a question that really is an open question and one that were very curious about. It’s also entirely possible, and I think this is likely that insulin may not be the only factor that mediates the effects of obesity on tumor growth, so it may be that you need high insulin levels to have an obesity affect to drive tumor growth, but that you also need other factors like inflammatory cytokines or leptin or other hormones. And in these lean type one diabetic individuals they may have high insulin levels but not these other factors that may be required to mediate the effects.

You know, and that makes me think of something else. Some people have these benign tumors in their pancreas that secrete insulin,
so it’s kind of a little insulin factory that they’ve got going on. Are those people at increased risk of developing cancer, or is it still this, you need the interplay of a number of factors so they may not really be at increased risk. So I believe that these folks and I could be wrong on this, this isn’t particularly my field, but I believe that those folks are at higher risk of pancreatic, at least benign tumors of other types, and maybe at higher risk of pancreatic cancer, so that would suggest that insulin may be acting within the pancreas as a tumor promoting factor, but I don’t believe they’re at substantially higher risk in other sites. Now this could be because it’s my understanding that those folks aren’t allowed to go continuously forever with high insulin levels secreted by a tumor from the pancreas. The tumor will be either removed, or they may be treated with somatostatin or some other agent to prevent the high insulin secretion,
but I would expect that if someone chronically having high insulin levels from continuous excess secretion of insulin, that they would in fact be at risk and that is a study that we’ve done in mice. So if you take mice and put a subcutaneous insulin pellet into them so that they chronically have high insulin levels, they do develop tumors more quickly and do worse with the tumors than mice that don’t have too much circulating insulin all the time. And when we talked about the fact that some of the cancers are increased with obesity and insulin is one factor that may be playing a role, sometimes people talk about this thing called insulin growth factor or my IGF, which can be found in some cancers. Are those related? So we find that insulin plays more of role in people who have tumors that have receptors, for example, that are more responsive to insulin, or is this something that is more ubiquitous? At least in these 13 tumor types, regardless of whether or not
the tumor secretes insulin or insulin related growth factor, there does seem to be a relationship between my IGF and insulin, so that comes in several different ways, mostly that the IGF1 and insulin receptors are very similar and both molecules can activate the other. So insulin can activate the IGF1 receptor and IGF1 can activate the insulin receptor and so I would absolutely expect there to be interplay between insulin an IGF1, particularly in those IGF one expressing tumors. This also brings up a good point that I want to highlight, and that is that the insulin receptor is not ubiquitously found in tumors. The tumor types that are associated with obesity on average have higher insulin receptor expression, but that’s not 100% across the board, because of this cross talk between IGF,1 and insulin that may explain some of the discrepancies there where a tumor may be at least weakly obesity associated. But may not have the insulin receptor and that may be because the IGF1 receptor compensates for that. Unfortunately,
tumors are evolved to survive very well, and so they’ve sort of developed mechanisms in their evolution to be able to survive, and one that I think is the redundancy of insulin, and IGF1 action.

In our last few minutes I really want to get back to something you said earlier which was breaking the cycle of obesity. Can have an impact on reducing cancer risk. I wanna make sure I got that straight. So if you’re overweight and you decide to lose weight by cutting calories or exercise, that actually can reduce your cancer risk. Absolutely, epidemiologically, even losing weight within the last couple years reduces your cancer risk, and so it’s best of course, if we’re normal weight, healthy weight throughout our lives. But it absolutely can have a huge impact to lower cancer risk.

Losing a little bit of weight at really anytime. And you know the other point I want to highlight is we don’t have to be back to our high school body weight. This is a case where
Losing 5 to 10% of body weight if you’re an overweight or obese individual can actually almost fully normalize your insulin sensitivity, and so that can be predicted to almost fully normalize or reduce the excess risk of obesity, and so that is something where that loss of five to 10% is something that would be much more achievable then returning to a quote unquote healthy weight for a lot of individuals.

Doctor Rachel Perry is an assistant professor in medicine and Endocrinology and cellular and Molecular Physiology at the Yale School of Medicine.

If you have questions, the address is canceranswers@yale.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.