Obesity & Cancer Webinar Series

The Intersection of Chronic Inflammation, Insulin Resistance, Obesity, and Cancer Risk
Webinar
June 3, 2021, 12:00–1:30 p.m. (Eastern Time)

Webinar Questions and Answers

Moderator:

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Panelists:

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Nathan A. Berger, M.D.
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1. **Adipose tissue, subcutaneous, visceral, and muscle – do you think muscle factors into the insulin resistance scenario as well?**

   Matthias Blüher, M.D.: This is an important question because what I missed out completely is the fitness level. Some people relate to the metabolically healthy obesity as the "fit and fat" phenotype in obesity, which seems to be true, at least in part. We do have data on muscle mass and the fitness level of our patients included in those studies. And we can confirm previous work from many groups worldwide who are experts in exercise physiology, for instance, who have found with metabolically healthy obesity that muscle strength and fitness level (but not so much total body skeletal muscle mass in humans) are related to the healthier phenotype. So, maybe it's more about muscle function, which may bring us back to mitochondrial function and Marcia and Alison's talks. This may play a role not only in adipose tissue, but also in the skeletal muscle. Maybe that's a common denominator between different tissues: that metabolic and mitochondrial function come into play. But I agree that fitness level and muscle function, if they are in a very good state or almost normal state, contribute to healthier obesity. We did not find any evidence that

both total body fat mass and total muscle mass are the determinants of this phenotype. But maybe this is a too-wide phenotype. If you just take total fat mass and total muscle mass, maybe that's not sophisticated enough to define a phenotype.

2. **Can you define metabolic healthy obesity?**

   Matthias Blüher, M.D.: In general, a metabolically healthy lifestyle is considered what we learned from the Look AHEAD study in the United States as the intervention group. This consisted of approximately 60 minutes of mixed strength and endurance training three times a week and about 500 kilocalories per day energy-reduced mixed diet. That is considered a diet to keep you at a normal body weight and at a fitness level that supports metabolic health, even independently of your body weight, whether you are lean or obese. But what I think is also important in this context is that it's very difficult to really distinguish which individual factor, at least in humans. I'm very grateful for the beautiful presentation of our three scientists who presented after my introduction to identify which mechanism is the most prominent. I think human model systems are really weak because they can lead to a mix of causation and only associations, and the variation in human phenotypes is quite high.

   So, we define metabolically healthy obesity as those individuals who have no evidence for cardiovascular manifestations, no evidence for type II diabetes, no hypertension, and no dyslipidemia as defined by low HDL cholesterol and high triglycerides in the fasting state. When we look into our own cohorts, we see that only approximately 5 to 10% of individuals with obesity fulfill these strict criteria. But you can use them as a good model system to study obesity outcomes, including cancer, in the future. This is an ongoing study, and we can only report 5- to 10- to 15-year outcomes; this has not been published yet, and it's only for diabetes and cardiovascular diseases.

3. **Dr. Haigis mentioned the positive effect of the ketogenic diet on cancer. This is a high-fat diet, and yet leads to weight loss for many. What are your thoughts on the Ketogenic diet and cancer?**

   Marcia Haigis, Ph.D.: I think there are some really exciting studies looking at different diets that are protective in cancer, like the ketogenic diet or even a calorie-restricted or intermittent fasting type of diet. With these diets, we're still understanding what they do at the molecular level. But these diets often affect how fuels are utilized by our tissues and bodies. As I mentioned before in my talk, the ketogenic diet also lowers insulin. So that's also very protective. It could be that certain fuels are beneficial. There was another question in the chat that brought up fuel usage between tumor and T cells. We know that different cell types in our body and even in the tumor microenvironment – the protective immune cells versus antitumor immune cells versus the pro-tumorigenic immune cells –

have different fuel preferences. So, one question is, can we create diets that also improve antitumor immunity?

I want to add that all of the speakers are speaking about a particular cancer type. I don't want to say generically, but we illustrated one type of cancer. It's certainly not true that one shoe fits all sizes, right? So, every tumor type has different signaling pathways depending on the microenvironment, depending on the tissue of origin, and different oncogenic drivers. And so, it's really important to consider each type of cancer case by case in a personalized way. There is no one metabolic effect that's going to be a cure-all. There is no one diet that's going to be a cure-all for every type of cancer.

Nathan Berger, M.D.: If I can just make a comment, I think great care needs to be exercised when putting patients on ketogenic diets. Probably the first demonstration of a ketogenic diet altering tumor metabolism and progression was reported by Dr. Linda Nebeling, when she was here with CWRU. We have now experienced in some tumor models, in animals at least, that the ketogenic diet may promote the growth of cancer. So, you need to be really careful, monitoring for tumor growth, in patients on ketogenic diets.

4. **Is the high-fat diet that the mice were fed considered ketogenic? Or more of a Western diet?**

Alison Ringel, Ph.D.: That's an excellent question and an important distinction. The high-fat diet that we used is not ketogenic because it does contain carbohydrates. It's not considered a Western diet by most researchers who feed animals because the sucrose content is not high enough or the fructose content is not high enough. So, it's somewhere in between. It's mostly animal fat. Palmitate and monounsaturated fatty acids that come from lard are the primary fat sources for this diet.

Nathan Berger, M.D.: The high-fat diets that we use to promote tumor growth in the ApcMin/+ mice are all plant-based, either with coconut oil or corn oil. These high-fat diets promote tumor growth whether they are combined with high or low sucrose, thus precluding a ketogenic effect.

5. **Can Dr. Berger please repeat what is meant by the complement factor involvement in your studies?**

Nathan Berger, M.D.: With the consomic mouse that had the A/J chromosome 2 on the C57Bl6 background, we found that a high-fat diet was not as effective in promoting polyp growth as it was in the C57Bl6 mouse. And that mouse, the A2 mouse, has a mutation in the C5 component of complement. We then did a number of experiments with mice that were genetically engineered to either have a homozygous defect in the C3 component or the C5 component of complement, and we also used an inhibitor of complement metabolism,

PMX53. All three of those conditions interfered with the development of intestinal polyps in the ApcMin/+ mice fed a high-fat diet. So, it was clear that the complement system, usually involved in host immunity defense, is an early and essential component mediating the obesity acceleration and promotion of intestinal cancer.

6. **Have you evaluated immunity when the model is underfed? I'm curious how undernutrition would present, when considering the sweet spot of energy availability– thinking of a model with greater than 30% energy restriction.**

   Nathan Berger, M.D.: Sounds like a great idea, but sorry to say we have not done undernutrition, nor have we specifically looked at immune function. We'll have to do it.

7. **What comes first: is it insulin resistance or is it chronic inflammation? In other words, what's the initial or earlier driver of obesity-related cancer? Or is it context dependent?**

   Alison Ringel, Ph.D.: I think there's evidence that at least adipose inflammation can precede insulin resistance. But in the tumor microenvironment, which is a bit of a privileged location, I think that more studies are really warranted trying to disentangle the local inflammation from systemic inflammation and how this impacts the process of tumorigenesis.

   Matthias Blüher, M.D.: I fully agree. From the human or clinical standpoint, it's indeed extremely difficult to distinguish what is the hen and what is the egg in this context. I think personally that there are two options for how a person may enter this increased obesity risk, and this would be both ways. It could be insulin resistance, because we do see patients with obesity but without insulin resistance, but with subclinical chronic inflammation. For those patients, inflammation may be the predominant factor contributing to cancer risk, but we also see patients in whom insulin resistance seems to be the predominant factor. This does not necessarily translate into inflammation at the whole-body level, even though we see an association with adipose tissue inflammation and either increasing cell stress in hepatocytes, for instance, or in skeletal muscles – all the important metabolic cells. But I agree with Alison that it's more likely that this inflammatory response at the cellular level may drive chronic insulin resistance. There is much more evidence for that causality chain from animal studies.

   Nathan Berger, M.D.: Our animal studies, where three-day high-fat feeding clearly accelerates tumor development, indicate that metabolic inflammation precedes any signs of insulin resistance. You can prevent it all from happening by interfering with complement metabolism. There are also similar indications from the Jain Lab, with pancreatic cancer using losartan to block the AT1, the angiotensin 2 type 1 receptor, which blocks inflammation. So, what we're talking about is very early, maybe even before you get obese. Just the obesogenic diet can stimulate inflammation and promote tumor development. But

the important question from my viewpoint is, how can you block this process to prevent both inflammation and insulin resistance from promoting cancer? We need to think about whether preventing inflammation very early on, even when people are just eating too many fast-food meals and before they actually develop obesity.

Marcia Haigis, Ph.D.: I have a few comments to add. I agree that inflammation is an early adaptation to obesity. But I think that more systematic studies should be done to disentangle the role of insulin signaling and then insulin resistance as well as inflammation, particularly at a cellular level in the tumor microenvironment. We know there's been a lot of attention to how obesity affects insulin resistance in signaling among different tissues in model organisms. But less is known and less focus has been given to how these diets and different interventions affect cellular insulin or metabolic homeostasis within the tumor microenvironment, and how those pathways interact with inflammatory pathways. We've talked a lot in this really exciting session about obesity. But there are other diets. I think this is really the tip of the iceberg and just highlights how much there is to understand and do in this important area. For instance, fasting, intermittent fasting, calorie restriction, and ketogenic diets can all be beneficial in the tumor microenvironment, and some of those effects are very rapid.

8. **Do you foresee a potential role for pharmacological options used in the management of obesity in chemoprevention and/or as metronomic chemotherapy?**

Matthias Blüher, M.D.: I'll start with the obesity treatment. I think what we have learned today from all the talks is that although one size doesn't fit all and obesity treatment does not prevent all types of cancer, we have solid evidence that by treating obesity properly – more importantly by preventing obesity properly – we have the chance to reduce the individual risk for certain types of cancers significantly. So, this puts treatment of obesity and prevention of obesity into a new light in the context of cancer prevention. Although we are lacking data and we need more prospective data, we have at least epidemiological evidence for certain types of cancer closely and strongly related to obesity mechanisms. For those types of cancer, I think we can expect that reducing body weight and obesity-related comorbidities may not only reduce the risk of getting cancer, but also improve individual outcomes.

9. **Is there evidence that obesity or insulin resistance affects therapeutic response to immune checkpoint inhibitors?**

Alison Ringel, Ph.D.: This is a question that comes up a lot. The answer is that it depends on the patient cohort that's studied and the type of cancer studied and whether it's first-line or non-first-line. There are a lot of complicating factors. Some studies, for instance one in melanoma, said that patients with a high BMI respond better. There have been subsequent studies that came to different conclusions. It also depends on the cancer type being

analyzed. If this had been two years ago, I would have said, it does seem to be a good predictor, but that has now been diluted with subsequent studies. I think the jury is still out. This is the primary challenge, or one of the challenges, of using BMI as a stratifier. In most of these studies using BMI, BMI is confounded with a lot of different variables, many of which are difficult to disentangle. Also, many of these studies are retrospective. We've actually done these experiments in animals, and we see that there is no difference in response to checkpoint blockade in obese and nonobese animals. I'll finish by saying there actually aren't studies looking at the connection, as far as I know, to insulin resistance. But there is a small subset of patients who do develop hyperglycemia and insulin resistance after being treated with checkpoint blockade, which speaks to this chicken-and-egg question about inflammation and insulin resistance.

Marcia Haigis, Ph.D.: It really highlights the importance of future studies and thinking more holistically about a patient's metabolic health when considering cancer treatment and care. Most clinicians don't keep in mind: what's the insulin-resistant or metabolic fitness of that patient? What are they taking for that state, and how does that intercept with their cancer therapy? I think that we really need to understand more about how insulin resistance or insulin sensitivity affect checkpoint blockade outcomes.

10. If you were and had been obese for a long time but then lost weight, does your risk of developing obesity-related problems decrease or has the damage already been done?

Nathan Berger, M.D.: Multiple studies suggest that Bariatric-Metabolic Surgery in patients with obesity, compared to non-surgically managed controls, reduces the risk of obesity-related problems including heart disease, Type II diabetes mellitus, and cancer. The reduced cancer risk occurs predominantly in women. In contrast, lifestyle modification to lose weight has not been shown to effectively reduce cancer risk (Bruno and Berger 2020).

Matthias Blüher, M.D.: There are very little data on cancer risk changes after a history of long-time obesity and weight loss. However, at least in women, breast cancer risk decreases after significant weight loss by bariatric surgery (Sjöström et al., 2009). For men, decreased cancer risk upon weight loss in the same cohort (Swedish Obese Subject´s study) could only be shown in (statistically non-significant) trends. In other words, at least to some extent for some cancers, and more pronounced in women compared to men, obesity-related cancer mechanisms may be reversible.

11. **Can the panelists address fasting as a means to prevent, halt, or slow the progression of cancer? There is some evidence that intermittent fasting, particularly when a low-carb diet is consumed during eating intervals, can improve insulin sensitivity, immune functioning, and markers of inflammation.**

Matthias Blüher, M.D.: Unfortunately, there are no long-term data on the effects of intermittent fasting on cancer risk. Recently, it has been shown that long-term intermittent fasting may increase insulin resistance and subclinical inflammation (Fanti et al., 2021) and (Carter et al., 2019), which would, in contrast to the assumption, rather affect mechanisms known to promote certain types of cancer. On the other hand, fasting associated with chemotherapy could improve the efficacy of anticancer treatments without increasing their adverse effects.

12. **Are insulin sensitivity and obesity different between the sexes in terms of cancer risk?**

Nathan Berger, M.D.: In ongoing mouse model studies, we have shown that, compared to male mice, ovarian function delays high fat-induced obesity, insulin resistance, and acceleration of tumor growth. These protective effects are abrogated by oophorectomy.

Matthias Blüher, M.D.: One could hypothesize that insulin sensitivity and obesity differentially affect individuals also as a function of sex. In this context, differences in response to weight loss-associated improvements of cancer risk are different between men and women (Sjöström et al., 2009). The Cremona study further investigated this aspect (Perseghin et al., 2012). Hyperinsulinemia and insulin resistance may be the link with cancer, but whether this is independent of the diabetes status, obesity/visceral obesity, and metabolic syndrome is uncertain. Fifteen-year all-cause CVD and cancer mortality data were obtained through the Regional Health Registry for 2,011 out of 2,074 Caucasian middle-aged individuals in the Cremona Study. This population study on the prevalence of diabetes mellitus in Italy collected anthropometric and metabolic characteristics. During the 15-year observation period, 495 deaths were registered: 221 CVD-related and 180 cancer-related. Age and sex were independently associated with all-cause, cancer, and CVD mortality rates. Age- and sex-adjusted analysis showed that HOMA-IR, cigarette smoking, and diabetes were independently associated with all-cause mortality; HOMA-IR, systolic blood pressure, and fibrinogen were independently associated with CVD mortality; and HOMA-IR and smoking habit were independently associated with cancer mortality. Individuals in the highest quintile of serum insulin had a 62% higher risk of cancer mortality (HR = 1.62 95% CI: 1.19-2.20; $P < 0.0022$) and a 161% higher risk of gastrointestinal cancer mortality (HR = 2.61 95% CI: 1.73-3.94; $P < 0.0001$). Age- and sex-adjusted analysis showed that hyperinsulinemia/insulin resistance is associated with cancer mortality independently of diabetes, obesity/visceral obesity, and the metabolic syndrome. Another example from colorectal cancer suggests a sex difference in the obesity and/or insulin resistance-related cancer risk (Association Among Obesity, Metabolic Health, and the Risk for Colorectal

Cancer in the General Population in Korea Using the National Health Insurance Service-National Sample Cohort (Shin et al., 2017).

13. Are any humans resistant to obesity or is this only in genetically modified mice?

Matthias Blüher, M.D.: There seem to be humans who are resistant to developing obesity, even with high-fat diets (Toledo et at., 2018 and Gupta et al., 2012). However, the underlying mechanisms are not well understood, and there are no data on human "obesity resistance" and cancer risk.